Development and Application of Parameters based on Chemical Reactivity Theory

THESIS

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Under the Supervision of

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Dedicated to My Parents
and
My Husband

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
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CERTIFICATE

This is to certify that the thesis entitled Development and Application of Parameters based on Chemical Reactivity Theory and submitted by Rituparna Bhattacharjee ID No. 2010PHXF409P for award of Ph.D. of the Institute embodies original work done by her under my supervision.

Signature of the Supervisor

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(RITUPARNA BHATTACHARJEE)

ABSTRACT

This thesis offers a comprehensive study on the theoretical development and applications of Chemical Reactivity Theory (CRT) based parameters for predicting the intra as well as intermolecular reactivity of large (i. e., higher number of electrons present) molecules. A CRT based formalism is developed to have a clear perception of diverse chemical and biological phenomena in a computationally economic way.

In Chapter I, an overview of objectives, theoretical foundation, and organization of the thesis is given. Past and recent advances to predict the chemical reactivity using CRT based reactivity descriptors are discussed thoroughly.

Chapter II confers a formalism of hardness potential (defined by R. G. Parr and J. L. Gazquez, *J. Phys. Chem.*, **1993**, *97*, 3939) to encounter the *N*-dependence problem of local hardness. The merits of corresponding electrophilic [$\Delta^{+}h(k)$] and nucleophilic [$\Delta^{-}h(k)$] variants of the hardness potential is discussed in detail. The association between these two variants of the hardness potential and Fukui potential (conceived by M. Berkowitz, *J. Am. Chem. Soc*. **1987**, *109*, 4823) is also emphasized.

Chapter III comprises the study on the relative contribution of the sum of kinetic [$\frac{10}{9}C_F\rho(\bar{r})^{2/3}$] and exchange energy [$\frac{4}{9}C_X\rho(\bar{r})^{1/3}$] terms to that of the electronic part of the molecular electrostatic potential [$V_{el}(\bar{r})$] in the variants of Hardness Potential to evaluate the proposed definition of variants of the hardness potential for some substituted benzenes and polycyclic aromatic hydrocarbons (PAHs) (undergoing electrophilic aromatic substitution), carboxylic acids and their derivatives. A systematic analysis of intermolecular reactivity trends for systems with multiple reactive sites is also highlighted.

Chapter IV explores the trends of electronic contribution to molecular electrostatic potential [$V_{el}(\bar{r})_{r=0}$], Fukui potential [$v_f^{+}\big|_{r=0}$ and $v_f^{-}\big|_{r=0}$] and hardness potential derivatives [$\Delta^{+}h(k)$ and $\Delta^{-}h(k)$] for isolated atoms as well as atoms in molecules. An explicative analysis is provided on how the generated numerical values of these three reactivity descriptors vary in these two electronically different situations, for several commonly used molecules containing carbon as well as hetero atoms. Sum of Fukui potential and sum of hardness potential derivatives in molecules are also discussed briefly.

Chapter V explains the correlation between orbital relaxation effect and nature of atomic Fukui functions for the chosen s and p block elements. The usefulness of the nodal nature of the highest occupied and lowest unoccupied orbitals is also evaluated.

Chapter VI summarizes the key ideas of the thesis. The scope of the plausible extension of this thesis work is also pointed out.

LIST OF ABBREVIATIONS AND SYMBOLS

B3LYP	Becke three parameter Lee-Yang-Parr functional
χ	Electronegativity
cc-pVDZ	Correlation consistent polarized valence double zeta (basis set)
cc-pVTZ	Correlation consistent polarized valence triple zeta (basis set)
CDASE	Comprehensive decomposition analysis of the stabilization energy
CI	Configuration interaction
FMO	Frontier Molecular Orbital
CRT	Chemical Reactivity Theory
DFT	Density Functional Theory
DFRT	Density Functional Reactivity Theory
DMM	Density matrix minimization
DNA	Deoxyribonucleic acid
E	Energy
E_a	Activation energy
ΔE_{SE}	Stabilization energy
E[ρ]	Total electronic energy
EA	Electron affinity
EEM	Electro negativity equalization method
$E_{XC}[\rho]$	Exchange correlation energy
$f(\rho)$	Fukui function
$F[\rho]$	Hohenberg Kohn universal Functional
FC	Frozen core
FF	Fukui function
GTO	Gaussian type orbital
ΔN	Electron transfer
η	Chemical hardness
$\eta(\bar{r})$	Local hardness
$\eta(\bar{r},\bar{r}')$	Hardness kernel
h	Planck's constant
$h(\bar{r})$	Hardness potential

HOMO	Highest occupied molecular orbital
HPA	Hirshfeld population analysis
HSAB	Hard and soft acid and base
IP	Ionization potential
$J(\rho)$	Coulombic interaction energy
k	Rate of reaction
k_B	Boltzmann constant
LUMO	Lowest unoccupied molecular orbital
μ	Chemical potential
MESP	Molecular electrostatic potential
MPA	Mulliken population analysis
N	Total number of electrons
NOA	Natural orbital analysis
P_k	Gross electronic population of atom k in the molecule
PMH	Principle of maximum hardness
q_k	Effective atomic charge
$\bar{r}$	Electronic position
RHF	Restricted Hartree Fock
$\rho(r)$	Electron density
S	Global softness
$s(\bar{r})$	Local softness
$s(k)$	Condensed-to-atom local softness
$s(\bar{r},\bar{r}')$	Softness kernel
SP-DFT	Spin-polarized Density Functional Theory
STO	Slater type orbital
T	Temperature
$T_k(\rho)$	Electronic kinetic energy
TFD	Thomas-Fermi-Dirac theory
TS	Transition state
w	Global electrophilicity index
$w(\bar{r})$	Local electrophilicity index

$v(\bar{r})$	External potential
$V_{ee}[\rho]$	Electron-electron repulsion energy
$v_{XC}(\bar{r})$	Exchange correlation potential
Ψ	Electronic wave function

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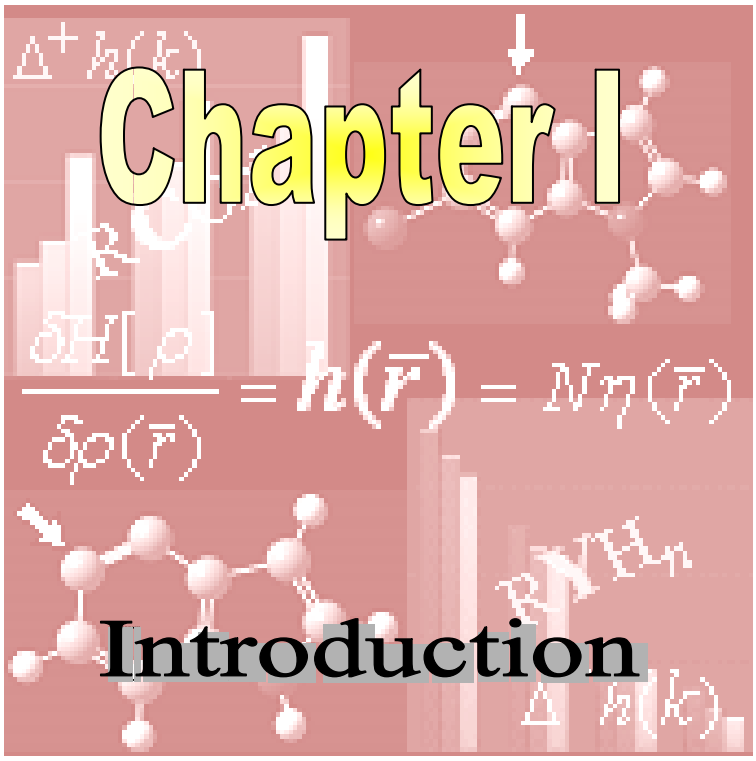

Chapter I
Introduction

1.1. Introduction

The trends of intra (i. e., regioselectivity) and intermolecular (between two different species) reactivities play a pivotal role in chemistry (specifically organic chemistry and biochemistry) since its inception. Intramolecular reactivity i. e., regioselectivity[1,2] refers to the proclivity of formation of a particular structural isomer over all others that are conceptually feasible. If one product is favoured over the other (i. e., the major product), the reaction is said to be regioselective, whereas if only a single product is obtained, the reaction is termed as regiospecific. Intermolecular reactivity involves two different species and compares the relative reactivity trends among them. A deep insight into intra and intermolecular reactivities of chemical reactions is beneficial for understanding the corresponding reaction mechanisms as well as for obtaining desired products. In order to describe them vividly, several electronic parameters i. e., Frontier Molecular Orbital (FMO),[3-6] Electron Localized Function (ELF),[7,8] Molecular electrostatic Potential (MEP)[9-17] are prevalently used in the last few decades for different type of reactions. On the other hand, many empirical principles such as the hard and soft acids and bases (HSAB).[18-22] Electronegativity equalization method (EEM),[23-28] etc. are evolved to rationalize various chemical phenomena. It is also common that the electron density provides key information about structural properties of molecules and materials.[29,30] The use of electron density along with its response to perturbations to study chemical reactivity, is the focal theme of 'Conceptual Density Functional Theory' or 'Chemical Reactivity Theory' or 'Density Functional Reactivity Theory (DFRT), a branch of density functional theory (DFT).[31-43] CRT quantifies the reactivity of isolated species through the formation of a set of reactivity descriptors. It was initiated by R. G. Parr and subsequent workers developed a formulation of CRT by providing the theoretical basis for formal definitions of many empirical concepts.[44-54] Chemical Reactivity Theory is able to suggest a new quantitative principle, the 'principle of maximum hardness' (PMH),[55-65] which can predict the most stable state of a chemical species. It may not be valid for all instances,[66,67] but it marks one of the biggest achievements of CRT because the principle cannot be conceived otherwise.

DFT, from which CRT extracts its analytical and conceptual justifications, cuts down the steep rise in computational cost efficiently compared to ab initio wave function techniques. To apply Hartree-Fock (HF), DFT or post-HF calculations to macromolecules, linear-scaling methods are available that are simply based on the principle of quantum locality[68] or "near-sighted-ness"[69] (i. e., the properties of a certain region of interest are subtly influenced by factors that are spatially far away from this region) but many issues are yet to be addressed. In fragment-based approaches,[70-97] a large molecule is divided

into a set of fragments, and the energy or molecular properties of this molecule are obtained by conventional quantum chemical calculations on a series of subsystems, each of which is constructed by connecting a fragment with its local surroundings. Molecular fragmentation approaches are of two main types. One is the density matrix-based fragmentation approach,[70,71,74,76,79,81,84,89,92] in which the density matrix of the target molecule is obtained by assembling the density matrices or localized molecular orbitals from various subsystems, which is then utilized to calculate the total energy or some properties of the target molecule. Another type can be named as the energy-based fragmentation (EBF) approach.[75,77,80,83,85,86,88] In this approach, the total energy of a molecule is approximately determined as linear combinations of the energies of its various subsystems, like, energy or heat of formation of a molecule being approximated as a sum of bond energies or enthalpies.

A new model to study regioselectivity of large chemical or biochemical systems termed as "one-into-many" model is developed[98] and applied to right-handed B-DNA (PDB ID: 1BNA).[99] It is broken into smaller fragments and the local reactivity of the concerned atomic sites in the individual fragments are evaluated on the basis of the Thomas-Fermi-Dirac (TFD)[100-102] approach of density functional theory by using the approximated form of local hardness, i. e., $\eta(\bar{r}) = \frac{-V_{el}(\bar{r})}{N}$ (N is the number of electrons and $V_{el}(\bar{r})$ is the electronic contribution to molecular electrostatic potential). To mimic the chemical environment, buffer zones are considered surrounding the active site (in triple base pair systems). But in another article by the same authors,[103] it is also shown that the $\frac{1}{N}$ factor in the definition of $\eta(\bar{r})$ makes it unreliable to predict intermolecular reactivity trends between systems of different sizes but having common reactive centers. Saha and Roy[103] critically illustrated the limitation of $\eta(\bar{r})$ (evaluated from two composite functions i.e., $\lambda[\rho(\bar{r}')] = \rho(\bar{r}')$ and $\lambda[\rho(\bar{r}')] = Nf(\bar{r}')$) when used for comparison of intermolecular reactivity trends between systems of different sizes but having common reactive centers. After a careful analysis they revealed that as the number of electrons increases with the size of the system, the $\frac{1}{N}$ factor alters the expected trends of $\tilde{\eta}_D^{TFD}(\bar{r})$ or $\tilde{\eta}_D^{TFD'}(\bar{r})$ (i.e., when the composite function, $\lambda[\rho(\bar{r}')] = \rho(\bar{r}')$) values. It was also shown that when the composite function, $\lambda[\rho(\bar{r}')] = Nf(\bar{r}')$, although $\frac{1}{N}$ problem solved apparently, the N-dependence problem appears implicitly through the normalization condition of the Fukui function. So, the broader applicability of

$\eta(\bar{r})$ as a reliable intermolecular reactivity descriptor necessitates the removal of its N-dependence. However, no mathematical justification to resolve the N-dependence problem of local hardness is provided. The strategy of taking care of the loopholes in $\eta(\bar{r})$ is discussed in connection with Hardness Potential Derivatives.[104]

Recent theoretical developments on parameters based on Chemical Reactivity Theory and their fruitful applications are highlighted in different subsections in the present chapter. Before describing the detailed theoretical treatment of CRT based parameters and their applications, a brief discussion on the background of the reactivity descriptors, which are closely related for the above purpose, is provided. The second part of this chapter (i.e., Section 1.2), deals with the Chemical Reactivity Theory which builds the theoretical foundations of different reactivity descriptors. The third part (i.e., Section 1.3) takes into account more recent developments of CRT based parameters to study the reactivity of large chemical or biomolecular systems. Organization of the thesis is summarized in the last part (i. e., Section 1.4).

1.2. Theoretical Background

A. Foundation

Pierre Hohenberg and Walter Kohn[105] formulated DFT as a full-fledged theory where electron density, $\rho(r)$ behaves as the carrier of all information in the molecular or atomic ground state. It is said that E is a functional of ρ and can be expressed as:

$$E = E[\rho] \tag{1.1}$$

where the square brackets denote a functional relation. Density Functional Theory (DFT) aims at calculating E and other ground state molecular properties from the ground state electron density ρ, as follows:

$$E[\rho] = F[\rho] + \int v(\bar{r})\rho(\bar{r})d\bar{r} \tag{1.2}$$

where the functional $F[\rho]$, the so-called Hohenberg-Kohn functional,[31,32] is the sum of the kinetic energy functional $T[\rho]$ and the electron-electron interaction energy functional $V_{ee}[\rho]$; $v(\bar{r})$ is the external potential (it is the potential acting on an electron at position $\bar{r}$ due to the nuclear attraction along with other external forces which may be present in the system). A variational principle is formulated stating that ground state density is the density which minimizes the energy of the system for a fixed number of electrons,

$$\delta(E[\rho] - \mu\int \rho(\bar{r})d\bar{r}) = 0 \tag{1.3}$$

where μ is a Lagrange multiplier arising from normalization constraint $\int \rho(\bar{r})d\bar{r} = N$. Otherwise,

$$\mu = v(\bar{r}) + \frac{\delta F[\rho]}{\delta\rho(\bar{r})} = \text{constant} \tag{1.4}$$

The pragmatic approach towards Eq. (1.4) was provided by Kohn and Sham,[32] who insightfully turned it into an orbital equation as shown below:[105]

$$\left[-\frac{1}{2}\nabla^2 + \nu(\bar{r}) + \nu_{xc}(\bar{r}) + \int \frac{\rho(r')}{|\bar{r}-\bar{r}'|}dr'\right]\psi_i = \varepsilon_i\psi_i \tag{1.5}$$

$\nu_{xc}(\bar{r})$ is the exchange-correlation potential, the functional derivative of the exchange-correlation energy functional $E_{xc}[\rho]$, i. e.,

$$\nu_{xc}(\bar{r}) = \frac{\delta E_{xc}(\rho)}{\delta\rho(\bar{r})} \tag{1.6}$$

In Eq. (1.5), ψ_i's are the Kohn-Sham orbitals, the squares of which must sum up to the total electron density of the system

$$\rho(\bar{r}) = \sum_i|\psi_i|^2 \tag{1.7}$$

The KS method solves Hartree-like equations in which one part of the potential is unknown which is investigated over years by the scientific community to look for better approximations of this unknown part of the energy functional, namely the exchange-correlation energy.[106-109]

The density-functional language is advantageous as it closely corresponds to the language of structural chemistry. DFT based Chemical Reactivity Theory (CRT) tries to define and elucidate important universal concepts of molecular structure and molecular reactivity.The central theme of CRT is that the response of a system to perturbations governs its reactivity.[110,111] If a system is stabilized after reacting with a certain class of reagents (i.e., the lowering of energy), the reaction is considered as favorable. Thus, differentials of the energy may be interpreted as reactivity indicators. They are nothing but the response functions.[46,49,52,54] They estimate the response of the chemical system to perturbations in its number of electrons, N, and/or the external potential, $v(\bar{r})$.

B. DFT based Reactivity Descriptors

The response functions can be classified as: global, local, and nonlocal. Differentiability of E with respect to N and $v(\bar{r})$ gives rise to a series of response functions. Two types of quantities evolve in the first-order derivatives: a global quantity, which is a characteristic of the entire system. They do not

depend on the spatial position r within the molecular framework. The other one is a local quantity, value of which varies from one point to the other and hence they are useful for describing the molecular selectivity. A kernel emerges out in the second derivatives which measures the response of a local quantity at a given point r to a perturbation at a point r'. Nonlocal reactivity descriptors can determine molecule's polarization with respect to its environment or the change in polarization associated with electron transfer. Besides, higher order derivatives are also used as response functions. All these descriptors are suitable to understand experimental observations in a lucid way.

(i) ***Global Reactivity Descriptors***: Global reactivity descriptors estimate the overall reactivity of a molecule. These reactivity descriptors can be considered as response functions describing the system's response to perturbations in the number of electrons N at constant $v(\bar{r})$.

The foundation of CRT was laid by Parr and collaborators where interpretation of the Lagrangian multiplier μ in the Euler equation (1.4) is discussed.

It can be expressed as the partial derivative of the system's energy with respect to the number of electrons at fixed external potential (i. e., identical nuclear charges and positions):

$$\mu = \left(\frac{\delta E}{\delta N}\right)_{v(\bar{r})} \tag{1.8}$$

The chemical potential measures the escaping tendency of electron cloud. So, it is closely related to the electronegativity. Iczkowski and Margrave,[112] defined electronegativity as:

$$\chi = -\left(\frac{\delta E}{\delta N}\right) \tag{1.9}$$

Mulliken's[113] definition of electronegativity is expressed as the arithemetic average of two experimentally measurable quantities, i.e., ionization potential (IP) and electron affinity (EA):

$$\chi = \frac{IP+EA}{2} \tag{1.10}$$

The expression is the finite difference approximation to the term $-\left(\frac{\delta E}{\delta N}\right)$. Parr and his collaborators[44] have provided the theoretical justification in a natural way as follows:

$$\chi = -\mu = -\left(\frac{\delta E}{\delta N}\right)_{v(\bar{r})} \tag{1.11}$$

It provides a systematic way to calculate electronegativity values for atoms, functional groups, clusters, and molecules. The idea that electronegativity is a chemical potential originates with Gyftopoulos and Hatsopoulos.[114]

The practical definition of μ and χ are provided by the finite difference approximation[20] from $E(N)$ vs N curve, in which the first derivative $\left(\frac{\delta E}{\delta N}\right)$, i. e., μ is calculated as the average of the left and right hand side derivatives. The left derivative is the finite difference of energy of cation, $N-1$ and neutral, N. This is simply equal to negative of IP. Similarly, the right derivative is the difference of neutral (N) and anion (N +1) electrons. This is equal to the negative of EA.

$$\mu^- = E(N-1) - E(N) = -IP \tag{1.12}$$

$$\mu^+ = E(N+1) - E(N) = -EA \tag{1.13}$$

$$\left(\frac{\delta E}{\delta N}\right)_{v(\bar{r})} = \mu = \frac{1}{2}(\mu^+ + \mu^-) = -\frac{1}{2}(IP + EA) \tag{1.14}$$

Thus, from Eq (1.11) electronegativity (χ) can be written as:

$$\chi = -\mu = \frac{1}{2}(IP + EA) \tag{1.15}$$

The expression of χ originated from here is similar to that of Mulliken [i.e., Eq. (1.11)].[113] Chemical potential (μ) can be related to the frontier orbital energies by Koopman's approximation[115] within the molecular orbital theory whereas IP and EA can be replaced by frontier orbital energies (i.e., HOMO and LUMO energy, in conventional notation LUMO represents the lowest unoccupied molecular orbital and HOMO the highest occupied molecular orbital).[55,116-117] It is as follows:

$$-E_{HOMO} = IP \tag{1.16}$$

$$-E_{LUMO} = EA \tag{1.17}$$

Using Koopman's Theorem,[115] it can be written that,

$$\mu = -\chi = \frac{E_{LUMO} + E_{HOMO}}{2} \tag{1.18}$$

It is interesting to note that the importance of HOMO is also highlighted earlier in some different context. It is postulated that the gross equilibrium molecular geometry is controlled primarily by the behavior of HOMO.[118-120]

The physical significance of Eq. (1.18) lies in the fact that the negative of χ represents a horizontal line at the energy midpoint between HOMO and LUMO. This approximation might be useful when large systems are considered as it requires a single calculation (i.e., only for neutral system),

whereas the evaluation of Eq. (1.15) necessitates three calculations (i.e., for cationic and anionic systems along with the neutral one), which is computationally expensive and sometimes quite difficult to compute. Also, for systems leading to metastable $N+1$ electron systems (typically anion), the problem of negative electron affinities can be tackled to some extent via Eq. (1.18).[121-123] It is also implicitly exploited by Roy and Pal,[124] while calculating the theoretical values of chemical potential and hardness[20] for open shell free radicals by wave function approach.

Also, it attempts to provide theoretical justification of Sanderson's principle of electronegativity equalization,[23,125,26,126] (which states that when a molecule is formed, the electronegativities of the constituent atoms become equal, yielding a molecular electronegativity, which is the geometric mean of the original electronegativities of the constitutent atoms). Chemical potential of DFT is the property of an equilibrium state. The chemical potential (synonymous with electronegativity) is assumed to be sensitive to the external potential and may not be calculated easily, but it is an underlying concept in DFT. Semiempirical electronegativity equalization methods are also used now in a large scale.[28]

E versus N graphs do not yield straight lines, but are usually convex upward. A quantity of immense importance is defined by their curvatures, the chemical hardness η,[20]

$$\eta = \left(\frac{\delta^2 E}{\delta N^2}\right)_{v(\vec{r})} = \left(\frac{\delta \mu}{\delta N}\right)_{v(\vec{r})} \tag{1.19}$$

Hardness was highly used since its introduction by Pearson for the rationalization of hard and soft acids and bases principle (HSAB),[18,19,127,56,128-130] but it was not well-understood. This analytical expression (i. e. Eq. (1.19)) was first introduced by Parr and Pearson[20] to give a precise definition for hardness. It is postulated that hard acids prefer to bind to hard bases and soft acids to soft bases. Parr and Pearson[20] have introduced an arbitrary numerical factor in their definition, which is omitted by Parr himself.[131,132] Again, using a finite difference approximation and a quadratic $E = E(N)$ curve, this equation reduces to

$$\eta = IP - EA \tag{1.20}$$

On using Koopman's theorem,[115] we get,

$$\eta = \varepsilon_{LUMO} - \varepsilon_{HOMO} \tag{1.21}$$

Thus, hardness is the band gap for an insulator or semiconductor. If the gap is large (other things being equal), it is expected to have high stability and low reactivity and vice versa, for smaller gaps. These predictions work reasonably well to justify the existing correlation between HOMO-LUMO gap and the organic chemists' concept of aromaticity.[133] It is also established in the 'maximum hardness principle',[55] which states that "molecules will arrange themselves to be as hard as possible". Parr and Chattaraj

endorsed this principle with rigorous mathematical treatment based on the fluctuation-dissipation theorem.[57,66,67,134,135]

The inverse of the global hardness is defined as the global softness,[128,131]

$$S = \frac{1}{\eta} = \left(\frac{\delta N}{\delta \mu}\right)_{v(\vec{r})} \tag{1.22}$$

It can be empirically shown to be proportional to the polarizability of the system.[136-141] The hardness may be sensed as the resistance to charge transfer, while the softness accounts for the ease of transfer.

Parr and Pearson[20] framed the first theoretical proof for the HSAB principle with the use of Taylor series energy expansion in terms of the number of electrons (N) as a perturbation variable by drawing analogy from classical thermodynamics. The expression of energy lowering due to electron transfer ΔN from a species B to another species A is given as,

$$\Delta E = (E_A - E_A^0) + (E_B - E_B^0) = (\mu_A^0 - \mu_B^0)\Delta N + \frac{1}{2}(\eta_A + \eta_B)(\Delta N)^2 \tag{1.23}$$

where $\Delta N = N_A - N_A^0 = N_B^0 - N_B$ (which indicates that B is electron donor and A is electron acceptor). The terms E_A^0 and E_B^0 denote the energies of systems A and B, respectively, before the electron transfer. Similarly, E_A and E_B denote the corresponding quantities after the electron transfer. It is the formalism for energy lowering i.e., the stabilization energy (SE), due to electron transfer between two chemical species A and B. If chemical potentials of the two species are μ_A^0 and μ_B^0 respectively, and $\mu_B^0 > \mu_A^0$ (i.e., A is more electronegative than B) then electrons flow from B to A in the formation of AB. It is assumed that there are no other complicating factors and the electron transfer (ΔN) is very small. Hence electron flow and corresponding energy expression can be expressed from the definition of μ and η as:

$$\Delta N = \frac{\mu_B^0 - \mu_A^0}{2(\eta_A + \eta_B)} \tag{1.24}$$

$$\Delta E_{AB} = -\frac{(\mu_B^0 - \mu_A^0)^2}{2(\eta_A + \eta_B)} \tag{1.25}$$

It can be observed that the energy lowering results from the electron transfer and the difference in electronegativity or chemical potential drive the electron transfer.

In a recent paper, Roy and collaborators[142] have shown that not only ΔN, but also components of ΔE_{SE} can provide substantial information regarding the direction of electron transfer when (i) two systems, A and B, form a complex AB and (ii) when A and B go further to react and give different products (i.e., $A + B \Rightarrow [AB]^{\#} \Rightarrow C + D$). In case (ii) whether the reaction is spontaneous or required

some external assistance, could also be predicted from these energy components. By analyzing the energy components as obtained from Eq. (1.23), two expressions are given as:

$$\Delta E_{B(A)} = \frac{\mu_B^0 - \mu_A^0}{\eta_A + \eta_B}\left[-\mu_B^0 + \frac{1}{2}\eta_B\left(\frac{\mu_B^0 - \mu_A^0}{\eta_A + \eta_B}\right)\right] \tag{1.26a}$$

$$\Delta E_{A(B)} = \frac{\mu_B^0 - \mu_A^0}{\eta_A + \eta_B}\left[\mu_A^0 + \frac{1}{2}\eta_A\left(\frac{\mu_B^0 - \mu_A^0}{\eta_A + \eta_B}\right)\right] \tag{1.26b}$$

The value generated from the square bracketed term will be positive only if ΔN is a positive quantity (because μ_B^0 is a negative and η_B is a positive quantity). Now, ΔN is positive only if electrons flow from B to A (i. e., $\Delta N = N_B^0 - N_B$ = positive). Again, positive ΔN value causes a positive $\Delta E_{B(A)}$ value. Thus positive $\Delta E_{B(A)}$ value also indicates that B is the donor and A is acceptor. Similarly, $\Delta E_{A(B)}$ will be negative quantity when B is donor and A is acceptor and electron transfer from B to A causes the complex $[AB]$ more stable than the two individual species. If ΔN and $\Delta E_{B(A)}$ are negative and $\Delta E_{A(B)}$ is positive then, however, A is the donor and B is the acceptor in the complex.

Another global reactivity descriptor is global electrophilicity (w), also proposed by Parr et al.[143] while trying to validate the experimental findings of Maynard et al.[144] A model was used according to which, when an electrophilic system (atom, molecule, or ion) is immersed in an idealized zero-temperature free electron sea of zero chemical potential (e. g., a protein or a DNA coil), there would be an electron flow of amount ΔN from the sea to the system until the chemical potential of the system becomes zero. The change in the electronic energy as a function of the change in the number of electrons, N up to second order, at constant external potential $v(\vec{r})$ is,

$$\Delta E = \mu \Delta N + \eta \frac{\Delta N^2}{2} \tag{1.27}$$

where, μ and η are the electronic chemical potential and chemical hardness, respectively.

The saturation situation by soaking up the maximum amount of electrons, ΔN_{max}, of the system can be characterized by putting

$$\frac{\Delta E}{\Delta N} = 0 \tag{1.28}$$

implying

$$\Delta N_{max} = \frac{-\mu}{\eta} \tag{1.29}$$

which yields stabilization energy,

$$\Delta E = -\frac{\mu^2}{2\eta} \tag{1.30}$$

In Eq. (1.30), 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, i. e., charge transfer is an energetically favorable process. Parr et al.[143] defined $w = -\Delta E$ as a measure of electrophilicity of the system (atom, molecule, or ion).

The resulting equation is

$$w = \frac{\mu^2}{2\eta} \tag{1.31}$$

This quantity w is termed as the "electrophilicity index". An important local reactivity index is derived from this later (discussed in the next section).[144,145,146] An in-depth discussion, based on analytical reasoning, on the thermodynamic and kinetic aspects of w, were reported by Bagaria and Roy.[147] The 'thermodynamic' aspect helps to explain, qualitatively, favourable product formation. Chattaraj and collaborators[148] investigated thermodynamic and kinetic aspects of w by correlating it with the relative experimental rates of different types of reactions.

The expression of w can be elaborated in terms of first vertical IP and first vertical EA as follows: [143,144]

$$w = \frac{\mu^2}{2\eta} = \frac{[-(IP + EA)/2]^2}{2(IP - EA)} = \frac{(IP + EA)^2}{8(IP - EA)} \tag{1.32}$$

It can be seen from Eq. (1.32) that the electrophilicity value depends on the value of EA (also on the value of IP), the higher the EA, the higher the w value is. In a chemical reaction (where the substrate acts as an electron acceptor) it is expected that a substrate with higher EA value will enhance the rate of the reaction than that with a lower EA provided other factors (i.e., reactant, reaction conditions etc.) remain same. This establishes the kinetic aspect of global electrophilicity (w) values. The thermodynamic aspect of w is established from the fact that it was derived[139] by minimizing the energy change (ΔE) associated with the electron transfer (ΔN) from the free electron sea of zero chemical potential to the electrophile. When $\left(\frac{\Delta E}{\Delta N}\right)_v = 0$, $\Delta E \approx -\frac{\mu^2}{2\eta} = -w$ (by approximating ΔE, due to the electron transfer ΔN, up to second order). As $\eta > 0$, $\Delta E < 0$, i.e., charge transfer is an energetically favorable process.

Several other global reactivity descriptors e.g., nucleophilicity,[149-154] electrofugality and nucleofugality,[111,155,156] potentialphilicity and potentialphobicity,[157] chargephilicity and chargephobicity[158] are also derived recently, which are all conceptually related to w.

(ii) ***Local Reactivity Descriptors:*** Development of global descriptors are rightly accompanied by the evolution of several local reactivity descriptors which can be reliable for predicting local (site) reactivity (selectivity) of a chemical species. Local properties may vary from point to point in space and are one-point ($\vec{r}$) functions.

In case of a change from one ground state to another, E being a functional of the number of electrons and the external potential, $v(r)$ i.e., $E = E[N, v(r)]$ can be expressed as:

$$dE = \left(\frac{\partial E}{\partial N}\right)_{v(r)} dN + \int \left(\frac{\delta E}{\delta v(r)}\right)_N \delta v(r) dr \tag{1.33}$$

Similarly, E as the functional of electron density $\rho(r)$ i.e., $E = E[\rho]$ can be defined as:

$$dE = \int \left(\frac{\delta E}{\delta \rho(r)}\right)_{v(r)} \delta\rho(r) dr + \int \left[\frac{\delta E}{\delta v(r)}\right]_\rho \delta v(r) dr \tag{1.34}$$

The corresponding functional derivative with respect to the potential $v(r)$, will be

$$\rho(r) = \frac{\delta E[\rho]}{\delta v(r)} \tag{1.35}$$

It is the most fundamental local reactivity descriptor, the ground state electron density, $\rho(r)$.[33,159-165]

Likewise, the second order change in the energy due to the changes in the electron number and external potential reveals more information about the reactivity and this comes from the first order change of chemical potential,[166]

$$d\mu = \eta dN + \int \frac{\delta \mu}{\delta v(r)} dr \tag{1.36}$$

The first term in Eq. (1.36) contains the absolute hardness (η) and the second term is known as Fukui function [$f(r)$] that is formally defined as:[166]

$$f(r) = \left[\frac{\delta \mu}{\delta v(r)}\right]_N \tag{1.37}$$

Assuming that the total energy E as function of N and functional of $v(r)$ is an exact differential, the Maxwell relations between derivatives may be applied to the expression of the Fukui function as the first

derivative of the electron density $\rho(\bar{r})$ of a system with respect to the number of electrons N, at constant external potential, $v(r)$:

$$f(r) = \left[\frac{\partial \rho(r)}{\partial N}\right]_{v(r)} \tag{1.38}$$

This is the widely known representation of the Fukui function. It is named so because of its conceptual similarity with Fukui's frontier molecular orbital theory.[3,4]

The Fukui function,[47,166] is a reactivity index which measures the propensity of a region in a molecule to accept or donate electrons in a chemical reaction. In the molecular orbital (MO) framework, electrons are removed from the highest occupied molecular orbital (HOMO) and added to the lowest unoccupied molecular orbital (LUMO). Thus, Fukui function inherits the essence of frontier molecular orbital (FMO) theory but with corrections for orbital relaxation[167–169] and electron correlation.

For a molecular or atomic system, the derivative of Eq. (1.38) is discontinuous[32] and difficult to evaluate. Due to the discontinuity in this derivative at the N -value considered, different derivatives will be taken from right or the left side. A chemical species participates in chemical reactions either as an electrophile (or an electron acceptor), a nucleophile (or an electron donor), or an amphiphile. Thus, correspondingly, there exist three different functions, $f^{+}(r)$ when the derivative is taken as N increases from N to $N+\delta$, $f^{-}(r)$ when the derivative is taken as N increases from $N-\delta$ to N, and $f^{o}(r)$ the average of above two, can be written as:

$$f^{+}(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)^{+}_{v(r)} \qquad \text{governing nucleophilic attack} \tag{1.39a}$$

$$f^{-}(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)^{-}_{v(r)} \qquad \text{governing electrophilic attack} \tag{1.39b}$$

$$f^{o}(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)^{o}_{v(r)} = \frac{1}{2}\left[f^{+}(r) + f^{-}(r)\right] \qquad \text{governing radical attack} \tag{1.39c}$$

In a finite difference approximation, used for electronegativity and hardness earlier, these indices can be written as:

$$f^{+}(r) = \rho_{N+1}(r) - \rho_{N}(r) \qquad \text{: for nucleophilic attack} \tag{1.40a}$$

$$f^{-}(r) = \rho_{N}(r) - \rho_{N-1}(r) \qquad \text{: for electrophilic attack} \tag{1.40b}$$

$$f^{o}(r) = \frac{\rho_{N+1}(r) - \rho_{N-1}(r)}{2} \quad \text{: for radical attack} \tag{1.40c}$$

The function $f^{+}(r)$ is associated with the lowest unoccupied molecular orbital (LUMO) and measures reactivity toward a donor reagent, the function $f^{-}(r)$ is associated with the highest occupied molecular orbital (HOMO) and measures reactivity toward an acceptor reagent, and finally, the average of both, $f^{o}(r)$, measures reactivity toward a radical. Therefore, under frozen density approximation,[3-5,170-173] the Fukui function can be expressed as:

$$f^{+}(r) = \rho_{LUMO} \quad \text{: measures reactivity towards a nucleophilic reagent} \tag{1.41a}$$

$$f^{-}(r) = \rho_{HOMO} \quad \text{: measures reactivity towards an electrophilic reagent} \tag{1.41b}$$

$$f^{o}(r) = \frac{\rho_{LUMO} + \rho_{HOMO}}{2} \text{: measures reactivity towards a radical reagent} \tag{1.41c}$$

As chemists are interested with reactivities of atomic sites in reactions involving neutral systems and their monopositive and mononegative ions (i.e., when the electron number is changing by 1, instead of an infinitesimally small amount, δ), it would be more useful, if $f(\bar{r})$ indices of an atom in a molecule could be evaluated. In order to do that, Yang and Mortier [172] have developed an interesting approach, i. e., condensed Fukui functions to calculate the atomic condensed Fukui function indices based on the idea of integrating the Fukui function over atomic regions, similar to the procedure followed in population analysis techniques. The Fukui function on an atom k is then calculated as the change of the atomic charge with respect to a change in the total number of electrons in the molecule,

$$f_k = -\left(\frac{\partial q_k}{\partial N}\right)_{v(r)} \tag{1.42}$$

This procedure condenses the value of $f(r)$ around each atomic site into a single value that characterizes the atomic contribution in a molecule to describe the site-selectivity or site-reactivity of an atom in a molecule. Further, the finite difference approximation and the atomic Mulliken charges of the $N-1$, N and $N+1$ electron systems have been used to obtain three different types of condensed Fukui functions of an atom k in a molecule; depending upon the type of electron transfer, the following forms are defined as:

$$f_k^{+} = P_k(N+1) - P_k(N) \quad \text{: for nucleophilic attack} \tag{1.43a}$$

$$f_k^{-} = P_k(N) - P_k(N-1) \quad \text{: for electrophilic attack} \tag{1.43b}$$

$$f_k^o = \frac{P_k(N+1) - P_k(N-1)}{2} \quad \text{: for radical attack} \tag{1.43c}$$

where P_k is the gross electronic population of atom k in the molecule, f_k^+ and f_k^- describe the ability of an atom to accommodate an extra electron and to cope with the loss of an electron, respectively and f_k^o is then considered as indicator for radical reactivity. In other words, the corresponding Fukui function ($f_k^\alpha, \alpha = +,-,0$) can be written by replacing the associated electron densities by the respective electron population (P_k).

Formation of a molecule involves delocalization of electrons through a charge transfer mechanism, which is related to reactive sites. Parr and Yang proposed that larger value of Fukui function indicates more reactivity.[166] Hence, greater the value of the condensed Fukui function, the more reactive is the particular atomic center in the molecule.

In this calculation procedure, many different errors may be introduced. Among these errors, first one is in the use of finite difference approximation with $\Delta N = 1$ in Eqs. (1.43a-c), which is crude approximation for the calculation of the derivative as it is claimed that within DFT non-integral number of electrons may also be considered. Next to this one, another crude assumption is that the optimized structure of neutral molecule is considered to fit well for the cationic and anionic species for that molecule. The DFT functional and basis set should be equally accurate for the neutral molecule. One further needs to address the way how atoms are defined within the molecule. Usually this directs the problem toward the method used for population analysis.

Moreover, one of the often-cited problems with Fukui function is that of its negative values.[174-176] A negative Fukui function arises when addition of an electron to the molecule leads to reduction in the electron density in some spots (i.e., for nucleophilic attack), and removal of an electron from the molecule enhances the electron density somewhere in it (i.e., for electrophilic attack). If Fukui function indices are expected to be positive, then the above equalities should not occur, which is unreasonable and also has yet not been formally shown whether such behavior is physically correct or not. But it has been emphasized that Fukui function should be normalized, i.e., they should sum to one,

$$\sum_{k=1}^{N} f_k = 1 \tag{1.44}$$

To treat the problem regarding the negative Fukui function, Hirshfeld population analysis (HPA)[178] technique based on stockholders charge-partitioning technique, as proposed by Hirshfeld is used and

shown that HPA yields only positive Fukui functions.[61,150,175,177,179,180] Also, it was shown that electronic population derived on the basis of HPA produces more reliable intramolecular reactivity trends when compared to those obtained from Mulliken population analysis (MPA),[181] natural bond orbital (NBO) analysis,[182-185] and molecular electrostatic potential (MESP) based methods.[9] Even though it is difficult to make strong comments on the superiority of one method to the others, many studies by Roy et al.[174,175,177] clearly demonstrated that HPA is superior to other charge-partitioning schemes. But in this HPA technique, there is no definite prescription for evaluating atomic charges in the corresponding ionic species. In the first study in this series Roy et al.,[174] have shown that condensed Fukui function can be positive only when same weight factor for the neutral, cationic and anionic species is considered.

In order to encounter the problems associated with the above Hirshfeld scheme, Bultinck et al.[186] have proposed an alternative, iterative version of the Hirshfeld partitioning procedure, known as "Hirshfeld-I" method. They have verified this method on a test set of 168 molecules containing C, H, N, O, F and Cl atoms. On the basis of this study, it is assured that this iterative scheme (i) eliminates arbitrariness in the choice of the promolecule, so the atomic populations are determined solely by the molecular electron density, (ii) increases the magnitudes of the charges, and (iii) also treats open shell species without problem. Still, it is difficult to comment on its universal validity, as this method has yet not been used much by other researchers working in this area. However, it has been recognized that HPA is trustworthy[187] as long as small atoms (especially hydrogen atoms) are not embedded in regions with substantial negative or positive deformation densities. It also seems that HPA is rather trustworthy when "large" changes in atomic charge (on the order of a tenth of the charge on the electron) are of interest and less trustworthy when small nuances are being studied.

If negative Fukui function indices even occur at equilibrium geometries, then the molecule would be expected to have very interesting magnetic and redox properties.[188-190] This is important in view of the fact that although the problem of negative Fukui function indices has been discussed in detail, no definite answer is provided to the question whether negative values are physically acceptable or are artifacts. According to some computational studies, it is truly impossible to exclude negative Fukui function.[176,191-194] Further, it has been pointed out that the possibility of negative atom condensed Fukui function values depend critically on the properties of the hardness matrix.[179,188,195]

The Fukui function is a potent local reactivity indicator for regioselectivity, but it is not expected to provide an accurate indication of the overall reactivity of a molecule. When a reactivity indicator for overall reactivity is needed, usually grand canonical ensemble is considered.[196] Reactivity descriptors in

the grand canonical ensemble are obtained by replacing derivatives with respect to the number of electrons, N, with derivatives with respect to the electronic chemical potential, μ (the electronic chemical potential measures the intrinsic strength of Lewis acids and bases, so reactivity descriptors in the grand canonical ensemble represent how a molecule's reactivity changes as its electron-withdrawing power or electronegativity decreases). Local softness is one such descriptor, which was defined by Yang and Parr[131] as:

$$s(\bar{r}) = \left(\frac{\partial \rho(r)}{\partial \mu}\right)_{v(r)} \tag{1.45}$$

By applying the chain rule, $s(\bar{r})$ can be written in terms of Fukui function as follows:

$$s(\bar{r}) = \left(\frac{\partial \rho(r)}{\partial \mu}\right)_{v(r)} = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} \left(\frac{\partial N}{\partial \mu}\right)_{v(r)} = f(\bar{r}) S \tag{1.46}$$

where $f(\bar{r})$ is the Fukui function and S is global softness which is defined as:

$$S = \frac{1}{2\eta} = \left(\frac{\partial N}{\partial \mu}\right)_{v(r)} \tag{1.47}$$

Eq. (1.47) indicates that $f(\bar{r})$ redistributes the global softness among the different parts of the molecule and that $s(\bar{r})$ integrates to S

$$\int s(r)dr = \int Sf(r)dr = S\int f(r)dr = S \tag{1.48}$$

from the three types of $f(r)$ defined, which when multiplied by global softness (S), one can obtain three different local softness functions. By applying a finite difference approximation the condensed form of these three local softness functions for any particular atom (k) can be written as:[172]

$$s_k^+(r) = \left[P_k(N+1) - P_k(N)\right]S = f_k^+ S \qquad \text{for nucleophilic attack} \tag{1.49a}$$

$$s_k^-(r) = \left[P_k(N) - P_k(N-1)\right]S = f_k^- S \qquad \text{for electrophilic attack} \tag{1.49b}$$

$$s_k^o(r) = \frac{1}{2}\left[P_k(N+1) - P_k(N-1)\right]S = f_k^0 S \qquad \text{for radical attack} \tag{1.49c}$$

Here, $P_k(N)$, $P_k(N+1)$ and $P_k(N-1)$ represent the condensed electronic populations on atom (k) for neutral, anionic and cationic systems, respectively. Thus, in a molecule the atom (k) for which s_k^+ value is highest, is the most preferred atom to be attacked by a nucleophile. Similarly, highest values of s_k^-

and s_k^0 for any atom (k) indicate it to be the most preferable atom for electrophilic and radical attack, respectively.

Eqs (1.49 a-c) can be represented by a generalized expression as follows:

$$s_k^\alpha = f_k^\alpha S \tag{1.50}$$

where, α is +, -, and 0.

From Eq. (1.50) it is obvious that local softness contains the same information as Fukui function plus additional information about the total molecular softness. The Fukui function may be regarded as a normalized local softness.[131] Therefore, either the Fukui function or local softness can be used in the studies of intramolecular reactivity sequences (i.e., relative site reactivity in a molecule).[197] But only $s(\bar{r})$ (and not $f(\bar{r})$) should be a better descriptor of the global reactivity with respect to a reaction partner having a given hardness (or softness), as stated in the HSAB principle.[18] There is an interesting fluctuation formula for local softness in finite-temperature DFT, where the averages are over all members of a grand canonical ensemble at temperature T.[131] This formula and other similar DFT fluctuation formulae[223,224] may provide a basis for fluctuation theories of catalysis. $s(\bar{r})$ is measurable using scanning tunnelling microscopy. For an infinite system, $s(\bar{r})$ is approximately the local density of states at the Fermi level and S the total density of states at the Fermi level.[198,199]

It has been argued that the individual values of s_k^+ and s_k^- are strongly influenced by the basis set or correlation effects. But the ratio of s_k^+ and s_k^-, involving two differences of electron densities of the same system differing by one in their number of electrons, at constant nuclear framework, are expected to be less sensitive to the basis set and correlation effects. In favor of this argument, Roy et al.[200] introduced two new reactivity descriptors to find out the preferable reactive sites. These are defined as relative electrophilicity (s_k^+ / s_k^-) and relative nucleophilicity (s_k^- / s_k^+) of any particular atom k, to locate the preferable site for nucleophilic and electrophilic attack on it, respectively. That is, relative nucleophilicity is the nucleophilicity of any site as compared to its own electrophilicity and relative electrophilicity, is similarly the electrophilicity of any site as compared to its own nucleophilicity. The experimentally observed sites for gas-phase protonation in aniline and substituted anilines were successfully reproduced by Roy et. al.[201] It is, however, argued[202] that the DFT-based indices are defined at constant chemical potentials and hence they are not sensitive enough to take into account the situation with drastic changes following protonation. The cause for the reported exceptions and inadequacy in

predicting intramolecular and intermolecular reactivity trends has been discussed by Roy et al.,[203] thus until now no question has been raised regarding the conceptual validity of s_k^+ / s_k^- and s_k^- / s_k^+.

The search for a local counterpart of hardness (η)[20], the local hardness [$\eta(r)$][204-206] turns out to be more complicated compared to the global-local softness relationship. The search for $\eta(r)$ starts with the analytical definition of local hardness, in analogy with the local softness. Berkowitz and Parr[204] have given a derivation of local softness that reveals its relation to its reciprocal property, local hardness.[205-209] It is first proposed by Ghosh and Berkowitz[207] as:

$$\eta(r) = \left(\frac{\delta \mu}{\delta \rho(r)} \right)_{v(r)} \tag{1.51}$$

This quantity also appears in a natural way when the chain rule is applied to the global hardness (η).

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2} \right)_{v(r)} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N} \right)_{v(r)} = \frac{1}{2}\int \left(\frac{\delta \mu}{\delta \rho(r)} \right)_{v(r)} \left(\frac{\delta \rho(r)}{\delta N} \right)_{v(r)} dr = \frac{1}{2}\int \eta(r) f(r) dr \tag{1.52}$$

So that local hardness $\eta(r)$ and Fukui function $f(r)$ are related through Eq. (1.52) and an inverse relation is obtained with the local softness $s(r)$.

$$\int \eta(r) s(r) dr = 1 \tag{1.53}$$

To obtain explicit form of the local hardness $\eta(r)$, one can start from the Euler equation resulting from the application of the variation principle to the energy functional:[47]

$$v(r) + \frac{\delta F_E[\rho(r)]}{\delta \rho(r)} = \mu \tag{1.54}$$

with $F_E[\rho(r)]$ containing the kinetic energy and electron-electron interaction energy. Now multiplying Eq. (1.54) by a composite function $\lambda(\rho(r))$,[187,194] which integrates to N (i.e., total number of electrons of the system),

$$\int \lambda(\rho(r)) dr = N \tag{1.55}$$

one obtains after integration of both sides

$$N\mu = \int v(r)\lambda(\rho(r)) dr + \int \frac{\delta F_E}{\delta \rho(r)} \lambda(\rho(r)) dr \tag{1.56}$$

Taking the functional derivative with respect to ρ, at constant external potential $v(r)$, one can obtain the following expression:

$$\left(\frac{\delta\mu}{\delta\rho}\right)N+\mu=v(r)\left(\frac{\delta\lambda(\rho)}{\delta\rho}\right)_{v(r)}+\frac{\delta F_E}{\delta\rho}\left(\frac{\delta\lambda(\rho)}{\delta\rho}\right)_{v(r)}+\left(\int\frac{\delta^2F_E}{\delta\rho(r)\delta\rho(r')}\lambda\left(\rho(r')\right)dr'\right)_{v(r)} \tag{1.57}$$

yielding

$$\left(\frac{\delta\mu}{\delta\rho}\right)N=\left(v(r)+\frac{\delta F_E}{\delta\rho}\right)\left(\frac{\delta\lambda(\rho)}{\delta\rho}\right)_{v(r)}-\mu+\left(\int\frac{\delta^2F_E}{\delta\rho(r)\delta\rho(r')}\lambda\left(\rho(r')\right)dr'\right)_{v(r)} \tag{1.58}$$

Using Eq. (1.58), one can get,

$$\left(\frac{\delta\mu}{\delta\rho}\right)N=\left(\left(\frac{\delta\lambda(\rho(r))}{\delta\rho(r)}\right)_{v(r)}-1\right)\mu+\left(\int\frac{\delta^2F_E}{\delta\rho(r)\delta\rho(r')}\lambda\left(\rho(r')\right)dr'\right)_{v(r)} \tag{1.59}$$

Now if local hardness is forced to have an expression of the type

$$\left(\frac{\delta\mu}{\delta\rho(r)}\right)=\frac{1}{N}\int\frac{\delta^2F_E}{\delta\rho(r)\delta\rho(r')}\lambda\left(\rho(r')\right)dr' \tag{1.60}$$

which is desirable if a simple relationship with the second functional derivative of the Hohenberg-Kohn functional is the goal, then an additional constraint (in addition to that of Eq. (1.60)), for the composite function $\lambda(\rho(r))$ appears:[210]

$$\left(\frac{\delta\lambda(\rho(r))}{\delta\rho}\right)_{v(r)}=1 \tag{1.61}$$

In Eq. (1.60), $\frac{\delta^2F_E}{\delta\rho(r')\delta\rho(r)}=\eta(r,r')$ is defined as hardness kernel[205,211] the expression then becomes

$$\eta_\lambda(r)=\frac{1}{N}\int\eta(r,r')\lambda\left(\rho(r')\right)dr' \tag{1.62}$$

It should be noted that the definition of local hardness is not very clear and is defined in an ambiguous manner. This ambiguity has been pointed out by Harbola, Chattaraj and Parr,[209] Langenaeker et al.,[210] and Gazquez.[212] Restricting λ to functions of the first degree in ρ, the following possibilities emerge:

(i) A first function $\lambda(\rho(r))$ that satisfies both Eqs. (1.55) and (1.61)**,** is the electron density $\rho(r)$, originally used by Ghosh and Berkowitz,[207] that leads to the following equation for a local hardness $\eta_D(r)$ (D for density):

$$\lambda(\rho(r))=\rho(r) \tag{1.63}$$

yielding

$$\eta_D(r) = \frac{1}{N}\int \eta(r,r')\rho(r')dr' \tag{1.64}$$

(ii) A second choice satisfying Eq. (1.55) and (1.61), , is the $Nf(r)$ (the Fukui function integrates to 1) from which one obtains $\eta_F(r)$ (F for Fukui):

$$\lambda(\rho(r)) = Nf(r) \tag{1.65}$$

yielding

$$\eta_F(\bar{r}) = \int \eta(r,r')f(r')dr' \tag{1.66}$$

The latter case leads to a resulting local property $\eta_F(r)$ to be equal to the global hardness η at every point in space:[209]

$$\eta_F(\bar{r}) = \eta \tag{1.67}$$

As it is difficult to provide any accurate scheme for calculating $\eta_D(r)$, Langenaekar et al.[210] have proposed approximate working equations for it. These approximations are based on the Thomas-Fermi-Dirac (TFD) approach to DFT. Berkowitz et al.[206] obtained the following equation from the general form of the energy functional $E^{TFD}[\rho(r)]$ and keeping in mind that the nucleus-electron attraction is not contained in $F_E[\rho(r)]$, without any further approximations:

$$F_E^{TFD}[\rho(r)] = C_F\int \rho(r)^{5/3}dr + \frac{1}{2}\iint \frac{\rho(r)\rho(r')}{|r-r'|}dr'dr + C_X\int \rho(r)^{4/3}dr \tag{1.68}$$

Substituting Eq. 1.68 in Eq 1.64 and taking $\lambda = \rho$, the local hardness can be written as

$$\eta_D^{TFD}(r) = \frac{10}{9N}C_F\rho(r)^{2/3} - \frac{1}{2N}V_{el}(r) + \frac{4}{9N}C_X\rho(r)^{1/3} \tag{1.69}$$

where $V_{el}(r)$ is the electronic contribution to the molecular electrostatic potential.[9] Considering the exponential falloff of the electron density in the outer regions of the system, Eq. (1.69) can be approximated as:

$$\eta_D^{TFD}(r) \approx -\frac{1}{2N}V_{el}(r) \tag{1.70}$$

It is important to note that Eq. (1.70) contains $\frac{1}{N}$ factor which makes it unreliable to predict intermolecular reactivity trends between systems of different sizes but having common reactive centers.[103]

Another local reactivity descriptor, the hardness potential for the system, $h(\bar{r})$, is termed by Parr and Gázquez[213] which in turn is the product of N and $\eta(\bar{r})$. So, the hardness potential $h(\bar{r})$ can be defined by [from Eq. (1.60)],

$$h(r) = \int \frac{\delta^2 F[\rho]}{\delta\rho(\bar{r})\delta\rho(\bar{r}')} \rho(\bar{r}')d\bar{r}' = N\eta(\bar{r}) \tag{1.71}$$

$h(\bar{r})$ does not contain the $\frac{1}{N}$ factor. So it is expected that the use of $h(\bar{r})$ may formally resolve the N -dependence problem of $\eta(\bar{r})$. Thus, in principle, $h(\bar{r})$ has the ability to compare the reactivity of the same atomic site in different molecules (i.e., intermolecular reactivity comparison) apart from intramolecular reactivity i.e., regioselectivity.

To analyze the electrophilic and nucleophilic reactions better, another local electrophilicity index, $w(r)$, has been introduced, which varies from point to point in an atom or solid. It is defined as[143,144]

$$w = \int w(r)dr \tag{1.76}$$

where, w is the global electrophilicity index as proposed by Parr et al.[143]

In a similar line of work by Pérez et.al.,[145] they compared the experimental model of electrophilicity proposed by Mayr et. al.[146] with the definition of electrophilicity proposed by Parr et al., based on reactivity indexes for a series of benzhydryl cation. It is shown that,

$$w_k = \frac{\mu^2 S}{2} f_k^+ = w f_k^+ \tag{1.77}$$

Thus, it is concluded that the highest electrophilicity power in a molecule will accumulate at the site where the Fukui function for a nucleophilic attack i. e., f_k^+ is maximum.

By using resolution of the identity associated with the normalization condition of the Fukui function $f(r)$ [i.e., $\int f(r)dr = 1$], the best choice of $w(r)$ is proposed as

$$w = w\int f(r)dr = \int wf(r)dr = \int w(r)dr \tag{1.78}$$

where

$$w(r) = wf(r) \tag{1.79}$$

To take care of all types of reactions, three different forms of $w(r)$ can be defined as

$$w^{\alpha}(r) = wf^{\alpha}(r) \tag{1.80}$$

where $\alpha = +$, -, and 0 for nucleophilic, electrophilic, and radical attacks, respectively. It is more general as it takes care of all types of reactions, so named as "Philicity index".[214-216] The corresponding condensed-to-atom forms of the philicity index for atom k can be written as

$$w_k^{\alpha} = wf_k^{\alpha} \tag{1.81}$$

which in turn highlight the strength of the Fukui function and the frontier orbital theory.

In a study by Roy,[217] it has been shown that the philicity index $w(r)$ and the local softness $s(r)$ generate identical intramolecular reactivity (or site selectivity) trends. This is because $w(r)$ and $s(r)$ are analytically related as follows:

$$w(r) = wf(r) = \frac{\mu^2}{2\eta} f(r) = \mu^2 Sf(r) = \mu^2 s(r) \tag{1.82}$$

That is, $w(r)$ can be obtained after multiplying the $s(r)$ by a constant multiplier (i.e., μ^2) which varies from system to system. Therefore, it has been concluded that $w(r)$ will not provide any extra information than that of $s(r)$ or $f(r)$ as far as intramolecular reactivity is concerned.

In another study presented by Roy et al.,[203] concludes that the philicity index values of the corresponding strongest atoms will not provide the expected intermolecular electrophilicity (or nucleophiliicty) trend. This observation has been explained analytically on the basis of the arugument that, for any two systems A and B, if the global electrophilicity of system A (W^A) is higher than that of B (W^B), it does not mean that the philicity value of the strongest center K in species A i. e., w_K^A. is greater than the philicity value of the strongest center L in species B i. e., w_L^B. In other words, $W^A > W^B$ does not necessarily ensure that $w_K^A > w_L^B$. This is because of the following two equations:

$$\sum_{i=1}^{M} w_i{}^A = W^A \sum_{i=1}^{M} f_i^A = W^A \qquad (\text{as } \sum_{i=1}^{M} f_i{}^A = 1) \tag{1.83a}$$

$$\sum_{j=1}^{N} w_j{}^B = W^B \sum_{j=1}^{M} f_j^B = W^B \qquad (\text{as } \sum_{j=1}^{N} f_j{}^B = 1) \tag{1.83b}$$

That is, if two systems have comparable W values, the system in which numbers of atoms are more, will, in general, have lower W_K values because f_K^{α} values will be summed over to unity.

Also, it is important to note that, during an electrophile-nucleophile interaction process, at the initial stage of a reaction, when two reactants approach each other, charge will play a major role in determining the reactivity, i.e., intermolecular reactivity will better be explained by the hardness-based

reactivity descriptors and once the reaction starts, frontier orbitals play the major role in determining the reactivity of a particular site (or atom), i.e., intramolecular reactivity will better be explained by softness-based reactivity descriptors. This is why philicity indices fail to generate reliable intermolecular reactivity trends. It may be noted that Chattaraj[218] himself also later on mentioned that for intramolecular reactivity, philicity, local softness and FF produced the same trend. In another interesting article Ayers et al.,[196] have discussed the 'extensive', 'intensive' and 'subintensive' nature of DFT based reactivity descriptors. 'Intensive' nature of Fukui function $f(\bar{r})$ has made these two descriptors i. e., $s(\bar{r})$ and $w(\bar{r})$ 'intensive' (in spite of the fact that the number of electrons and energies associated with evaluating them for intermolecular comparison are extensive) and so constrained the applicability[58-62jcc] of these two indices as intermolecular reactivity descriptors. Also, the global softness part in these two descriptors is 'extensive', but true (unambiguously) for a conductor. For most of the commonly used chemical systems this may not always be true.

Roy et al.,[203] made a significant revelation regarding the correlation between global and local reactivity descriptors. It was concluded that reliable intermolecular reactivity trend can be generated by global electrophilicity (or may be local hardness) and that is possible with local electrophilicity only for the systems having one distinctly reactive site, (not for the systems containing many reactive sites of comparable strength).

(iii) Non-Local Reactivity Descriptors: The softness and hardness kernels are two point (r,r') functions. Their interest for reactivity studies comes from the fact that local softness and Fukui function are both defined as responses to a global perturbation, whereas in a chemical reaction, the electron density undergoes a nonlocal response to a local perturbation. Berkowitz and Parr[204] defined the softness kernel $s(r,r')$ and hardness kernel $\eta(r,r')$ expressions as,

$$s(r,r') = -\frac{\delta\rho(r)}{\delta u(r')} \tag{1.84}$$

and

$$\eta(r,r') = \frac{\delta^2 F}{\delta\rho(r)\delta\rho(r')} = -\frac{\delta u(r)}{\delta\rho(r')} \tag{1.85}$$

where F is the universal Hohenberg-Kohn functional and $u(r)$ is a modified potential defined as

$$u(r) = v(r) - \mu = -\frac{\delta F(\rho)}{\delta \rho(r)} \tag{1.86}$$

The two kernels are true inverses

$$2\int s(r,r')\eta(r',r'')dr' = \delta(r'' - r) \tag{1.87}$$

and integration of the softness kernel over one variable yields the local softness $s(r)$,

$$\int s(r,r')dr' = s(r) \tag{1.88}$$

Such a formula does not hold for the hardness kernel. Local hardness is obtained by multiplication of a functional $\lambda(\rho(r'))$, integrating to 1, with the hardness kernel and integrating[209]

$$\eta(r) = \frac{1}{N}\int \lambda\left(\rho(r')\right)\eta(r,r')dr' \tag{1.89}$$

Besides, another local quantity of great interest is the Fukui function, $f(r)$, which is proportional to the local softness through

$$s(r) = f(r)S \tag{1.90}$$

Here,

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} \tag{1.91}$$

and

$$\int \mathrm{f(r)dr} = 1 \tag{1.92}$$

S is the global softness, obtained from integration of the local softness

$$\int s(r)dr = \int f(r)Sdr = S\int f(r)dr = S \tag{1.93}$$

and similarly, one can express global hardness η as,

$$\eta = \int f(r)\eta(r)dr \tag{1.94}$$

In this way, from the correspondingly defined two-variable hardness and softness kernels, one can generate local softness, global softness, Fukui function, local hardness and global hardness.

1.3. Other Developments and Extensions in DFT framework:

The above defined reactivity and selectivity descriptors are inadequate to study the reactions which involve changes in spin multiplicity. For this purpose, the conceptual spin-polarized density functional theory (SP-DFT) was introduced by Galvan, Vela, and Gazquez.[220] This fact derives from the

explicit consideration of the electron and spin densities $\rho(r)$ and $\rho_S(r)$, respectively, written in terms of the spin-up $\rho_\alpha(r)$ and spin-down $\rho_\beta(r)$ components as,

$$\rho(r) = \rho_\alpha(r) + \rho_\beta(r) \tag{1.95}$$

and

$$\rho_S(r) = \rho_\alpha(r) - \rho_\beta(r) \tag{1.96}$$

which integrates to the electron number, N, and spin number, N_S, respectively.

$$N = N_\alpha + N_\beta = \int \rho(r)dr \tag{1.97}$$

$$N_S = N_\alpha - N_\beta = \int \rho_S(r)dr \tag{1.98}$$

The corresponding chemical potential (μ_N) and spin potential (μ_S) are given by

$$\mu_N = \left(\frac{\partial E}{\partial N}\right)_{N_S, v(r)} \tag{1.99}$$

and

$$\mu_S = \left(\frac{\partial E}{\partial N_S}\right)_{N, v(r)} \tag{1.100}$$

The corresponding expressions for hardness and Fukui functions may be written as

$$\eta_{NN} = \left(\frac{\partial \mu_N}{\partial N}\right)_{N_S, v(r)} \tag{1.101}$$

$$\eta_{NS} = \left(\frac{\partial \mu_N}{\partial N_S}\right)_{N, v(r)} = \left(\frac{\partial \mu_S}{\partial N}\right)_{N_S, v(r)} = \eta_{SN} \tag{1.102}$$

$$\eta_{SS} = \left(\frac{\partial \mu_S}{\partial N_S}\right)_{N, v(r)} \tag{1.103}$$

$$f_{NN}(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{N_S, v(r)} = \left(\frac{\partial \mu_N}{\partial v(r)}\right)_{N, N_S} \tag{1.104}$$

$$f_{NS}(r) = \left(\frac{\partial \rho(r)}{\partial N_S}\right)_{N, v(r)} = \left(\frac{\partial \mu_S}{\partial v(r)}\right)_{N, N_S} \tag{1.105}$$

The energy change (ΔE) due to a change in spin number ($\Delta \mathrm{N_s}$) at constant external potential ($v(r)$) and number of electrons (N) can be expressed in the $\{\mathrm{N}, \mathrm{N_s}\}$ representation of SP-DFT as:

$$\Delta E = \mu_s \Delta \mathrm{N_s} + \frac{1}{2}\eta_{ss} \Delta \mathrm{N_s}^2 \tag{1.106}$$

Now, considering a "sea of spins" on the basis of Eq (1.106) with a simple variational calculation as used for the derivation of the electrophilicity index, Perez et al. arrived at the following formula for the maximal energy change[221]

$$\Delta E_{max} = -\frac{{\mu_s}^2}{2\eta_{ss}} \tag{1.107}$$

Perez et al.[221] defined spin-philicity power (w_S^+) and the spin-donicity number (w_S^-) in the direction of increasing spin multiplicity ($\Delta N_S > 0$) and decreasing multiplicity ($\Delta N_S < 0$), respectively:

$$w_S^+ = \frac{(\mu_S^+)^2}{2\eta_{SS}} \tag{1.108}$$

and

$$w_S^- = \frac{(\mu_S^-)^2}{2\eta_{SS}} \tag{1.109}$$

Spin-polarized DFT allows one to get some insight into the chemical properties related to the change in spin number. In recent years, many studies have appeared,[222-225] on the basis of which one can say that in some cases spin-polarization plays an important role.

The time dependence of the electron density is governed by the time-dependent Kohn-Sham equations, which forms the basis of time-dependent density functional theory (TD-DFT), a promising approach for the computation of excitation energies.[226-236] As the elementary DFT is a theory for electronic ground states,[31] a rigorous treatment of reactivity indicators for excited states is very difficult.[196,226,237-242] TD-DFT is originally proposed by Runge and Gross.[243] Deb and Ghosh also has some important cotribution to the Schrödinger Fluid Dynamics of many-electron systems in TD-DFT framework.[244] Later, Casida[245] developed an effective linear-response (LR) formalism for TD-DFT to ably determine the solution of the TD-DFT equations for molecules. It is useful in modeling the energies, structures, and properties of electronically excited states. The applications of TD-DFT encompasses not only the simulation of vertical transition energies, but also the determination of excited state structures and emission wavelengths, the computation of vibrationally resolved optical spectra, the estimation of atomic point charges and dipole moments, as well as the simulation of photochemical reactions.[246] Similar to DFT, TD-DFT is also formally an exact theory, where the selection of an exchange correlation plays a crucial role. Chattaraj and co-workers, within the framework of quantum fluid DFT have done substantial amount of work.[247-252] The dynamics of concepts such as electronegativity, covalent radius, hardness, polarizability, electrophilicity, and its inverse, nucleophilicity, and the principles, such as the electronegativity equalization principle and the maximum

hardness and miminum polarizability principle, have been investigated. The time evolution of both the electronegativity and the covalent radius provided a method to divide the interaction of two colliding particles into three steps, i.e., approach, encounter, and departure. The time dependence of the global hardness appeared to be a manifestation of a dynamical version of the maximum hardness principle.[251] This was also confirmed for excited states. Moreover, the local hardness was found to be the highest in regions of accumulated electron density, implying indeed the applicability of this concept for charge-controlled reactions. In addition, the principle of minimum polarizability was also affirmed within this framework, as well as the maximum entropy principle. This maximization of the entropy happens during the encounter process, indicating that the charge transfer occurring due to the collision is a favorable process. An interesting study involving time dependence of DFT-based reactivity descriptors was conducted by Vuilleumier and Sprik.[253] The response properties calculated were the global hardness and the electronic and nuclear Fukui functions. For the hard cation, the HOMO was found to remain buried in the valence bands of the solvent, whereas for the soft cation, this orbital mixed with the lone pair orbitals of the four coordinating water molecules; this observation could possibly be a method to distinguish between hard and soft species.

Moreover, the whole mathematical formulation of DFRT can also be applied to the "nuclear reactivity".[255-260] Nuclear reactivity indicators can be easily computed and that is why they are widely accepted by many researchers to understand various phenomena such as crystal polymorphs of drug molecules[261-265] the fragmentation pathways of high explosives[266] and so on.

1.4. Organization of the Thesis:

Theoretical investigations on the electrophilic [$\Delta^{+}h(\bar{r})$] and nucleophilic [$\Delta^{-}h(\bar{r})$] variants of hardness potential $h(\bar{r})$ and their applications in intra and intermolecular reactivity studies for relevant chemical and biological systems is the central theme of this study. Prediction of intermolecular reactivity trends using local reactivity descriptors based on grand canonical ensemble (e.g. local softness, philicity) for systems with multiple reactive sites remains dubious till date. This is because one part of these descriptors is Fukui function $f(\bar{r})$, which integrates to unity for any chemical system. Although $h(\bar{r})$, $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$ are also generated from grand canonical ensemble, the local part in these descriptors is local hardness, not Fukui function. So it needs to be investigated (both analytically

as well as computationally) whether intra and intermolecular reactivity trends can be produced using these three descriptors.

In Chapter I, an overview of the research work is outlined along with theoretical background, limitations, and advantages of the DFT-based reactivity descriptors. The recent developments, relevant to the theme of the thesis, is discussed. This chapter also contains the main objectives and the overall organization of the work.

Chapter II deals in developing a formalism of hardness potential to take care of the *N*-dependence problem of local hardness. The corresponding electrophilic [$\Delta^{+}h(k)$] and nucleophilic [$\Delta^{-}h(k)$] variants of the hardness potential, which measure the reactivity toward a nucleophilic (i.e., Nu^{-}) and an electrophilic (i.e., El^{+}) reagent, respectively, is discussed. The relation between these two variants of the hardness potential and Fukui potential is highlighted.

In Chapter III, the relative contribution of the sum of kinetic [$\frac{10}{9}C_F\rho(\bar{r})^{2/3}$] and exchange energy [$\frac{4}{9}C_X\rho(\bar{r})^{1/3}$] terms to that of the electronic part of the molecular electrostatic potential [$V_{el}(\bar{r})$] in the variants of Hardness Potential is investigated to assess the proposed definition of variants of the hardness potential for some substituted benzenes and polycyclic aromatic hydrocarbons (PAHs) (undergoing electrophilic aromatic substitution), carboxylic acids and their derivatives. A detailed study on systems with multiple reactive sites and their intermolecular reactivity trends is also considered.

In Chapter IV, trends of electronic contribution to molecular electrostatic potential [$V_{el}(\bar{r})_{r=0}$], Fukui potential [$v_f^{+}\big|_{r=0}$ and $v_f^{-}\big|_{r=0}$] and hardness potential derivatives [$\Delta^{+}h(k)$ and $\Delta^{-}h(k)$] for isolated atoms as well as atoms in molecules is investigated. The generated numerical values of these three reactivity descriptors in these two electronically different situations is critically analyzed for several commonly used molecules containing carbon as well as hetero atoms. Sum of Fukui potential and sum of hardness potential derivatives in molecules is also touched upon.

Chapter V explores the correlation between orbital relaxation effect and nature of atomic Fukui functions for the chosen s and p block elements. In connection with that, the usefulness of the nodal nature of the highest occupied and lowest unoccupied orbitals is also evaluated.

The concluding section, i. e., Chapter VI recapitulates the content of the thesis and the horizon of future study is indicated distinctly.

References and Notes

1. A. Hassner, *J. Org. Chem*., **1968**, *33*, 2684.
2. J. March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 4th edn, Wiley and Sons, NY, **1992**.
3. K. Fukui, T. Yonezawa and H. Shingu, *J. Chem. Phys*., **1952**, *20*, 722.
4. K. Fukui, T. Yonezawa, C. Nagata and H. Shingu, *J. Chem. Phys*., **1954**, *22*,1433.
5. K. Fukui, Theory of orientation and stereoselection, Springer, Berlin, Heidelberg, New York, 1973.
6. K. Fukui, *Science*, **1987**, *218*, 747.
7. A. D. Becke and K. E. Edgecombe, *J. Chem. Phys*., **1990**, *92*, 5397.
8. A. Savin, O. Jepsen, J. Flad, O. Andersen, H. Preuss and H. von Schnering, Angew. *Chem. Int. Ed*., **1992**, *31*, 187.
9. R. Bonaccorsi, E. Scrocco and J. Tomasi, *J. Chem. Phys*., **1970**, *52*, 5270.
10. P. Politzer, *J. Chem. Phys*., **1980**, *72*, 3027.
11. P. Politzer, *J. Chem. Phys*., **1980**, *73*, 3264.
12. In Chemical Applications of Atomic and Molecular Electrostatic Potentials, ed. P. Politzer and D. G. Truhlar, Plenum: New York, 1981.
13. B. Pullman*, Int. J. Quantum Chem., Quantum Biol. Symp*., **1990**, *17*, 81.
14. P. Sjoberg and P. Politzer, *J. Phys. Chem*., **1990**, *94*, 3959.
15. J. Tomasi, R. Bonaccorsi and R. Cammi, Theoretical Models of Chemical Bonding, Maksic, R., Ed. Springer: Berlin, **1990**, 230.
16. G. Naray-Szabo and G. G. Ferenczy, *Chem. Rev*., **1995**, *95*, 829.
17. P. Politzer, J. V. Burda, M. Concha, P. Lane and J. S. Murray, *J. Phys. Chem. A.*, **2006**, *110*, 756.
18. R. G. Pearson, *J. Am. Chem. Soc*., **1963**, *85*, 3533.
19. R. G. Pearson, Hard and Soft Acids and Bases, Dowden, Hutchinson & Ross, Stroudsberg, PA, **1973**.
20. R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc*., **1983**, *105*, 7512.
21. S. Krishnamurty, R. K. Roy, R. Vetrivel, S. Iwata and S. Pal, *J. Phys. Chem. A.*, **1997**, *101*, 7253.
22. R. C. Deka, R. Vetrivel and S. Pal, *J. Phys. Chem. A.*, **1999**, *103*, 5978.

23. R. T. Sanderson, *Science*, **1951**, *114*, 670.
24. G. Klopman, *J. Chem. Phys*., **1965**, *43*, S124.
25. N. C. Baird, J. M. Sichel and M. A. Whitehead, *Theor. Chim. Acta*., **1968**, *11*, 38.
26. R. T. Sanderson, Chemical Bonds and Bond Energy, 2nd edn., Academic Press, New York, 1976.
27. N. K. Ray, L. Samuels and R. G. Parr, *J. Chem. Phys*., **1979**, *70*, 3680.
28. W. J. Mortier, S. K. Ghosh and S. Shankar, *J. Am. Chem. Soc*., **1986**, *108*, 4315.
29. P. Coppens, *Angew Chem Int Ed.,* **2005**, *44*:6810.
30. T. S. Koritsanszky and P. Coppens, *Chem Rev.,* **2001,** *101*, 1583.
31. P. Hohenberg and W. Kohn, *Phys. Rev. B*, **1964,** *136*, 864.
32. W. Kohn and L. J. Sham, *Phys. Rev. A*, **1965,** *140*, 1133.
33. A. S. Bamzai and B. M. Deb, *Rev. Mod. Phys*., **1981**, *53*, 95.
34. S. Ghosh and B. Deb, *Phys. Rep*, **1982**, *92*, 1.
35. R. Dreizler and E. Gross, Density functional theory: an approach to the quantum many-body problem, Springer-Verlag Berlin, **1990**.
36. T. Ziegler, *Chem. Rev*., **1991**, *91*, 651.
37. E. J. Baerends and O. V. Gritsenko, *J. Phys. Chem. A,* **1997**, *101*, 5383.
38. W. Koch and M. Holthausen, A chemist's guide to density functional theory, Wiley-Vch Weinheim, **2000**.
39. P. W. Ayers and W. Yang, in Computational Medicinal Chemistry for Drug Discovery, ed. P. Bultinck, H. De Winter, W. Langenaeker and J. P. Tollenaere, Marcel Dekker Inc: Basel, **2004**, pp. 89.
40. R. G. Parr, *J. Chem. Sci*., **2005**, *117*, 613.
41. K. Capelle, *Brazilian Journal of Physics*, **2006**, *36*, 1318.
42. A. J. Cohen, P. Mori-Sanchez and W. Yang, *Science*, **2008**, *321*, 792.
43. J. P. Perdew, A. Ruzsinszky, L. A. Constantin, J. Sun and G. b. I. Csonka, *J. Chem. Theory Comput.*, **2009**, *5*, 902.
44. R. G. Parr, R. A. Donnelly, M. Levy and W. E. Palke, *J. Chem. Phys*., **1978**, *68*, 3801.
45. R. G. Parr, *Annu. Rev. Phys. Chem*., **1983**, *34*, 631.
46. R. F. Nalewajski, *J. Phys. Chem*., **1985**, *89*, 2831.
47. R. G. Parr and W. Yang, Density–Functional Theory of Atoms and Molecules, Oxford

University Press, New York, **1989**.

48. R. G. Parr and W. Yang, *Annu. Rev. Phys. Chem*., **1995**, *46*, 701.
49. H. Chermette, *J. Comput. Chem*., **1999**, *20*, 129.
50. P. Geerlings and F. De Proft, *Int. J. Mol. Sci*., **2002**, *3*, 276.
51. P. Geerlings, F. De Proft and W. Langenaeker, *Chem. Rev*., **2003**, *103*, 1793.
52. M. H. Cohen and A. Wasserman, *J. Phys. Chem. A*., **2007**, *111*, 2229.
53. J. L. Gazquez, *J. Mex. Chem. Soc*., **2008**, *52*, 3.
54. In Chemical reactivity theory: a density functional view, ed. P. K. Chattaraj, CRC, **2009**.
55. R. G. Pearson, *J. Chem. Educ*., **1987**, *64*, 561.
56. R. G. Pearson, *Acc. Chem. Res*., **1990**, *23*, 1.
57. R. G. Parr and P. K. Chattaraj, *J. Am. Chem. Soc*., **1991**, *113*, 1854.
58. R. G. Pearson and W. E. Palke, *J. Phys. Chem*., **1992**, *96*, 3283.
59. S. Pal, N. Vaval and R. K. Roy, *J. Phys. Chem*., **1993**, *97*, 4404.
60. R. G. Pearson, *Acc. Chem. Res*., **1993**, *26*, 250.
61. P. W. Ayers and R. G. Parr, *J. Am. Chem. Soc*., **2000**, *122*, 2010.
62. A. K. Chandra and T. Uchimaru, *J. Phys. Chem. A*, **2001**, *105*, 3578.
63. M. Torrent-Sucarrat, J. M. Luis, M. Duran and M. Sola, *J. Am. Chem. Soc*., **2001**, *123*, 7951.
64. K. R. S. Chandrakumar and S. Pal, *Int. J. Mol. Sci.,* **2002**, *3*, 324.
65. M. Torrent-Sucarrat, J. M. Luis, M. Duran and M. Sola, *J. Chem. Phys*., **2002**, *117*, 10561.
66. K. L. Sebastian, *Chem. Phys. Lett*., **1994**, *231*, 40.
67. P. K. Chattaraj, G. H. Liu and R. G. Parr, *Chem. Phys. Lett*., **1995**, *237*, 171.
68. S. Goedecker, *Rev. Mod. Phys*., **1999**, *71*, 1085.
69. W. Kohn, *Phys. Rev. Lett*., **1996**, 76, 3168.
70. W. Yang, *Phys. Rev. Lett*., **1991**, *66*, 1438.
71. W. Yang and T.-S. Lee, *J. Chem. Phys*., **1995**, *103*, 5674.
72. T. E. Exner and P. G. Mezey, *J. Phys. Chem. A*., **2004**, *108*, 4301.
73. D. G. Fedorov and K. Kitaura, *J. Chem. Phys*., **2004**, *120*, 6832.
74. F. L. Gu, Y. Aoki, J. Korchowiec, A. Imamura and B. Kirtman, *J. Chem. Phys*., **2004**, *121*, 10385.
75. W. Li and S. Li, *J. Chem. Phys*., **2004**, *121*, 6649.
76. X. Chen, Y. Zhang and J. Z. H. Zhang, *J. Chem. Phys*., **2005**, *122*, 184105.

77. V. Deev and M. A. Collins, *J. Chem. Phys*., **2005**, *122,* 154102.

78. D. G. Fedorov and K. Kitaura, *J. Chem. Phys*., **2005**, *123*, 134103.

79. X. He and J. Z. H. Zhang, *J. Chem. Phys*., **2005**, *122*, 031103.

80. S. Li, W. Li and T. Fang, *J. Am. Chem. Soc*., **2005,** *127*, 7215.

81. W. Li and S. Li, *J. Chem. Phys*., **2005**, *122*, 194109.

82. Y. Mei, D. W. Zhang and J. Z. H. Zhang, *J. Phys. Chem. A.*, **2005**, *109*, 2.

83. R. P. A. Bettens and A. M. Lee, *J. Phys. Chem. A.*, **2006**, *110*, 8777.

84. X. H. Chen and J. Z. H. Zhang, *J. Chem. Phys*., **2006**, *125*, 044903.

85. M. A. Collins and V. A. Deev, *J. Chem. Phys*., **2006,** *125*, 104104.

86. V. Ganesh, R. K. Dongare, P. Balanarayan and S. R. Gadre, *J. Chem. Phys*., **2006**, *125*, 104109.

87. N. Jiang, J. Ma and Y. Jiang, *J. Chem. Phys*., **2006**, *124*, 114112.

88. W. Li, T. Fang and S. Li, *J. Chem. Phys*., **2006**, *124*, 154102.

89. T. Akama, M. Kobayashi and H. Nakai, *J. Comput. Chem*., **2007**, *28*, 2003.

90. D. G. Fedorov, T. Ishida, M. Uebayasi and K. Kitaura, *J. Phys. Chem. A*, **2007**, *111*, 2722.

91. D. G. Fedorov and K. Kitaura, *J. Phys. Chem. A*, **2007**, *111*, 6904.

92. M. Kobayashi, Y. Imamura and H. Nakai, *J. Chem. Phys*., **2007**, *127*, 074103.

93. A. M. Lee and R. P. A. Bettens, *J. Phys. Chem. A.*, **2007**, *111*, 5111.

94. W. Li, S. Li and Y. Jiang, *J. Phys. Chem. A.*, **2007**, *111*, 2193.

95. D. G. Fedorov, J. H. Jensen, R. C. Deka and K. Kitaura, *J. Phys. Chem. A.*, **2008**, *112,* 11808.

96. S. Li and W. Li, *Annu. Rep. Prog. Chem., Sec C (Physical Chemistry).,* **2008**, *104*, 256.

97. S. Hirata, *Phys. Chem. Chem. Phys*., **2009**, *11*, 8397.

98. S. Saha and R. K. Roy, *J. Phys. Chem. B.,* **2007,** *111,* 9664.

99. H. R. Drew, R. M. Wing, T. Takano, C. Broka, S. Tanaka, K. Itakura and R. E. Dickerson, *Proc. Natl. Acad. Sci. U.S.A.,* **1981**, *78*, 2179.

100. L. H Thomas, *Proc. Cambridge Philos. Soc*., **1927**, *23*, 542.

101. E. Z. Fermi, Z. *Phys*., **1928**, *48*, 73.

102. P. A. M Dirac, *Proc Cambridge Philos*. Soc**.,** **1930**, *26*, 376.

103. S. Saha and R. K. Roy, *Phys. Chem. Chem. Phys*., **2008**, *10*, 5591.

104. S. Saha, R. Bhattacharjee and R. K. Roy, *J. Comp. Chem.,* **2013,** *34***,** 662.

105. P. Hohenberg, W. Kohn and L. Sham, *Adv. Quantum Chem.,* **1990**, *21*, 7.

106. E. J. Baerends and P. Ros, *Int. J. Quantum Chem., Quantum Chem. Symp*., **1978**, *12*, 169.

107. B. I. Dunlap, J. W. D. Connolly and J. R. Sabin, *J. Chem. Phys*., **1979**, *71*, 3396.

108. P. M. Boerrigter, G. Velde and E. J. Baerends, *Int. J. Quantum Chem.,* **1988**, *33*, 87.

109. J. Andzelm and E. Wimmer, *J. Chem. Phys*., **1992**, *96*, 1280.

110. P. Senet, *J Chem Phys.,* **1996**, *105*:6471.

111. P. W. Ayers, J. S. M. Anderson and L. J.Bartolotti, *Int J Quantum Chem*., **2005**, *101*, 520.

112. R. P. Iczkowski and J. L. Margrave, *J. Am. Chem. Soc*., **1961**, *83*, 3547.

113. R. S. Mulliken, *J. Chem. Phys*., **1934**, *2*, 782.

114. E. P. Gyftopoulos and G. N. Hatsopoulos, *Proc. Natl. Acad. Sci. U.S.A*., **1968**, *60*, 786.

115. T. A. Koopmans, *Physica.,* **1933,** *1*, 104.

116. R. G. Pearson, *Proc. Natl. Acad. Sci. U. S. A*., **1986**, *83*, 8440.

117. R. G. Pearson, *J. Chem. Educ*., **1999**, *76*, 267.

118. B. M. Deb, *J. Am. Chem. Soc*., **1974**, *96*, 2030.

119. B. M. Deb, P. N. Sen and S. K. Bose, *J. Am. Chem. Soc*., **1974**, *96*, 2044.

120. B. M. Deb, *J. Chem. Educ*., **1975**, *52*, 314.

121. J. Simons and K. D. Jordan, *Chem. Rev*., **1987,** *87*, 535.

122. A. Z. Szarka, L. A. Curtiss and J. R. Miller, *J. Chem. Phys*., **1999**, *246*, 147.

123. A. Dreuw and L. S. Cederbaum, *Chem. Rev*., **2002**, *102*, 181.

124. R. K. Roy and S. Pal, *J. Phys. Chem*., **1995**, *99*, 17822.

125. R. T. Sanderson, *Science*, **1955**, *121*, 207.

126. R. T. Sanderson, Polar Covalence, Academic Press, New York, **1983**.

127. R. G. Pearson, Coord. *Chem. Rev*., **1990**, *100*, 403.

128. R. G. Pearson, Chemical Hardness, Wiley, New York, **1997**.

129. S. Pal and K. R. S. Chandrakumar, *J. Am. Chem. Soc*., **2000**, *122*, 4145.

130. K. R. S. Chandrakumar and S. Pal, *J. Phys. Chem. A*., **2002**, *106*, 5737.

131. W. Yang and R. G. Parr, *Proc. Natl. Acad. Sci. U.S.A*., **1985**, *82*, 6723.

132. The Factor of 2 is arbitrary, to create a symmetry between Mulliken's electronegativity and chemical hardness.

133. F. De Proft and P. Geerlings, *Chem. Rev*., **2001**, *101*, 1451.

134. K. L. Sebastian, *Chem. Phys. Lett*., **1995**, *236*, 621.

135. P. K. Chattaraj, A. Cedillo and R. G. Parr, *Chem. Phys*., **1996**, *204*, 429.

136. P. Politzer, *J. Chem. Phys*., **1987**, *86*, 1072.

137. K. D. Sen, M. C. Bohm and P. C. Schmidt, in Electronegativity (Structure and Bonding), ed. K. D. Sen and C. K. Jorgenson, Springer-Verlag, Berlin, Heidelberg, **1987**, vol. 66, p. 99.

138. T. K. Ghanty and S. K. Ghosh, *J. Phys. Chem*., **1993**, *97*, 4951.

139. S. Hati and D. Datta, *J. Phys. Chem*., **1994**, *98*, 10451.

140. R. K. Roy, A. K. Chandra and S. Pal, *J. Phys. Chem*., **1994,** *98*, 10447.

141. Y. Simon-Manso and P. Fuentealba, *J. Phys. Chem. A*, **1998**, *102,* 2029.

142. P. Bagaria, S. Saha, S. Murru, V. Kavala, B. Patel and R. K. Roy, *Phys. Chem. Chem. Phys.,* **2009**, *11*, 8306.

143. R. G. Parr, L. von Szentpaly and S. Liu, *J. Am. Chem. Soc*., **1999**, *121*, 1922.

144. A. T. Maynard, M. Huang, W. G. Rice and D. G. Covell, *Proc. Natl. Acad. Sci.U.S.A*., **1998**, *95*, 11578.

145. P. P*é*rez*,* A. Torro-Labb*é*, A. Aizman *and* R. Contreras, *J. Org. Chem.* **2002**, *67*, 4747.

146. H. Mayr, H.; T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov and H. Schimmel, *J. Am. Chem. Soc*. **2001**, *123*, 9500.

147. P. Bagaria and R. K. Roy, *J. Phys. Chem. A*., **2008**, *112*, 97.

148. M. Elango, R. Parthasarathi, G. K. Narayanan, A. M. Sabeelullah, U. Sarkar, N.S. Venkatasubramaniyan, V. Subramanian and P. K. Chattaraj, *J. Chem. Sci*., **2005**, *117*, 61.

149. K. D. Sen and C. K. Jorgensen,. *Electronegativity, Structure and Bonding*; Springer-Verlag: Berlin, **1987**.

150. P. W. Ayers and R. G. Parr, *J. Am. Chem. Soc*., **2001**, *123*, 2007.

151. P. Jaramillo, P. Fuentealba and P. Perez, *Chem. Phys. Lett*., **2006**, *427*, 421.

152. P. Jaramillo, P. Perez, R. Contreras, W. Tiznado and P. Fuentealba, *J. Phys.Chem. A*., **2006**, *110,* 8181.

153. A. Cedillo, R. Contreras, M. Galvan, A. Aizman, J. Andres and V. S. Safont, *J. Phys. Chem. A*., **2007,** *111*, 2442.

154. F. D. Vleeschouwer, V. V. Speybroeck, M. Waroquier, P. Geerlings and F. D.Proft, *Org. Lett*., **2007**, *9,* 2721.

155. P. W. Ayers, J. S. M. Anderson, J. I. Rodriguez and Z. Jawed, *Phys. Chem. Chem.Phys*., **2005**, *7*, 1918

156. P. R. Campodonico, C. Perez, M. Aliaga, M. Gazitua and R. Contreras, *Chem.Phys. Lett.,* **2007**, *447*, 375.

157. S. Liu, T. Li and P. W. Ayers, *J. Chem. Phys*., **2009**, *131*, 114106.

158. P. W. Ayers, S. Liu and T. Li, Chem. Phys. Lett., **2009**, *480*, 318.

159. The quantity ρ (r) is of course of much interest, being directly accessible experimentally and readily visualizable - just the classical density of the electronic system. The properties of $\rho(\bar{r})$ should be mentioned: see Refs. 171-173,31,174-176.

160. R. F. W. Bader, *Acc. Chem. Res*., **1975**, *8*, 34.

161. V. H. Smith Jr and I. Absar, *Israel J. Chem*., **1977**, *16*, 87.

162. R. F. W. Bader, T. T. Nguyen-Dang, *Adv. Quantum Chem*. **1981**, *14*, 63.

163. R. F. W. Bader, Y. Tal, S. Anderson and T. Nguyen-Dang, *Israel J. Chem.*, **1980**, *19*, 8.

164. R. F. W. Bader and C. Chang, *J. Phys. Chem.,* **1989**, *93*, 2946.

165. R. F. W. Bader, Atoms in Molecules: A Quantum Theory., **1990**.

166. R. G. Parr and W. Yang, *J. Am. Chem. Soc*., **1984**, *106,* 4049.

167. W. Langenaeker, K. Demel and P. Geerlings, *J Mol Struct. (THEOCHEM),* **1991**, *80*, 329.

168. M. H. Cohen and M. V. Ganduglia-Pirovano, *J Chem Phys.*, **1994,** *101*:8988.

169. L. J. Bartolotti and P. W. Ayers, *J Phys Chem A.,* **2005**, *109*:1146.

170. S. Nagakura, and J. Tanaka, *J. Chem. Soc. Japan.,* **1954**, *75*, 993.

171. K. Fukui, In *Molecular Orbitals in Chemistry, Physics and Biology*; Lowdin, P. O., Pullman, B., Eds.; Academic Press: New York, **1964**.

172. W. Yang and W. J. Mortier, *J. Am. Chem. Soc*., **1986**, *108*, 5708.

173. W. T. Yang, R. G. Parr and R. Pucci, *J Chem Phys.,* **1984**, *81*, 2862.

174. R. K. Roy, S. Pal, S. and K. Hirao, *J. Chem. Phys.,* **1999**, *110*, 8236.

175. R. K. Roy, K. Hirao and S. Pal, *J. Chem. Phys.,* **2000**, *113*, 1372.

176. P. Fuentealba, P. Perez and R. Contreras, *J. Chem. Phys.,* **2000**, *113*, 2544.

177. R. K. Roy, K. Hirao, S. Krishnamurty, and S. Pal, *J. Chem. Phys.,* **2001**, *115*, 2901.

178. F. L. Hirshfeld, *Theor. Chim. Acta.,* **1977**, *44*, 129.

179. P. W. Ayers, R. C. Morrison and R. K. Roy, *J. Chem. Phys.,* **2002**, *116*, 8731.

180. J. Olah, C. Van Alsenoy and A. B. Sannigrahi, *J. Phys. Chem. A.,* **2002**, *106*, 3885.

181. R. S. Mulliken, *J. Chem. Phys.,* **1955**, *23*, 1833.

182. J. P. Foster and F. Weinhold, *J. Am. Chem. Soc.,* **1980**, *102*, 7211.

183. A. B. Rives and F. Weinhold, *Int. J. Quantum Chem. Symp.,* **1980**, *14*, 201.

184. A. E. Reed and F. Weinhold, *J. Chem. Phys.,* **1983**, *78*, 4066.

185. A. E. Reed, R. B. Weinstock and F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 735.

186. P. Bultinck, C. Van Alsenoy, P. W. Ayers and R. Carbo-Dorca, *J. Chem. Phys*., **2007**, *126*, 144111.

187. S. Saha, R. Roy and P. Ayers, *Int. J. Quantum Chem***., 2009**, *109*, 1790.

188. P. W. Ayers, *Phys. Chem. Chem. Phys*., **2006**, *8*, 3387.

189. J. Melin, P. W. Ayers and J. V. Ortiz, *J. Phys. Chem. A,* **2007**, *111*, 10017.

190. K. S. Min, A. G. DiPasquale, J. A. Golen, A. L. Rheingold and J. S. Miller, *J. Am.Chem. Soc.,* **2007**, *129*, 2360.

191. J. Cioslowski, M. Martinov and S. T. Mixon, *J. Phys. Chem*., **1993**, *97*, 10948.

192. W. Yang, Y. Zhang and P. W. Ayers, *Phys. Rev. Lett*., **2000**, *84*, 84.

193. P. W. Ayers, F. De Proft, A. Borgoo and P. Geerlings, *J. Chem. Phys*., **2007**, *126*, 224108.

194. P. Bultinck, S. Fias, C. Van Alsenoy, P. W. Ayers and R. Carbo-Dorca, *J. Chem.Phys*., **2007,** *127,* 34102.

195. P. Bultinck and R. Carbo-Dorca, *J. Math. Chem*., **2003**, *34*, 67.

196. P. W. Ayers, C. Morell, F. De Proft and P. Geerlings, *Chem. Eur. J.,* **2007**, 1*3*, 8240.

197. A. K. Chandra and M. T. Nguyen, *Int. J. Mol. Sci.,* **2002,** *3*, 310.

198. M. K. Harbola, P. K. Chattaraj and R. G. Parr, *Israel J. Chem*., **1991**, *31*, 395.

199. B. G. Baekelandt, A. Cedillo and R. G. Parr, *J. Chem. Phys*., **1995**, *103*, 8548.

200. R. K. Roy, K. Hirao, S. Krishnamurty, P. Geerlings and S. Pal, *J. Phys.Chem. A,* **1998**, *102*, 3746.

201. R. K. Roy, F. de Proft and P. Geerlings, *J. Phys.Chem. A,* **1998**, *102*, 7035.

202. O. Tishchenko, N. Pham-Tran, E. S. Kryachko and M. T. Nguyen, *J. Phys. Chem. A.,* **2001**, *105*, 8709.

203. R. K. Roy, V. Usha, J. Paulovič and K. Hirao, *J. Phys. Chem. A*., **2005**, *109*, 4601.

204. M. Berkowitz and R. G. Parr, *J. Chem. Phys*., **1988**, *88*, 2554.

205. R. F. Nalewajski, *Int. J. Mol. Sci*., **2002**, *3*, 237.

206. M. Berkowitz, S. K. Ghosh and R. G. Parr*, J. Am. Chem. Soc*., **1985**, *107*, 6811.

207. S. K. Ghosh and M. Berkowitz, J. Chem. Phys., **1985**, *83*, 2976.

208. P. K. Chattaraj, D. R. Roy, P. Geerlings and M. Torrent-Sucarrat, *Theor. Chem.Acc*., **2007**,

118, 923.

209. M. K. Harbola, P. K. Chattaraj and R. G. Parr, *Isr. J. Chem.*,**1991**, *31*, 395.
210. W. Langenaeker, F. De Proft and P. Geerlings, *J. Phys. Chem.,* **1995**, *99*, 6424.
211. R. F. Nalewajski,. J. Phys. Chem., **1985**, *89*, 2831.
212. J. L. Gazquez, In *Chemical Hardness*; K. D. Sen, K. D., Ed.; Springer-Verlag: Berlin, **1993**; Vol. 80.
213. R. G. Parr and J. L. Gazquez, *J. Phys. Chem*. **1993**, *97*, 3939.
214. P. K. Chattaraj, B. Maiti and U. Sarkar, *J. Phys. Chem. A.*, **2003**, *107*, 4973.
215. P. K. Chattaraj, U. Sarkar and D. R. Roy, *Chem. Rev*., **2006**, *106,* 2065.
216. P. K. Chattaraj and S. Giri, *Annu. Rep. Prog. Chem., Sec C (Physical Chemistry)*, **2009**, *105*, 13.
217. R. K. Roy, *J. Phys. Chem. A.*, **2004**, *108*, 4934
218. D. R. Roy, R. Parthasarathi, J. Padmanabhan, U. Sarkar, V. Subramanian and P.K. Chattaraj, *J. Phys. Chem. A.*, **2006,** *110*, 1084.
219. R. F. Nalewajski, *J. Chem. Phys*., **1984**, *81*, 2088.
220. M. Galvan, M.; A. Vela, and J. L. Gazquez, *J. Phys. Chem.,* **1988**, *92*, 6470.
221. P. Perez, P.; J. Andres, V. S Safont, O. Tapia and R. Contreras, *J. Phys. Chem. A.,* **2002**, *106*, 5353.
222. A. L. Buchachenko and V. L. Berdinsky, *Chem. Rev.,* **2002**, *102*, 603.
223. J. Olah, F. De Proft, T. Veszpremi and P. Geerlings, *J. Phys. Chem. A.,* **2004**, *108*, 490.
224. F. De Proft, C. Van Alsenoy and P. Geerlings, *J. Phys. Chem. A.,* **2005**, *109*, 6335.
225. R. Vargas, M. Galvan and A. Vela, *J. Phys. Chem. A.,* **1998**, *102*, 3134.
226. P. W. Ayers Variational principles for describing chemical reactions. PhD dissertation, Department of Chemistry, University of North Carolina at Chapel Hill, **2001.**
227. R. Singh and B. M. Deb, *Phys Lett*., **1999,** *311*, 48.
228. A. K. Theophilou and N. I. Gidopoulos, *Int J. Quantum Chem.*, **1995***, 56*, 333.
229. A. K. Theophilou, .*J Phys. C.*, **1979,** *12*, 5419.
230. Ayers PW, Levy M (2009). Phys Rev A., 80:012508
231. Nagy A, Levy M (2001).Phys Rev A 63:052502
232. M. Levy and A. Nagy, *Phys Rev Lett.,* **1999,** *83*, 4361.
233. M. Levy and A. Nagy *Phys Rev A*., **1999**, *59*, 1687.

234. M. Levy, In:Proceedings of the 1st international workshop electron correlation and material properties. Rhodes, Greece, **1999,** pp 299.

235. A. Gorling, *Phys Rev A.,* **1996,** *54*, 3912.

236. A. Nagy, *J Chem Sci*, **2005,** *117*, 437.

237. P. Fuentealba, Y. Simon-Manso and P. K. Chattaraj, *J. Phys. Chem. A.,* **2000,** *104*, 3185.

238. P. K. Chattaraj and A. Poddar, *J. Phy.s Chem. A.,* **1999** *103*, 8691.

239. P. K. Chattaraj and A. Poddar, *J. Phys. Chem. A*., **1999**, *103*, 1274.

240. P. K. Chattaraj, A. Poddar, *J. Phys. Chem. A.,* **1998**, *102*, 9944.

241. P. W. Ayers and R. G. Parr, *J. Phys. Chem. A*., **2000**, *104*, 2211.

242. C. Morell, V. Labet, A. Grand, P. W. Ayers, F. De Proft, P. Geerlings and H. Chermette, *J. Chem. Theory. Comput.,* **2009**, *5*:2274.

243. E. Runge, E. K. U. Gross, *Phys. Rev. Lett*., **1984**, *52*, 997.

244. B. M. Deb and S. K. Ghosh, *J. Chem. Phys.,* **1982,** *77,* 342.

245. M. E. Casida, Recent Advances in Density Functional Methods, Vol. 1;World Scientific: Singapore, **1995**, pp. 155.

246. A. D. Laurent and D. Jacquemin, *Int. J. Quantum Chem*., **2013**, *113*, 2019.

247. P. K. Chattaraj, *Int. J. Quantum Chem.,* **1992**, *41*, 845.

248. P. K. Chattaraj and S. Nath, *Int. J. Quantum Chem.,* **1994**, *49*, 705.

249. P. K. Chattaraj and S. Nath, *Chem. Phys. Lett.,* **1994**, *217*, 342.

250. P. K. Chattaraj and S. Sengupta, *J. Phys. Chem.,* **1996**, *100*, 16126.

251. P. K. Chattaraj and S. Sengupta, *J. Phys. Chem. A,* **1997**, *101*, 7893.

252. P. K. Chattaraj and B. Maiti, *J. Phys. Chem. A.,* **2001**, *105*, 169.

253. R. Vuilleumier and M. Sprik, *J. Chem. Phys.,* **2001**, *115*, 3454.

254. R. Car and M. Parinello, *Phys. Rev. Lett.* **1985**, *55*, 2471.

255. C. Cardenas C, Chamorro, M. Galvan and P. Fuentealba, *Int J. Quantum Chem.,* **2007**, *107*, 807.

256. C. Cardenas, A. M. Lamsabhi and P. Fuentealba, *Chem. Phys*., **2006**, *322*, 303.

257. R. F. Nalewajski, *Comput Chem.,* **2000**, *24*, 243.

258. F. De Proft, S. B. Liu and P. Geerlings, .*J. Chem. Phys*., **1998** *108*, 7549.

259. R. F. Nalewajski, J. Korchowiec and A. Michalak, Reactivity criteria in charge sensitivity analysis. In: R. F. Nalewajski (ed) Density functional theory IV: theory of chemical

reactivity. Springer, Berlin, **1996**, pp 25.

260. R. F. Balawender, F. De Proft and P. Geerlings, *J. Chem. Phys.* **2001,** *114*:4441.

261. T. L. Li, P. W. Ayers, S. B. Liu, M .J. Swadley and C. Aubrey-Medendorp, *Chem. Eur. J.* **2009** *15*:361.

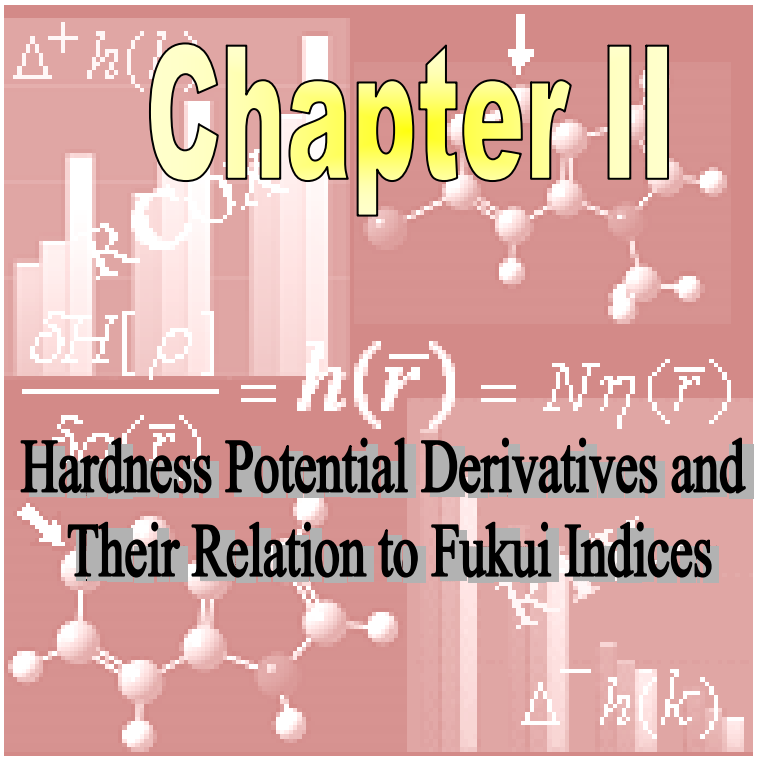
262. T. L. Li, *J. Pharm. Sci.,* **2007**, *96*, 755.

263. T. L. Li, *Cryst. Growth. Des.*, **2006**, *6*, 2000.

264. T. L. Li and S. X. Feng, *Pharm. Res.,* **2005** *22*, 1964.

265. S. X. Feng and T. L. Li, *J. Phys. Chem. A.*, **2005**, *109*, 7258.

266. M. J. Swadley and T. L. Li, *J. Chem. Theory. Comput.*, **2007**, *3*, 505.


Chapter II
$\frac{\delta H[\rho]}{\delta \rho(\vec{r})} = h(\vec{r}) = N\eta(\vec{r})$
Hardness Potential Derivatives and Their Relation to Fukui Indices

2.1. Introduction:

Conceptual Density Functional Theory (or Chemical Reactivity Theory)[1-6] tries to define and elucidate important universal concepts of molecular structure and molecular reactivity. The basic ingredient is the electron density, $\rho(\bar{r})$. Furthermore, the total electronic energy of a system, having N electrons, is given by the formula

$$E[\rho] = F[\rho] + \int v(\bar{r})\rho(\bar{r})d\bar{r} \tag{2.1}$$

where the functional $F[\rho]$, the so-called Hohenberg-Kohn functional,[1] is the sum of the kinetic energy functional $T[\rho]$ and the electron-electron interaction energy functional $V_{ee}[\rho]$; $v(\bar{r})$ is the external potential (it is the potential acting on an electron at position $\bar{r}$ due to the nuclear attraction along with other external forces which may be present in the system). A variational principle is formulated stating that ground state density is the density which minimizes the energy of the system for a fixed number of electrons

$$\delta(E[\rho] - \mu\int \rho(\bar{r})d\bar{r}) = 0 \tag{2.2}$$

where μ is a Lagrange multiplier arising from normalization constraint $\int \rho(\bar{r})d\bar{r} = N$. Otherwise

$$\mu = v(\bar{r}) + \frac{\delta F[\rho]}{\delta\rho(\bar{r})} = constant \tag{2.3}$$

The Lagrange multiplier μ of Eq. (2.2) is the negative of electronegativity[7] and known as chemical potential. Its derivative with respect to N at constant $v(\bar{r})$ is the chemical hardness, η.[8] The inverse of the global hardness is called the global softness, S[9]. Three local quantities are of great interest: the Fukui function $f(\bar{r})$,[10] local softness $s(\bar{r})$[9] and the local hardness $\eta(\bar{r})$[11-13]. These descriptors are, respectively, formulated as,

$$f(\bar{r}) = \left(\frac{\delta\mu}{\delta v(\bar{r})}\right)_N = \left(\frac{\partial\rho(\bar{r})}{\partial N}\right)_{v(\bar{r})} \tag{2.4}$$

$$s(\bar{r}) = \left(\frac{\partial\rho(\bar{r})}{\partial\mu}\right)_{v(\bar{r})} \tag{2.5}$$

and

$$\eta(\bar{r}) = \frac{1}{N}\int \frac{\delta^2 F[\rho]}{\delta\rho(\bar{r}')\delta\rho(\bar{r})}\lambda[\rho(\bar{r}')]d\bar{r}' \tag{2.6}$$

here $\lambda[\rho(\bar{r}')]$ is a composite function,[5.a,14] which integrates to N, i.e., $\int \lambda[\rho(\bar{r}')]d\bar{r}' = N$. Two important choices of the composite function $\lambda[\rho(\bar{r}')]$ are $\rho(\bar{r}')$ [11] and $Nf(\bar{r}')$ [15]. The $f(\bar{r})$, $s(\bar{r})$ and $\eta(\bar{r})$ are related among themselves and with η and S by the following equations

$$s(\bar{r}) = f(\bar{r})S \tag{2.7}$$

$$\eta = \int \eta(\bar{r}) f(\bar{r}) d\bar{r} \tag{2.8}$$

$$\int \eta(\bar{r}) s(\bar{r}) d\bar{r} = 1 \tag{2.9}$$

$$\int s(\bar{r}) d\bar{r} = S \tag{2.10}$$

It has been recognized that an important quantity is the hardness kernel, $\eta(\bar{r},\bar{r}')$.[16]

$$\eta(\bar{r},\bar{r}') = \frac{\delta^2 F[\rho]}{\delta\rho(\bar{r}')\delta\rho(\bar{r})} \tag{2.11}$$

By introducing the symbol of $\eta(\bar{r},\bar{r}')$ in Eq. (2.6), one can write

$$\eta(\bar{r}) = \frac{1}{N}\int \eta(\bar{r},\bar{r}')\lambda[\rho(\bar{r}')]d\bar{r}' \tag{2.12}$$

The inverse of $\eta(\bar{r},\bar{r}')$ is the softness kernel $s(\bar{r},\bar{r}')$.[16]

Eq. (2.6) (or Eq. (2.12)) does not always provide a practical route to explore the site selectivity (i.e., regioselectivity) of the system. Saha and Roy[17] critically illustrated the limitation of $\eta(\bar{r})$ (evaluated from the above mentioned two composite functions i.e., $\lambda[\rho(\bar{r}')] = \rho(\bar{r}')$ and $\lambda[\rho(\bar{r}')] = Nf(\bar{r}')$) when used for comparison of intermolecular reactivity trends between systems of different sizes but having common reactive centers. After a careful analysis they revealed that as the number of electrons increases with the size of the system, the $\frac{1}{N}$ factor alters the expected trends of $\tilde{\eta}_D^{TFD}(\bar{r})$ or $\tilde{\eta}_D^{TFD'}(\bar{r})$ (i.e., when the composite function, $\lambda[\rho(\bar{r}')] = \rho(\bar{r}')$) values. It was also shown that when the composite function, $\lambda[\rho(\bar{r}')] = Nf(\bar{r}')$, although $\frac{1}{N}$ problem solved apparently, the N-dependence problem appears implicitly through the normalization condition of the Fukui function. So, the broader applicability of $\eta(\bar{r})$ as a reliable intermolecular reactivity descriptor necessitates the removal of its N-dependence. Therefore, it is suggested[17] that the best way to incorporate the electronic

(or any other) effects of the rest of the system, without overemphasizing $\frac{1}{N}$ factor, is to consider only the active site (or atoms or group) for which the number of electrons is same. However, no mathematical justification was provided to resolve the N -dependence problem of local hardness when evaluated in the way as suggested above. Here, it is shown how hardness potential $h(\bar{r})$[18] formally resolves the N-dependence problem of local hardness descriptor and how its two derivatives (or variants) have emerged out to be identical to the left and right derivatives of Fukui potential.[19] To demonstrate the ability of these two variants of hardness potential in handling the N-dependence problem of local hardness as well as variation of atom types of reactive centres these are used to explain both intermolecular and intramolecular reactivity trends of systems having different sizes (i. e., number of electrons) and characteristics.

2.2. Theoretical Background:

A. The formulation of Hardness Potential

Substitution of Eq. (2.3) into Eq. (2.1) follows, for a ground state

$$E[\rho] = N\mu - \left[\int \frac{\delta F[\rho]}{\delta\rho(\bar{r})}\rho(\bar{r})d\bar{r} - F[\rho]\right]$$

$$= N\mu - H[\rho] \tag{2.13}$$

where the *hardness functional* $H[\rho]$ is defined by the formula[18,20]

$$H[\rho] = \int \frac{\delta F[\rho]}{\delta\rho(\bar{r})}\rho(\bar{r})d\bar{r} - F[\rho] \tag{2.14}$$

Thus, $H[\rho]$ must be added to E to get $N\mu$. The differential of $H[\rho]$ surprisingly has a simple form. From Eq. (2.14) one has[7]

$$dH[\rho] = -dF[\rho] + d\left[\int \frac{\delta F[\rho]}{\delta\rho(\bar{r})}\rho(\bar{r})d\bar{r}\right]$$

$$= -\int \frac{\delta F[\rho]}{\delta\rho(\bar{r})}d\rho(\bar{r})d\bar{r} + \int \frac{\delta F[\rho]}{\delta\rho(\bar{r})}d\rho(\bar{r})d\bar{r} + \int\left[d\left(\frac{\delta F[\rho]}{\delta\rho(\bar{r})}\right)\right]\rho(\bar{r})d\bar{r}$$

$$= \iint \frac{\delta^2 F[\rho]}{\delta\rho(\bar{r})\delta\rho(\bar{r}')}d\rho(\bar{r})\rho(\bar{r}')d\bar{r}d\bar{r}' \tag{2.15}$$

One can find accurate to all orders,

$$\frac{\delta H[\rho]}{\delta \rho(\bar{r})} = h(\bar{r}) \tag{2.16}$$

Parr and Gázquez have termed $h(\bar{r})$ the hardness potential for the system[18] which in turn is the product of N and $\eta(\bar{r})$. So, the hardness potential $h(\bar{r})$ can be defined by,

$$h(r) = \int \frac{\delta^2 F[\rho]}{\delta \rho(\bar{r}) \delta \rho(\bar{r}')} \rho(\bar{r}') d\bar{r}' = N\eta(\bar{r}) \qquad \text{(from Eq.(2.6))} \tag{2.17}$$

It is important to notice that unlike local hardness [$\eta(\bar{r})$], $h(\bar{r})$ does not contain the $\frac{1}{N}$ factor. So it is expected that the use of $h(\bar{r})$ formally resolves the N-dependence problem of $\eta(\bar{r})$. Thus, in principle, $h(\bar{r})$ has the ability to compare the reactivity of the same atomic site in different molecules (i.e., intermolecular reactivity comparison) apart from intramolecular reactivity i.e., regioselectivity. Going further deep, one can argue that only descriptors from the grand canonical ensemble can do this job. The local descriptors from this ensemble generally combine a local and a global descriptor [e.g., local softness: $s(\bar{r}) = f(\bar{r})S$, see Eq. (2.7)]. One can connect the hardness functional to the grand canonical ensemble as, $E - \mu N = -H[\rho] = \Omega$. So, derivatives of the hardness functional also belong to the grand canonical ensemble. The hardness potential obviously is a combination of a global property (the total number of electrons) and a local reactivity descriptor (the local hardness) [i.e., $h(r) = N\eta(\bar{r})$]. It is worth mentioning here that, local softness, $s(\bar{r})$, although originates from grand canonical ensemble, it is mainly used to investigate the regioselectivity (or site selectivity) within a chemical system (i.e. intramolecular reactivity comparison). This is probably because of its local part (i.e., $f(\bar{r})$), which can take care of only orbital-orbital (i.e. short-range) interaction.

B. Working Equation of Hardness Potential using TFD approach

To obtain complete mathematical definition of $h(\bar{r})$, one needs to approximate the Hohenberg-Kohn functional $F[\rho]$.[1] $F[\rho(\bar{r})]$ can be approximated on the basis of Thomas-Fermi-Dirac (TFD)[21-23] approach to DFT. Considering the fact that $F[\rho]$ does not contain the nucleus-electron attraction term, the following equation is obtained from the general form of the energy functional $E^{TFD}[\rho(\bar{r})]$,[2] without further approximations:

$$F^{TFD}[\rho(\bar{r})] = C_F \int \rho(\bar{r})^{5/3} d\bar{r} + \frac{1}{2}\iint \frac{\rho(\bar{r})\rho(\bar{r}')}{|\bar{r}-\bar{r}'|} d\bar{r}' d\bar{r} - C_X \int \rho(\bar{r})^{4/3} d\bar{r} \tag{2.18}$$

Here, $C_F = \frac{3}{10}\left(3\pi^2\right)^{\frac{2}{3}} = 2.8712$ and $C_X = \frac{3}{4}\left(\frac{3}{\pi}\right)^{\frac{1}{2}} = 0.7386$ are the coefficients of the kinetic energy and exchange-energy functionals, respectively.[2] It is worth mentioning here that one can systematically improve TFD functional by considering $\frac{1}{9}$ of the Weizsäcker functional[24] (for gradient expansion) and a Wigner-type[25] local correlation functional. A survey of the implications of the improved TFD functional in local hardness can be found elsewhere.[13,26] It was shown that the effect of including $1/9^{th}$ of the Weizsäcker functional[24] contribute zero to the local hardness, $\eta(\bar{r})$ (and hence to the hardness potential, $h(\bar{r})$) when density, $\rho(\bar{r})$, is used as composite function, $\lambda[\rho(\bar{r}')]$ (see Eq. (2.6)).[13] The contribution of the Wigner-type[25] local correlation functional was also found to be negligible.[13]

Inserting Eq. (2.18) in Eq. (2.17), one may find the expression of hardness potential, $h(\bar{r})$ as,

$$h(\bar{r}) = \frac{10}{9} C_F \rho(\bar{r})^{2/3} - V^{el}(\bar{r}) - \frac{4}{9} C_X \rho(\bar{r})^{1/3} \tag{2.19}$$

where, $V_{el}(\bar{r})$ is the electronic part of the molecular electrostatic potential[5.a,27]

$$V_{el}(\bar{r}) = -\int \frac{\rho(\bar{r}')}{|r-r'|} dr' \tag{2.20}$$

Like $\eta(\bar{r})$,[17,27-29] the hardness potential, $h(\bar{r})$ can be evaluated though Eq. (2.19). Since, the electronic part of the molecular electrostatic potential, $V_{el}(\bar{r})$, is usually dominant when compared to the other two terms (i.e., kinetic and exchange energy terms) and the negative sign in the third term (i.e., the exchange energy term) cancels out, to some extent, the effect of the first term (i.e., the kinetic energy term),[29,30] one may further approximate $h(\bar{r})$ as,

$$h(\bar{r}) = -V_{el}(\bar{r}) \tag{2.21}$$

Incidentally, some similar kind of idea (i.e., change of kinetic energy functional equals to the negative of the sum of changes of exchange and correlation energy functional at isodensity

contours of 0.00872) was first used by Politzer et. al[31] when they tried to establish the relationships between atomic chemical potentials, electrostatic potentials, and covalent radii.

Instead of evaluating electronic contribution to the molecular electrostatic potential at a specific site (i.e., $V_{el}(\bar{r})$) we will consider the value at the nucleus (i.e., at $\vec{r} = 0$) of a particular atom k (i.e., $V_{el}(k)$).[17,28,29] So, $h(\bar{r})$ is replaced by $h(k)$ as,

$$h(k) = -V_{el}(k) \tag{2.22}$$

Thus, $h(k)$ appears to be a hard (i.e., electrostatically controlled or charge controlled) descriptor when it is evaluated through Eq. (2.22). It should be able to take care of the hard-hard interaction (i.e. charge-controlled, which is a long distance interaction). But as it is evaluated from the electronic contribution of the molecular electrostatic potential, it depends only on the 'electronic' (and not 'nuclear') charge. Electron transfer changes the electron density (and so also, $V_{el}(k)$) around the concerned atom. In that sense it is rational to argue that $h(k)$ can be used for comparing intermolecular reactivity sequence because it can take care of long distance effects. It is worth mentioning here that because $h(\bar{r})$ (in Eq. (2.19)) contains nonlinear functions of $\rho(\bar{r})$ (the first and the third terms), the condensation of $h(\bar{r})$ (as it is in Eq. (2.19)) is mathematically inexact.[32] However, the approximated definition of $h(\bar{r})$ (albeit a crude approximation), which contains only the $V_{el}(\bar{r})$ term, when evaluated at the nucleus does not suffer from this mathematical inexactness. Regarding interpretation of reactivity using $h(k)$ values, it is obvious that higher the value of $h(k)$ of an atom, more reactive it will be toward an electrophilic (El^+) reagent and less reactive toward a nucleophilic (Nu^-) reagent.

C. Can Electrophilic and Nucleophilic Variants of Hardness Potential efficiently take care of the basic loopholes in Hardness Potential $h(k)$?

Systematic analysis on several model systems are performed to test the effectiveness of $h(k)$ (Table 2.1, 2.2 and 2.3) as a reliable tool to measure intermolecular and intramolecular chemical reactivity. Some irregularities were found in generating such trends from the evaluated $h(k)$ values. It prompted us to argue that the differential behaviour of various functional groups in different systems (in which the effective electronegativity values of the concerned reactive atoms are different) in the event of an approaching electrophile or nucleophile cannot be ascribed

simply on the basis of $h(k)$ values of those atoms in the neutral systems. In reality this approaching electrophile (or nucleophile) induces polarization of the electron density of the concerned target species. But this effect is not taken into account here since $h(\bar{r})$ [or $h(k)$] corresponds to the electron density of the unperturbed neutral system.

To take care of the response of the system (in terms of changing electron density) as an electrophile or nucleophile approaches the system, we can invoke an idea similar to the one conceived by Parr and Yang[10.a] to define electrophilic and nucleophilic Fukui function. We would like to propose two variants of $h(\bar{r})$ and denote them as $\Delta^{-}h(\bar{r})$ and $\Delta^{+}h(\bar{r})$, which measure reactivities toward an approaching electrophilic (i.e., El^{+}) and nucleophilic (i.e., Nu^{-}) reagent, respectively. This seems to be particularly rational here because the response of reactive centres, having different effective electronegativity values (e.g., when the reactive atoms or functional groups are different, i.e., having different nuclear charge), towards an approaching electrophile or nucleophile will be different. Therefore, similar to the Fukui function indices,[10] one may split $h(\bar{r})$ in two parts $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$, which measure reactivity towards an approaching nucleophile (Nu^{-}) and an electrophile (El^{+}), respectively, as,

$$\Delta^{+}h(\bar{r}) = \left(\frac{\partial h(\bar{r})}{\partial N}\right)^{+} \quad \text{measures reactivity towards an approaching nucleophile } (Nu^{-})$$

$$\Delta^{-}h(\bar{r}) = \left(\frac{\partial h(\bar{r})}{\partial N}\right)^{-} \quad \text{measures reactivity towards an approaching electrophile } (El^{+})$$

Going further, using Eq. (2.22), one can get the relationship between the variants of hardness potential and the Fukui potentials[19] as,

$$\Delta^{+}h(\bar{r}) = \left(\frac{\partial h(\bar{r})}{\partial N}\right)^{+} = -\left(\frac{\partial V_{el}(\bar{r})}{\partial N}\right)^{+} = \frac{\partial}{\partial N}\left(\int \frac{\rho(\bar{r}')}{|\bar{r}-\bar{r}'|}d\bar{r}'\right)^{+} = \int \frac{\left(\frac{\partial \rho(\bar{r}')}{\partial N}\right)^{+}}{|\bar{r}-\bar{r}'|}d\bar{r}' = \int \frac{f^{+}(\bar{r}')}{|\bar{r}-\bar{r}'|}d\bar{r}' \tag{2.23}$$

Similarly,

$$\Delta^{-}h(\bar{r}) = \int \frac{f^{-}(\bar{r}')}{|\bar{r}-\bar{r}'|}d\bar{r}' \tag{2.24}$$

where, $\int \frac{f(\bar{r}')}{|\bar{r}-\bar{r}'|} d\bar{r}'$ is Fukui potential.[19] It is interesting to note that the variants of hardness potential (or Fukui potentials[19]) can be further justified from the Kohn-Sham (KS) formulation of DFT.[5.a,33] The relation between local hardness and Fukui potentials is an approximation of the KS potential derivative within the Hartree approximation.

The $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$ values when evaluated at the nucleus (i.e., $\Delta^{+}h(\bar{r})\Big|_{r\to 0}$ and $\Delta^{-}h(\bar{r})\Big|_{r\to 0}$) and denoted as $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$, respectively, can be written as:

(i) hardness potential descriptor for studies of nucleophilic attack on the system

$$\Delta^{+}h(k) = h^{N+1}(k) - h^{N}(k)$$

or, $$\Delta^{+}h(k) = -V_{el}^{N+1}(k) - [-V_{el}^{N}(k)] \qquad \text{(using Eq. (2.22))}$$

or, $$\Delta^{+}h(k) = -[V_{el}^{N+1}(k) - V_{el}^{N}(k)] \qquad (2.25)$$

(ii) hardness potential descriptor for studies of electrophilic attack on the system

$$\Delta^{-}h(k) = h^{N}(k) - h^{N-1}(k)$$

or, $$\Delta^{-}h(k) = -V_{el}^{N}(k) - [-V_{el}^{N-1}(k)] \qquad \text{(using Eq (2.22))}$$

or, $$\Delta^{-}h(k) = -[V_{el}^{N}(k) - V_{el}^{N-1}(k)] \qquad (2.26)$$

It is important to mention here that these two variants of hardness potential are originated (with some approximation) from hardness functional, $H[\rho]$,[18,20] which in turn belongs to grand canonical ensemble.(i.e., $-H[\rho] = E - \mu N = \Omega$). As local descriptors from this ensemble has the ability to take care of both intramolecular (i.e. site selectivity) as well as intermolecular reactivity (e.g., local softness), $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ can, in principle, serve both the purpose. Also, the operational definitions of these two reactivity descriptors, involve the difference of 'electronic part of the electrostatic potential'. Because, electrostatic potential can take care of long range effect, these two may act as more suitable descriptors than local softness, [$s(\bar{r})$] for intermolecular comparison. Moreover, as argued above (in the second paragraph of this sub-section), $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ can take care of the response of the system when the reactive atoms or functional groups are different. Recently, Cárdenas et. al. have also argued that "Fukui

potential at the position of the nuclei is equal to the variation of the chemical potential with the nuclear charge and therefore measures the sensitivity of the system to changes in atom type".[19.d] As $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ are also evaluated at the nucleus the same argument applies here also.

Some years ago, Jin et al[34] have shown that the equation $\eta(\bar{r}) = \frac{-V_{el}(\bar{r})}{N}$ or $h(\bar{r}) = -V_{el}(\bar{r})$ cannot be accepted. Because most of their observations were not satisfactory at a surface of 0.001 electrons/Bohr^3 (based on the cancellation of first and third term in Eq. (2.19)). However, the definiton of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ as projected by Eqs. (2.25) and (2.26), respectively, seems to be more acceptable because electron density differences (of neutral systems and its ions) at the atomic nuclei may be very small (even if not 0.001 a.u.) and thus net contribution of the first and third terms will be almost negligible. Also, it is highly likely that values of $h(k)$ (which is obtained by crude approximation) will be less reliable than those of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ values, which take care of the changing electron density scenario when an electrophile or a nucleophile approaches the system.

2.3. Computational Details:

To investigate the superiority of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ values over those of $h(k)$ ones in explaining intermolecular reactivity trends (i.e., site selectivity) we chose some homologous series of chemical systems containing common functional groups, *viz*, *–COOH, –COF, –CONH$_2$, –OH, –SH, –NH$_2$, –PH$_2$*. Some bioactive indolynes and unsymmetrical arynes are also chosen to demonstrate the ability of $\Delta^{+}h(k)$ in reproducing intra-molecular reactivity trend. The carbon atom in the first three functional groups (i.e., *–COOH, –COF* and *–CONH$_2$*) is expected to be the most reactive site toward an electron donating species (i.e., nucleophile, Nu^{-}) whereas *O*, *S*, *N*, *P* atoms in the *–OH*, *–SH*, *–NH$_2$*, and *–PH$_2$* groups are, respectively, the most reactive sites toward an electron accepting species (i.e., electrophile, El^{+}). Thus, based on the nature of the functional groups the chosen homologous series of systems can be grouped as electrophiles (systems having functional groups *–COOH, –COF* and *–CONH$_2$*) and nucleophiles (systems

having functional groups *–OH*, *–SH*, *–NH_2*, *–PH_2*). The homologous series generated from above functional groups are as follows:

Category A: Series generated from carboxylic acid and its derivatives

(i) *H**C**OOH, CH_3**C**OOH, CH_3CH_2**C**OOH*

(ii) *H**C**OF, CH_3**C**OF, CH_3CH_2**C**OF*

(iii) *H**C**ONH_2, CH_3**C**ONH_2, CH_3CH_2**C**ONH_2*

***Category B*:** Series generated from nucleophilic functional groups:

(i) *CH_3**O**H, CH_3CH_2**O**H, $CH_3CH_2CH_2$**O**H*

(ii) *CH_3**S**H, CH_3CH_2**S**H, $CH_3CH_2CH_2$**S**H*

(iii) *CH_3**N**H_2, CH_3CH_2**N**H_2, $CH_3CH_2CH_2$**N**H_2*

(iv) *CH_3**P**H_2, CH_3CH_2**P**H_2, $CH_3CH_2CH_2$**P**H_2*

***Category C*:** To elucidate the biological applicability of hardness potential derivatives in predicting the regioselectivity of the nucleophilic addition reactions, we have chosen several indolynes and unsymmetrical arynes[35-39] (See Fig. 2.1). The indolynes are mainly of three types – 4,5-indolynes (**1**), 5,6-indolynes (**2**) and 6,7-indolynes (**3**). Also, the impact of N-substituents on the regioselectivity towards nucleophilic addition reactions on indolynes are envisaged with methyl (Me) and tert-butoxycarbonyl (Boc) as substituents (**4-9**). The influence of halide substitution on the regioselectivity of 4,5-indolyne is tested by Br-substitution at C3 (**10**) and C6 (**11**) positions. The chosen unsymmetrical arynes are of three different types. These are benzynocyclo-n-alkenes (n = 4-6) (**12-14**), naphthalyne (**15**) and 3-methoxybenzyne (**16**). These are some of the systems chosen by Im et al.[38.a] and Cheong et al.[38.b] in their combined (experimental and theoretical) study.

Geometry optimizations as well as subsequent single point calculations of Category A and B are carried out at MP2(FC)/6-31G** (here 'FC' stands for 'frozen core') and B3LYP/6-31G** levels. It was confirmed that there is no imaginary frequency at any of the optimized geometries. For studying indolynes and unsymmetrical arynes (i.e., Category C), geometry optimization followed by single point calculations are performed at B3LYP/6-31G** level [for Br, Hay-Wadt LANL2DZ effective core potential[40] is used] and the solvation effects are taken care by CPCM model of acetonitrile[41] defining the solute surface by UAKS radii[42]. All

the calculations (i.e., evaluation of $V_{el}(k)$ at the atomic nucleus) have been performed using Gaussian 03 program suite[43.a,b]. The SCF density is used to evaluate $V_{el}(k)$.

2.4. Results and Discussions:

(i) (a) *Intermolecular Electrophilicity Trends for Systems Belonging to the Same Homologous Series in Category A*

In this case when a nucleophile (Nu^-) attacks the electrophilic centre (i.e., $\boldsymbol{C}_{C=O}$) the electron density increases on it resulting in higher $V_{el}^{N+1}(k)$ value (absolute value) than that of $V_{el}^{N}(k)$. So the quantity inside the square-bracket in Eq. (2.25) will be negative [as $V_{el}(k)$ is a negative quantity] making $\Delta^+h(k)$ a positive quantity. Normally, higher the $\Delta^+h(k)$ value higher should be the reactivity of that site (here atom) towards an approaching nucleophile. But in these particular systems, as the number of intervening $-CH_2-$ moiety increases electron density (and hence, $V_{el}^{N+1}(k)$) on the $\boldsymbol{C}_{C=O}$ does not enhance as expected in the event of an approaching nucleophile because of the existence of already pushing $+I$ effect. So, in case of intermolecular comparison within a homologous series as the size of the alkyl moiety increases the quantity inside the square-bracket in Eq. (2.25) becomes less negative and so $\Delta^+h(k)$ less positive. This means as the size of the alkyl moiety in a particular homologous series increases the electrophilicity of $\boldsymbol{C}_{C=O}$ decreases and so also does $\Delta^+h(k)$ values. From Table 2.1. (third column) and Figs. 2.2 (a) & (b) we observe the trend of $\Delta^+h(k)$ values as,

(i) $CH_3CH_2\boldsymbol{C}OOH < CH_3\boldsymbol{C}OOH < H\boldsymbol{C}OOH$

(ii) $CH_3CH_2\boldsymbol{C}OF < CH_3\boldsymbol{C}OF < H\boldsymbol{C}OF$

(iii) $CH_3CH_2\boldsymbol{C}ONH_2 < CH_3\boldsymbol{C}ONH_2 < H\boldsymbol{C}ONH_2$

which is just as expected. Interestingly values of hardness potential $h(k)$ are also able to predict the expected reactivity in this case (Table 2.1, second column).

(b) ***Intermolecular Electrophilicity Trends for Systems Belonging to Different Homologous Series in Category A***

Here, reactivity (i.e., electrophilicity) difference of $\boldsymbol{C}_{C=O}$ arises due to the difference of electron withdrawing power of attached groups (i.e., of $-OH$, $-F$ and $-NH_2$). As electron withdrawing power changes in the sequence $-F > -OH > -NH_2$ (in fact the last two groups are electron pushing), the relative increase of electron density on $\boldsymbol{C}_{C=O}$ in the $N+1$ electron system (i.e., assuming complete one electron transfer from the approaching nucleophile to the electrophile) also follows the same trend. Thus, the absolute value of $V_{el}^{N+1}(k)$ for $\boldsymbol{C}_{C=O}$ will follow the trend,

$$R\boldsymbol{C}OF > R\boldsymbol{C}OOH > R\boldsymbol{C}ONH_2; \qquad \text{where } R = -H, -CH_3, -CH_2CH_3$$

Considering the negative sign of $V_{el}(k)$ from Eq. (2.25) we should get the trend of positive $\Delta^{+}h(k)$ values of $\boldsymbol{C}_{C=O}$ as,

$$R\boldsymbol{C}OF > R\boldsymbol{C}OOH > R\boldsymbol{C}ONH_2; \qquad \text{where } R = -H, -CH_3, -CH_2CH_3$$

Results from Table 2.1 (third column) and Figs. 2.2 (a) & (b) confirm the above trend in both the methods (with the sole exception that in B3LYP/6-31G** method the $\Delta^{+}h(k)$ value of $CH_3CH_2\boldsymbol{C}OF$ is lower than that of $CH_3CH_2\boldsymbol{C}OOH$). Thus, higher is the $\Delta^{+}h(k)$ value of $\boldsymbol{C}_{C=O}$, higher is its reactivity (i.e., electrophilicity) in systems belonging to different homologous series. But hardness potential $h(k)$ provides results contrary to our expectation for these molecules [Table 2.1. Second column].

(ii) (a) ***Intermolecular Nucleophilicity Trends for Systems Belonging to the Same Homologous Series In Category B***

During an electrophilic (i.e., by El^{+}) attack electron density over the nucleophilic atom (printed in bold) is normally reduced. As a result the $V_{el}(k)$ value (absolute) of the nucleophilic atom is expected to decrease after transfer of some electron density to the electrophile. Now considering the fact that $V_{el}(k)$ is a negative quantity and assuming a full one electron transfer from nucleophilic atom to the approaching electrophile we get a positive value of $\Delta^{-}h(k)$ from Eq. (2.26). However, this reduction in electron density on the nucleophilic atom (printed in bold) is increasingly compensated as the number of intervening $-CH_2-$ moiety increases (because of

increasing $+I$ effect). So, the absolute value of $V_{el}^{N-1}(k)$ of the nucleophilic atom increases in a particular homologous series as, *e.g.*,

$$CH_3CH_2CH_2\mathbf{O}H > CH_3CH_2\mathbf{O}H > CH_3\mathbf{O}H$$

This is true for other homologous series also in category B. Here, it is worth mentioning that with increasing number of intervening $-CH_2-$ moiety the value of both $V_{el}^{N}(k)$ and $V_{el}^{N-1}(k)$ of the nucleophilic atom will increase. But what exactly happens is that relative increase of $V_{el}^{N-1}(k)$ is more than that of $V_{el}^{N}(k)$. This is understandable because the nucleophilic atom looses electrons to the approaching electrophile more (and hence the compensation is also more) as the $+I$ effect of the intervening $-CH_2-$ moieties increases. Now considering the negative sign of $V_{el}(k)$ from Eq. (2.26) we can argue that for this type of system (where rest part of the system is electron pushing) lower the positive value of $\Delta^{-}h(k)$ higher is the nucleophilicity of the corresponding nucleophilic atom (otherwise, as obvious from Eq. (2.26), higher the positive value of $\Delta^{-}h(k)$ for any atom, higher is its nucleophilicity). Based on this argument the expected $\Delta^{-}h(k)$ values of the nucleophilic atom of systems belonging to same homologous series of category B should be as follows,

(i) $CH_3CH_2CH_2\mathbf{O}H < CH_3CH_2\mathbf{O}H < CH_3\mathbf{O}H$

(ii) $CH_3CH_2CH_2\mathbf{S}H < CH_3CH_2\mathbf{S}H < CH_3\mathbf{S}H$

(iii) $CH_3CH_2CH_2\mathbf{N}H_2 < CH_3CH_2\mathbf{N}H_2 < CH_3\mathbf{N}H_2$

(iv) $CH_3CH_2CH_2\mathbf{P}H_2 < CH_3CH_2\mathbf{P}H_2 < CH_3\mathbf{P}H_2$

This is what we have observed in both the methods (see Table 2.2, third column and Figs 2.3 (a) and (b)). Hardness potential $h(k)$ values also produced the expected reactivity trend in these series (Table 2.2, third column).

(b) ***Intermolecular Nucleophilicity Trends for Systems Belonging to Different Series in Category B***

Here, the electronegativity parameter of *O*, *S*, *N* and *P* plays the deciding role. The electronegativity values change in the sequence $P < S < N < O$. Because of the electronegativity difference the value of $\Delta^{-}h(k)$ (i.e., $-[V_{el}^{N}(k) - V_{el}^{N-1}(k)]$) is also not same for two systems having same alkyl moiety *R*- but belonging to different homologous series. As per argument in

the last paragraph of section 2.2.C., $\Delta^{-}h(k)$ at the nuclei is equal to the variation of chemical potential with the nuclear charge and therefore measures the sensitivity of the system when the type of reactive atom changes.[19.d] Since ***O*** atom has a stronger hold on its electron than *N* (say) $V_{el}^{N}(k)$ of ***O*** in *R*-***O****H* will be higher (absolute value) than that of ***N*** in *R*-***N****H*$_2$ (this is also obvious from $h(k)$ values of Table 2.2). However, the presence of electron pushing alkyl moiety (i.e., *R*-) makes the interpretation bit more complicated here. Relative compensation (due to $+I$ effect of *R*- moiety) after the loss of one electron will be more for ***N*** in *R*-***N****H*$_2$ than ***O*** in *R*-***O****H*. This is presumably because ***N*** atom in neutral *R*-***N****H*$_2$ does not pull that much electron as ***O*** does in *R*-***O****H*. So the left out electron density in the *R*- moiety is higher in *R*-***N****H*$_2$ than in *R*-***O****H*. This left-out electron density will be pulled by the ***N*** atom in *R*-***N****H*$_2$ when the electrophile attacks on it. As a result, the absolute value of $[V_{el}^{N}(k) - V_{el}^{N-1}(k)]$ for ***N*** in *R*-***N****H*$_2$ will be lower than that of ***O*** in *R*-***O****H*. Again considering the negative sign of $V_{el}(k)$ we get higher positive $\Delta^{-}h(k)$ value for ***O*** in *R*-***O****H* than ***N*** in *R*-***N****H*$_2$. Thus, lower the nucleophilicity higher is the $\Delta^{-}h(k)$ value of the nucleophilic atom.

The above argument holds true for systems of all four homologous series in category B and our observed trend of $\Delta^{-}h(k)$ values (Figs 2.3 (a) & (b) and Table 2.2) in both the methods is as follows,

R-***O****H* > *R*-***N****H*$_2$ > *R*-***S****H* > *R*-***P****H*$_2$; where *R* = –*CH*$_3$, –*CH*$_2$*CH*$_3$, –*CH*$_2$ *CH*$_2$*CH*$_3$

[There is only one exception and that is in B3LYP/6-31G** method the $\Delta^{-}h(k)$ value of *CH*$_3$*CH*$_2$*CH*$_2$***N****H*$_2$ is little higher than that of *CH*$_3$*CH*$_2$*CH*$_2$***O****H,* (see Table 2.2, third column and Fig. 2.3 (b)] This is similar to the trend of electronegativity values of the nucleophilic atoms and, as expected, opposite to the trend of their nucleophilicity. However, this reverse trend of $\Delta^{-}h(k)$ values may be specific for systems where electron pushing group or moieties (here, *R*-moiety) are attached to the concerned atom. Also, as in category A [see section 2.4.(i).(b)], here also generated trends of $h(k)$ values are not as per expectation when systems belonging to different series are compared (for interpretation of nucleophilicity using $h(k)$ values, please see last para of sub-section 2.2.B.). Specifically, hardness potential (i.e., $h(k)$) fails to follow the expected

trend between $CH_3(CH_2)_n\mathbf{O}H$ and $CH_3(CH_2)_n\mathbf{N}H_2$ and also between $CH_3(CH_2)_n\mathbf{S}H$ and $CH_3(CH_2)_n\mathbf{P}H_2$.[Table 2.2, second column]

(iii) ***Regioselectivity of Nucleophilic addition to Indolynes and unsymmetrical arynes***

Based on the argument as stated in Section 2.2 (except that here we are interested in intramolecular reactivity i.e., regioselectivity), the $h(k)$ and $\Delta^{+}h(k)$ values can be used to predict the regioselectivity of biological active indolyne derivatives and unsymmetrical arynes as follows:

(i) **Indolynes:** The corresponding $\Delta^{+}h(k)$ values are tabulated in Table 2.3, fourth column. In case of 4,5-indolyne **(1)** the value of $\Delta^{+}h(k)$ is higher in C5-position than in C4 position. Similarly, C5 position in 5,6-indolyne **(2)** and C6 position in 6,7-indolyne **(3)** have higher $\Delta^{+}h(k)$ values. It is encouraging to notice that the same trends were observed by Im et al.[38.a] in their combined experimental and theoretical study. However, in case of 5,6-indolyne **(2)** $h(k)$ values provide result contrary to that of Im et. al.[38.a] [Table 2.3, third column; for interpretation of electrophilcity using $h(k)$ values, see last para of sub-section 2.2.B.]

(ii) **N-substituted Indolynes:** The values of both $h(k)$ and $\Delta^{+}h(k)$ (Table 2.3, third and fourth column) clearly show that the regioselectivity remain unchanged even after N-substitution by –Me and -Boc (tert-butoxycarbonyl) groups (compounds **4-9**). The trend generated here is similar to that observed by Im et al.[38(a)] in their combined study.

(iii) **C3 and C6 Halide Substituted 4,5-Indolynes:** The values of $\Delta^{+}h(k)$ (Table 2.3, fourth column) confirm that after Br substitution at C3 (**10**), the electrophilicity of C5 position enhances to some extent when compared to C4, which is in line with the earlier study by Im. et. al[38(a)]. It is worth mentioning here that $\Delta^{+}h(k)$ values are in favour of C4 position for C6-substituted 4,5-indolyne (**11**). This trend is also similar to that obtained experimentally by Bronner et al.[44] which reports that with aniline as a nucleophile 6-bromo-4,5-indolyne showed C5:C4 product ratio as 1:13, favoring significantly C4 attack. But the trend of $h(k)$ values observed for C6 substituted 4,5-indolyne **(11)** is not as per expectation.

(iv) **Unsymmetrical Arynes:** We observe that the $\Delta^{+}h(k)$ values at C2 in benzynocyclo-n (n = 4-6)-alkenes (compounds **12-14**) are higher than those of C1 positions, showing higher electrophilicity for the same (i.e., C2) (see Table 2.3). However, the difference in $\Delta^{+}h(k)$ values between C2 and C1 positions are not that significant. It is worth mentioning here that due to small difference between the internal angle values at C1 and C2, regioselectivity could not be concluded unambiguously in benzynocyclo-n (n = 5-6)-alkenes (i.e., compounds **13-14**) by 'distortion model'[38.b]. Activation energy difference (although the difference is very small), however, somewhat favours the nucleophilic attack at C2 (in **13**). Also, for benzocyclo-4-alkene (**12**) the trend of $\Delta^{+}h(k)$ values are as observed earlier[38.b]. The values of $h(k)$ (see Table 2.3) could not generate the expected intramolecular electrophilicity trends in case of benzynocyclo-5-alkene (**13**) and benzynocyclo-6-alkene (**14**) as these values demonstrate unambiguous high electrophilicity for C2 position. In case of naphthalyne (**15**) and 3-methoxybenzyne (**16**) values of both $h(k)$ and $\Delta^{+}h(k)$ could reproduce the expected reactivity trends towards nucleophilic addition reaction (C2 position in naphthalyne (**15**) and C1 position in 3-methoxybenzyne (**16**)). All these findings correlated well to the experimental[39] and earlier theoretical observations.[38]

2.5. Conclusion:

In this chapter, it is shown how hardness potential [$h(k)$] can effectively solve the $\frac{1}{N}$ problem in local hardness [$\eta(\bar{r})$] parameter. While $h(k)$ appears to be a useful descriptor for analyzing and predicting the reactivity behavior for systems belonging to the same homologous series, an intrinsic limitation upon its use is also recognized. Hardness potential, $h(k)$, in its original working definition (Eqn. (2.22)), is unable to explain the reactivity sequence when the systems belong to different homologous series i.e., when the reactive centres in the chemical systems vary from each other. To overcome this limitation we have proposed electrophilic and nucleophilic variants of the original hardness potential as $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$, respectively (Eqs. (2.25) and (2.26)). The superiority of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ over $h(k)$ stems from the fact that they take care of the response (i.e., the changing electron density scenario) of the reactive

centres toward a nucleophilic (Nu^-) or an electrophilic (El^+) attack on them. It is interesting to observe that both of these two new descriptors, when evaluated at the nuclei, correlate very well with the expected reactivity trends. It is also worth mentioning here that the electronegativity differences of the reactive atoms are also well taken care by these new descriptors. Pushing further it could be shown that these two variants of hardness potential lead to the Fukui potential.[19.a,b,c,33] A further justification in favour of using these two descriptors for comparison between reactive centres having different atom types (i.e., having different electronegativity values) is cited from a recent work of Cárdenas et al.[19.d] They have argued that "Fukui potential at the position of the nuclei is equal to the variation of the chemical potential with the nuclear charge and therefore measures the sensitivity of the system to changes in atom type". The applicability of the elctrophilic variant of hardness potential [$\Delta^+h(k)$] in predicting the regioselectivity of biologically important indolynes and unsymmetrical arynes is also validated. The trends of regioselectivity generated by $\Delta^+h(k)$ for these systems also correctly reproduce the trends observed earlier.[38,39,44]

From the generated data and subsequent analysis the authors are of the opinion that $\Delta^+h(k)$ and $\Delta^-h(k)$ descriptors have the potential to be used for explaining different types of reactivity trends and phenomena,[17,28,29,45,46] where electronic factor plays the major role. Also, the electronic factors should be operative through bonds (e.g., $\pm I$ and $\pm R$ effects etc.). Situations where steric factor plays a significant role or electronic factors operate through space (arising out of the artifact of different condensation schemes of electric potential or electronic density) the generated $\Delta^+h(k)$ and $\Delta^-h(k)$ values may not reproduce the expected trends. This is particularly true for intermolecular reactivity trends where wide structural variation causes large difference in the 'through space' effects of electronic and steric factors around the sites (i.e., atoms) of interest.

Also, in an earlier study,[47] it is shown that for a series of systems having more than one site of comparatively high reactivity, intermolecular reactivity trends cannot be predicted from the local reactivity of their strongest sites. This is true for local descriptors such as local softness and philicity (which are also originated from grand canonical ensemble). The above argument relies on the normalization criteria of the local counterpart (i.e. Fukui function, which is

normalized to unity) of these two local descriptors. Although, $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ are originated from $h(r)$ [$h(r) = N\eta(\bar{r})$, Eq. (2.17)], which in turn, originated from grand canonical ensemble ($E - \mu N = -H[\rho] = \Omega$), the local counterpart here (i.e., local hardness) does not have similar normalization criteria as Fukui function.

It is interesting to note that although the final working equations of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ (i.e., Eqs. (2.25) and (2.26) were arrived from the equation of local hardness (i.e., Eq. (2.19), with N in the denominator of all the three terms in the right hand side) after some assumptions these differences of electronic part of the electrostatic potential can be considered to be reactivity indicators in their own merit. This is because, (i) for atoms of a given type, the variation of electronic population is perfectly correlated with the variation of electrostatic potential and (ii) the differences of electron densities at the nucleus of atoms in a neutral molecule and its ions may be very small and hence the net contribution of the first and third terms in Eq. (2.19) will be negligible, making Eqs. (2.25) and (2.26) more acceptable than Eq. (2.22).

References and Notes

1. P. Hohenberg and W. Kohn, *Phys. Rev*. B, **1964**, *136*, 864.
2. R. G. Parr and W. Yang, Density–Functional Theory of Atoms and Molecules; Oxford University Press: New York, **1989**.
3. R. G. Parr, Annu. Rev. Phys. Chem., **1983**, *34*, 631.
4. R. G Parr and W. Yang, *Annu. Rev. Phys. Chem*., **1995**, *46*, 701.
5. (a) H. Chermette, *J. Comput. Chem.,* **1999,** *20*, 129; (b) P. Geerlings, F. De Proft and W. Langenaeker, *Chem. Rev*., **2003,** *103*, 1793.
6. J. L. Gázquez, *J. Mex. Chem. Soc*., **2008,** *52*, 3.
7. R. G. Parr, R. A. Donnelly, M. Levy and W. E. Palke, *J. Chem. Phys.,* **1978**, *68*, 3801.
8. R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc*., **1983,** *105*, 7512.
9. W. Yang and R. G. Parr, *Proc. Natl. Acad. Sci. U.S.A*., **1985,** *82*, 6723.
10. (a) R. G. Parr and W. Yang, *J. Am. Chem. Soc*., **1984,** *106*, 4049; (b) W. Yang and W. Mortier, *J. Am. Chem. Soc.,* **1986**, *108*, 5708.
11. S. K. Ghosh and M. Berkowitz, *J. Chem. Phys*., **1985,** *83*, 2976.
12. M. Berkowitz, S. K. Ghosh and R. G. Parr, *J. Am. Chem. Soc*., **1985,** *107*, 6811.
13. P. K. Chattaraj, D. R Roy, P. Geerlings and M. Torrent-Sucarrat, *Theor. Chem. Acc*., **2007,** *118*, 923.
14. M. K. Harbola, P. K. Chattaraj and R. G. Parr, *Isr. J. Chem*., **1991,** *31*, 395.
15. S. K. Ghosh, *Chem. Phys. Lett*., **1990,** *172*, 77.
16. M. Berkowitz and R. G. Parr, *J. Chem. Phys*., **1988,** *88*, 2554.
17. S. Saha and R. K. Roy, Phys. Chem. Chem. Phys., **2008**, *10*, 5591.
18. R. G. Parr and J. L. Gazquez, *J. Phys. Chem*., **1993,** *97*, 3939.
19. (a) M. Berkowitz, *J. Am. Chem. Soc*., **1987,** *109*, 4823; (b) M. Torrent-Sucarrat, F. De Proft, P. Geerlings and P. W. Ayers, *Chem.-Eur. J*., **2008,** *14*, 8652; (c) M. Torrent-Sucarrat, M.; F. De Proft, P. W. Ayers and P. Geerlings, *Phys. Chem. Chem. Phys*., **2010,** *12*, 1072; (d) C. Cárdenas, W. Tiznado, P. W. Ayers and P. Fuentealba, *J. Phys. Chem. A,* **2011,** *115*, 2325; (e) C. Cárdenas, *Chem. Phys. Lett*., **2011,** *513*, 127.
20. J. L. Gázquez, in Struct. Bonding; K. D. Sen, Ed.; Springer Verlag: Berlin, Vol. *80* pp. 27. **1993.**

21. L. H. Thomas, *Proc. Cambridge Philos. Soc*., **1927,** *23*, 542.

22. E. Fermi, *Z. Phys.,* **1928,** *48*, 73.

23. P. A. M. Dirac, *Proc. Cambridge Philos. Soc.,* **1930,** *26*, 376.

24. C. F. von Weizsäcker, *Z. Physik,* **1935**, *96*, 431.

25. E. Wigner, *Phys. Rev.,* **1932,** *40*, 749.

26. M. Torrent-Sucarrat, P. Salvador, M. Solà and P. Geerlings, *J. Comput. Chem*., **2008**, *29*, 1064.

27. W. Langenaeker, F. de Proft and P. Geerlings, *J. Phys. Chem*., **1995**, *99*, 6424.

28. S. Saha and R. K. Roy, *J. Phys. Chem. B,* **2007,** *111*, 9664.

29. S. Saha and R. K. Roy, *J. Phys. Chem. B,* **2008**, *112*, 1884.

30. In the literature several authors have shown that the Coulomb term is usually dominant[a-d] in the evaluation of local hardness, although the kinetic term is not negligible and can be compared to Coulomb term[f-h]: (a) Ref. 12 and 27; (b) P. K. Chattaraj, A. Cedillo and R. G. Parr, *J. Chem. Phys.,* **1995,** *103*, 10621; (c) S. Liu, F. De Proft and R. G. Parr, *J. Phys. Chem. A,* **1997,** *101*, 6991; (d) L. F. Pacios, *Chem. Phys. Lett.,* **1997,** *276*, 381; (e) A. Borgoo, M. Torrent-Sucarrat, F. De Proft and P. Geerlings, *J. Chem. Phys*., **2007,** *126*, 234104; (f) M. Torrent-Sucarrat and P. Geerlings, *J. Chem. Phys*., **2006,** *125*, 244101; (g) M. Torrent-Sucarrat, P. Salvador, P. Geerlings and M. Solà, *J. Comput. Chem*., **2007,** *28*, 574; (h) Ref. 26.

31. P. Politzer, R. G. Parr and D. R. Murphy, *J. Chem. Phys*., **1983,** *79*, 3859.

32. P. K. Chattaraj and S. Giri, *Annual Reports Sec. C (Physical Chemistry),* **2009,** *105*, 13.

33. (a) P. Senet, *J. Chem. Phys.,* **1997**,*107*, 2516; (b) P. Senet, *Chem. Phys. Lett.,* **1997,** *275*, 527.

34. P. Jin, J. S. Murray and P. Politzer, *Comp Lett*., **2007,** *3,* 373.

35. (a) R. J. Sundberg,. The Chemistry of Indoles; Academic Press: New York, **1970**; (b) R. J. Sundberg, Pyrroles and Their Benzoderivatives: Synthesis and Applications. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, Vol. *4*, pp 313, **1984**; (c) R. J. Sundberg, Indoles (Best Synthetic Methods); Academic Press: New York, pp 7, **1996**; (d) J. A. Joule,. Indole and its Derivatives. In Science of Synthesis: Houben-Weyl Methods of Molecular Transformations; E. J. Ed. Thomas, George Thieme Verlag: Stuttgart,; Category 2, Vol. *10*, Chapter 10.13, **2000**.

36. (a) D. A. Horton, G. T. Bourne and M. L. Smyth, *Chem. Rev.,* **2003,** *103*, 893; (b) F. R. de Sá Alves, E. J. Barreiro and C. A. M. Fraga, Mini-Rev. Med. Chem., **2009,** *9*, 782**.**

37. M. Bandini and A. Eichholzer, *Angew. Chem. Int. Ed.,* **2009,** *48*, 9608.

38. (a)G.-Y. J. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, and N. K. Garg, *J. Am. Chem. Soc*., **2010,** *132*, 17933; (b) P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G.-Y. J. Im, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc*., **2010,** *132*, 1267.

39. Z. Liu, R. C. Larock, *J. Org. Chem*., **2006,** *71*, 3198.

40. P. J. Hay and W. R. Wadt, *J. Chem. Phys*., **1985,** *82*, 299.

41. (a) V. Barone and M. Cossi, *J. Phys. Chem. A,* **1998,** *102*, 1995; (b) M. Cossi, N. Rega, G. Scalmani and V. Barone, *J. Comput. Chem*., **2003,** *24*, 669.

42. Y. Takano and K. N. Houk, *J. Chem. Theory Comput*., **2005**, *1,* 70.

43. (a) M. J. Frisch, et al. Gaussian 03, Revision E.01; Gaussian, Inc. Wallingford, CT **2004**; (b) help@gaussian.com, private communication.

44. S. M. Bronner, A. E. Goetz and N. K. Garg, *J. Am. Chem. Soc.,* **2011,** *133*, 3832.

45. (a) P. Bagaria, S. Saha, S. Murru, V. Kavala, B. K. Patel and R. K. Roy, *Phys. Chem. Chem. Phys.,* **2009,** *11*, 8306; (b) S. Saha and R. K. Roy, S. Pal, *Phys. Chem. Chem. Phys*., **2010,** *12*, 9328;

(c) **A.** Sarmah, S. Saha, P. Bagaria (Gupta) and R. K. Roy, *Chem Phys,* **2012,** *394*, 29; (d) R. K. Roy, V. Usha, and Bhisma K. Patel and K. Hirao, *J. Comput. Chem.,* **2006***, 27,* 773.

46. S. Saha and R. K. Roy, *Annu. Rep. Prog. Chem., Sect. C,* **2010,** *106*, 118.

47. R. K. Roy, V. Usha, J. Paulovic and K. Hirao, *J. Phys. Chem. A*., **2005**, *109*, 4601.

Table 2.1: Hardness potential [*h(k)*, Eq. (2.22)] as well as Electrophilic hardness potential [$\Delta^{+}h(k)$, Eq. (2.25)] values of $\boldsymbol{C}_{C=O}$ (carbon atom of the *C=O* moiety; shown in bold) in the chosen systems of the Category A. In each boxes the upper value is generated by MP2(FC)/6-31G** method and the lower one by *B3LYP/6-31G*** method using SCF densities. As is obvious the *h(k)* values are unable to produce the expected trends for different homologous series but $\Delta^{+}h(k)$ can. For details, please see Section 2.4.(i).b.

Chosen Systems for *Electrophilic Centre*	*h(k)* (eV)	$\Delta^{+}h(k)$ (eV)
-**C**OOH		
H**C**OOH	597.0617 599.0372	11.1784 10.6315
CH_3**C**OOH	661.0302 662.5921	10.7431 9.8097
CH_3CH_2**C**OOH	703.2106 704.4025	10.5335 9.5947
-**C**OF		
H**C**OF	600.3706 602.7434	11.6329 11.1431
CH_3**C**OF	664.1922 666.2820	11.0832 10.2097
CH_3CH_2**C**OF	706.2392 707.7631	10.7458 9.4696
-**C**ONH_2		
H**C**ONH_2	592.4466 593.9949	10.7920 10.1934
CH_3**C**ONH_2	655.7594 657.0084	10.2043 9.1131
CH_3CH_2**C**ONH_2	697.8364 697.2513	10.0519 9.0668

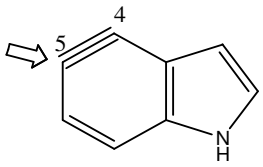
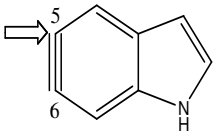
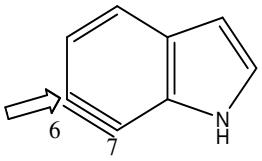
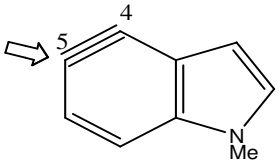
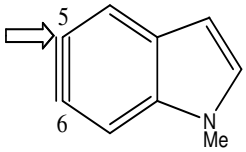
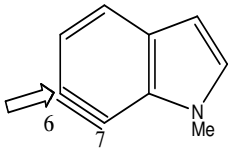
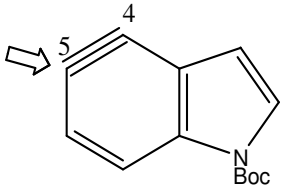
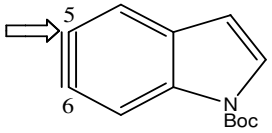
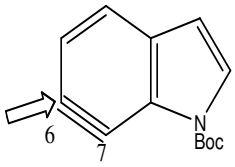
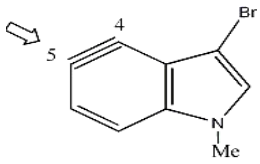
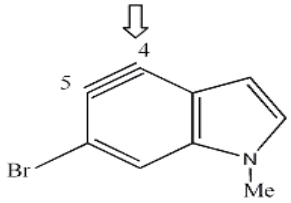
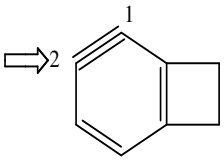
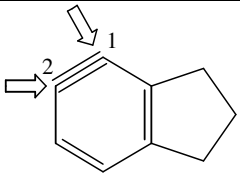
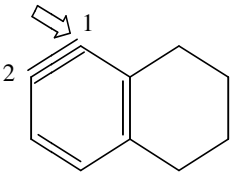
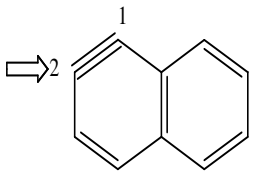
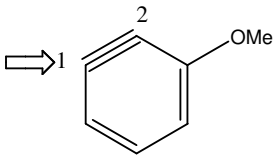
Table 2.2: Hardness potential [*h(k,)* Eq. (2.22)] as well as Nucleophilic hardness potential [Δ^{-} *h(k)*, Eq. (2.26)] values of the nucleophilic atoms (printed in bold) in the chosen systems of the Category B. In each boxes the upper value is generated by MP2(FC)/6-31G** method and the lower one by *B3LYP/6-31G*** method using SCF densities. As is obvious *h(k)* values are unable to produce the expected trends for some systems, but Δ^{-}*h(k)* can. For details, please see Section 2.4.(ii).b.

Chosen Systems for *Nucleophilic Centre*	*h(k)* (eV)	Δ^{-}*h(k)* (eV)
-**O**H		
CH_3**O**H	703.7684 703.9916	13.1431 12.1689
CH_3CH_2**O**H	748.4931 748.3543	12.7377 10.8954
CH_3CH_2 CH_2**O**H	775.6474 775.5167	12.4383 10.2124
-**S**H		
CH_3**S**H	1687.6480 1686.2310	9.8233 9.7607
CH_3CH_2**S**H	1726.9330 1724.9280	9.5729 9.3961
CH_3CH_2 CH_2**S**H	1758.8850 1756.4120	9.4342 9.1077
-**N**H_2		
CH_3**N**H_2	607.5789 607.6088	11.6274 11.2465
CH_3CH_2**N**H_2	651.0191 650.7225	11.3091 10.6043
CH_3CH_2 CH_2**N**H_2	679.4768 679.0795	11.1893 10.3104
-**P**H_2		
CH_3**P**H_2	1558.2010 1556.9030	9.1213 9.0832
CH_3CH_2**P**H_2	1595.6470 1593.9020	8.8300 8.5661
CH_3CH_2 CH_2**P**H_2	1621.3720 1619.4540	8.6913 8.1825

Table 2.3: Hardness potential [*h(k,)* Eq. (2.22)] as well as Electrophilic hardness potential [$\Delta^{+}h(k)$, Eq. (2.25)] values generated by B3LYP/6-31G** method and UAKS-CPCM model of solvation [preferred electrophilic positions (or sites of nucleophilic attack) are shown in bold. Please also see Fig. 2.1 and Section 2.4.(iii).]. The systems shown in bold, are the ones where *h(k)* values failed to predict expected reactivity, whereas $\Delta^{+}h(k)$ could.(discussed in Section 2.4. (iii).

Systems	Electrophilic Positions	$h(k)$ (eV)	$\Delta^{+}h(k)$ (eV)
Indolynes			
1. 4,5-Indolyne	C-4 **C-5**	741.5596 727.1757	7.9403 7.9838
2. **5,6-Indolyne**	**C-5** C-6	728.4410 727.3009	8.0138 7.9539
3. 6,7-Indolyne	**C-6** C-7	730.3611 741.2750	8.0491 7.9022
N-substituted Indolynes			
4. N-Me substituted 4,5-Indolyne	C-4 **C-5**	764.4553 749.0101	7.9022 7.9430
5. N-Me substituted 5,6-Indolyne	**C-5** C-6	750.2863 752.4660	7.9702 7.9076
6. N-Me substituted 6,7-Indolyne	**C-6** C-7	755.7721 775.5875	7.9757 7.7607
7. N-Boc substituted 4,5-Indolyne	C-4 **C-5**	864.4218 850.4460	7.8505 7.9485
8. N-Boc substituted 5,6-Indolyne	**C-5** C-6	850.0379 869.7661	7.9403 7.8886
9. N-Boc substituted 6,7-Indolyne	**C-6** C-7	874.1744 929.1877	7.9239 7.6954
C3 and C6 Halide Substituted 4,5-Indolynes			
10. C3-substituted 4,5-indolyne	C-4 **C-5**	785.8952 767.3506	7.6437 7.7906
11 **C6-substituted 4,5-indolyne.**	**C-4** C-5	764.8499 751.0755	7.7525 7.5784
Unsymmetrical Arynes			
12. Benzynocyclo-4-alkene	C-1 **C-2**	716.2421 707.5073	7.9974 8.0246
13. **Benzynocyclo-5-alkene**	**C-1** **C-2**	748.9094 730.2533	7.9811 8.0002
14. **Benzynocyclo-6-alkene**	**C-1** C-2	776.9508 751.2551	7.9158 7.9512
15. Naphthalyne	C-1 **C-2**	760.7382 741.1134	7.7552 7.8233
16. 3methoxybenzyne	**C-1** C-2	716.3592 731.2411	8.2369 8.0573

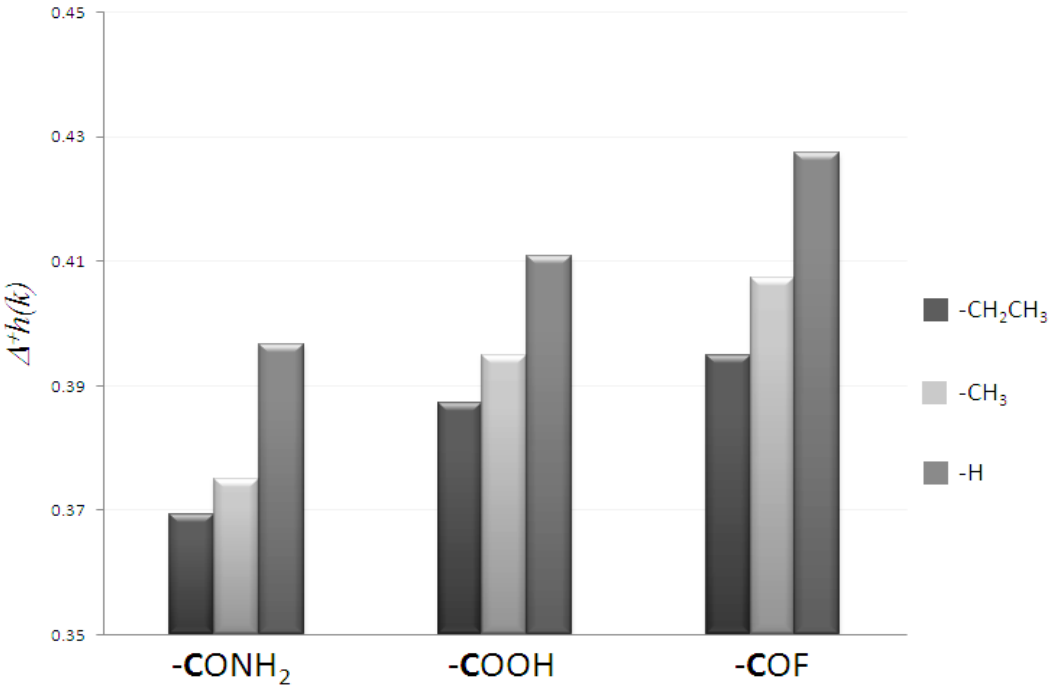
Figure 2.1: Chosen indole derivatives and unsymmetrical arynes

 **1. 4,5-Indolyne**	 **2. 5,6-Indolyne**	 **3. 6,7-Indolyne**	 **4. N-Me substituted 4,5-Indolyne**
 **5. N-Me substituted 5,6-Indolyne**	 **6. N-Me substituted 6,7-Indolyne**	 **7. N-Boc substituted 4,5-Indolyne**	 **8. N-Boc substituted 5,6-Indolyne**
 **9. N-Boc substituted 6,7-Indolyne**	 **10. C3-substituted 4,5-indolyne**	 **11. C6-substituted 4,5-indolyne**	 **12. Benzynocyclo-4-alkene**
 **13. Benzynocyclo-5-alkene**	 **14. Benzynocyclo-6-alkene**	 **15. Naphthalyne**	 **16. 3methoxybenzyne**

⇨ **Preferred Site of Nucleophilic attack**

Figure 2.2: Bar diagram presentation of the electrophilic hardness potential [$\Delta^{+}h(k)$] values of the electrophilic atom (shown in bold) in the chosen chemical systems of Category A **(a)** at MP2(FC)/6-31G** **(b)** B3LYP/6-31G**. See also Table 2.1.

(a)



(b)

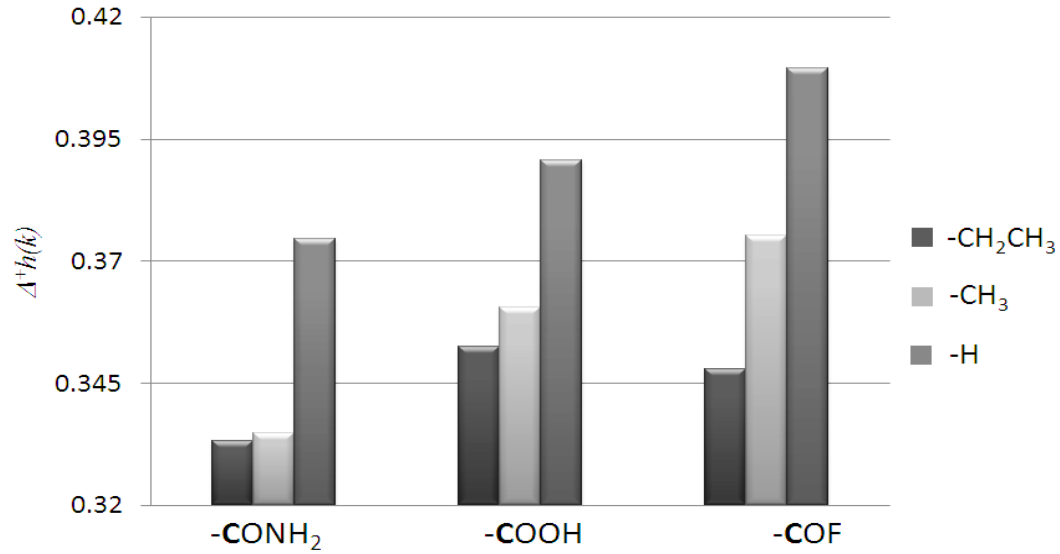
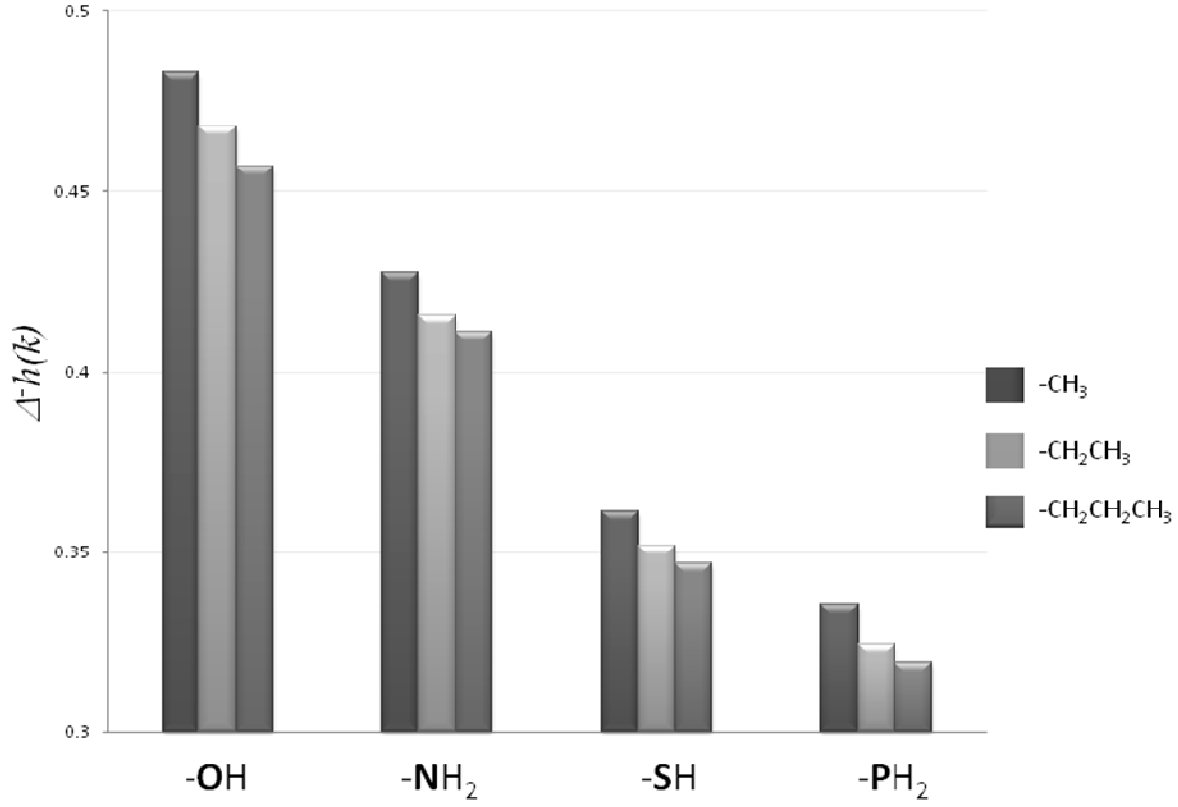
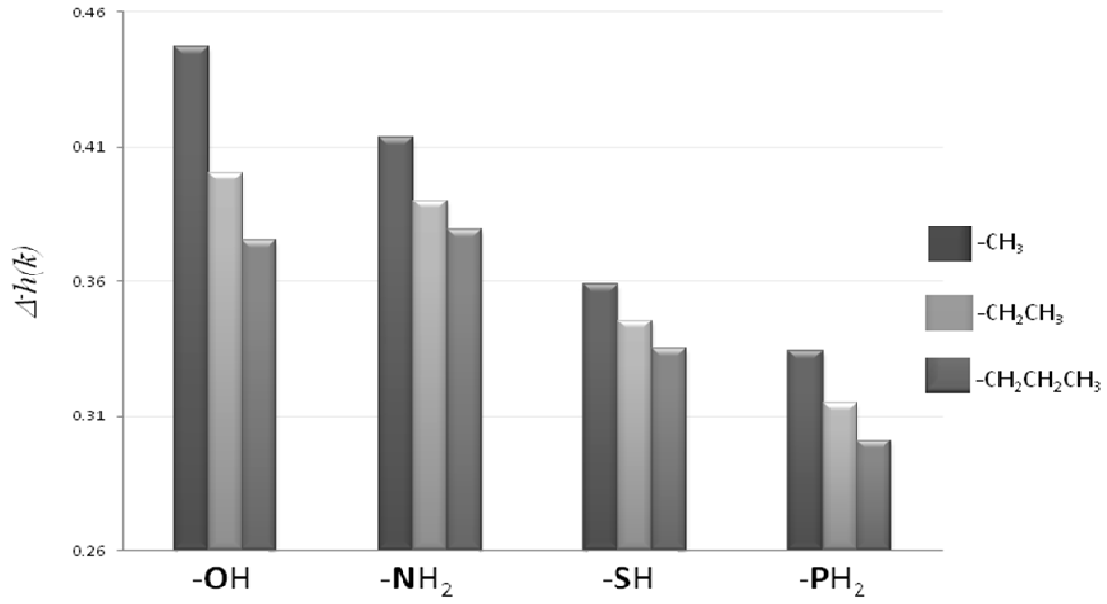


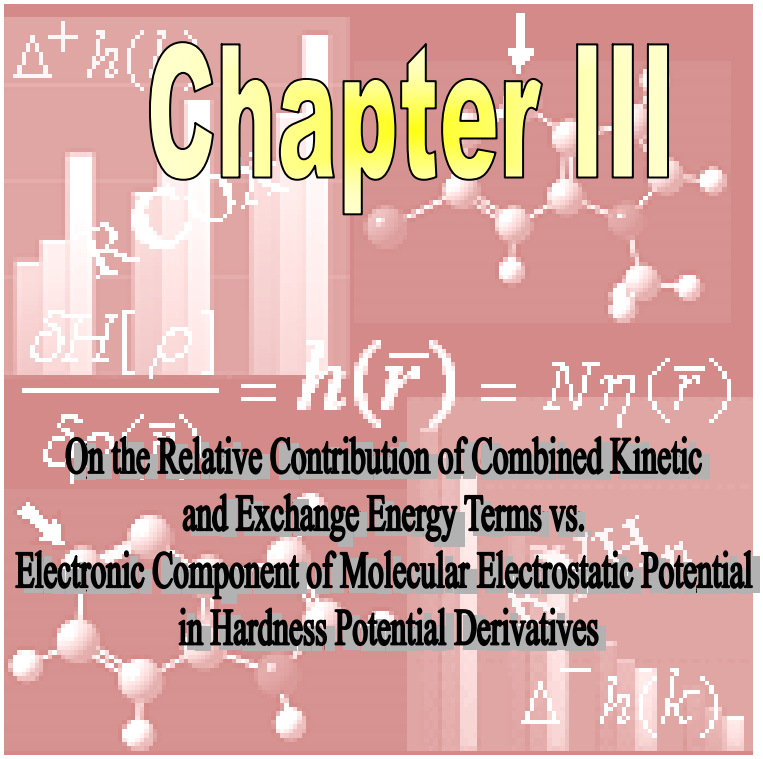
Figure 2.3: Bar diagram presentation of the nucleophilic hardness potential [$\Delta^{-}h(k)$] values of the nucleophilic atom (printed in bold) in the chosen chemical systems of Category B **(a)** at MP2(FC)/6-31G** **(b)** B3LYP/6-31G**. See also Table 2.2.

(a)



(b)




Chapter III
$\frac{\delta H[\rho]}{\delta \rho(\vec{r})} = h(\vec{r}) = N\eta(\vec{r})$
On the Relative Contribution of Combined Kinetic and Exchange Energy Terms vs. Electronic Component of Molecular Electrostatic Potential in Hardness Potential Derivatives

3.1. Introduction:

Parr and his collaborators proposed several systematic and simple methods to gain an insight into the chemical reactivities of various electronic systems by exploiting mathematical formulation of DFT which led to the foundation of 'Conceptual Density Functional Theory' or 'Chemical Reactivity Theory' or 'Density Functional Reactivity Theory (DFRT).[1-66] In the earlier chapter, the DFRT based reactivity descriptor, hardness potential is used to formally address the *N*-dependence problem of local hardness. Moreover, the corresponding electrophilic [$\Delta^{+}h(k)$] and nucleophilic [$\Delta^{-}h(k)$] variants of the hardness potential (which can take care of the loopholes in hardness potential) are also discussed in detail from the viewpoint of theory and fruitful applications.[6,66] These two derivatives (or variants), generated from the approximated form of $h(\bar{r})$ [i.e., $h(\bar{r}) = -V_{el}(\bar{r})$], have emerged out to be identical to the left and right derivatives of Fukui potential.[56] Now, in this chapter, the focus will be on the relative contribution of the sum of kinetic [$\frac{10}{9}C_F\rho(\bar{r})^{2/3}$] and exchange energy [$\frac{4}{9}C_X\rho(\bar{r})^{1/3}$] terms to that of the electronic part of the molecular electrostatic potential [$V_{el}(\bar{r})$] in the variants of hardness potential, to assess the proposed definition of $\Delta^{+}h(k) = -[V_{el}^{N+1}(k) - V_{el}^{N}(k)]$ and $\Delta^{-}h(k) = -[V_{el}^{N}(k) - V_{el}^{N-1}(k)]$.

In literature, analysis of several local indices revealed that Fukui function remains a suitable descriptor for regioselectivity,[41,46-56] but it cannot be applied to intermolecular cases due to its normalization condition or more precisely, 'intensive'[57] nature. It is worth mentioning here that local descriptors from the grand canonical ensemble should be able to predict intra as well as intermolecular reactivity because they generally possess a combination of a local and a global part [e.g., local softness: $s(\bar{r}) = f(\bar{r})S$ and philicity $\omega^{\alpha}(\bar{r}) = \omega f^{\alpha}(\bar{r}) = (\mu^2/2\eta) f^{\alpha}(\bar{r}) = \mu^2 S f^{\alpha}(\bar{r})$]. But 'intensive' nature of Fukui function $f(\bar{r})$ has made these two descriptors 'intensive' (in spite of the fact that the number of electrons and energies associated with evaluating them for intermolecular comparison are extensive) and so constrained the applicability[58-62] of these two indices as intermolecular reactivity descriptors. Also, the global softness part in these two descriptors is 'extensive', but true (unambiguously)

for a conductor. For most of the commonly used chemical systems this may not always be true. Hard-hard interaction is charge-controlled[63] and hence suitable to account for long range interactions. Hardness potential [$h(\bar{r})$] is one such descriptor whose approximated analytical form is,

$$h(\bar{r}) = \frac{10}{9} C_F \rho(\bar{r})^{2/3} - V^{el}(\bar{r}) - \frac{4}{9} C_X \rho(\bar{r})^{1/3} \tag{3.1}$$

and then it was approximated further as $h(\bar{r}) = -V_{el}(\bar{r})$, where $V_{el}(\bar{r})$ is the electronic contribution to the molecular electrostatic potential. It is worth mentioning here that complete mathematical definition of $h(\bar{r})$ requires some pretty strong approximations. The Hohenberg–Kohn functional $F[\rho]$[9,10] is approximated on the basis of Thomas–Fermi–Dirac (TFD)[67-69] approach (which has its own limitations[70]) plus the Weizsäcker[71] term, to DFT. So, basically, the universal functional of Hohenberg and Kohn is approximated by Thomas-Fermi-Dirac-Weizsäcker approach while obtaining mathematical definition of $h(\bar{r})$. One can systematically improve TFD functional by considering $\frac{1}{9}$ of the Weizsäcker functional (for gradient expansion).[71] Thus, formally, the presence of the Weizsäcker term in the kinetic energy description compensates for several of the deficiencies of the Thomas–Fermi–Dirac functional. However, it was also shown that the contribution of the Weizsäcker term to the local hardness, $\eta(\bar{r})$ [and hence to the hardness potential, $h(\bar{r})$] when density, $\rho(\bar{r})$, is used as composite function, $\lambda[\rho(\bar{r}')]$[39] is equal to zero.

Theoretical investigations are done to overcome the limitations of TFD for years. It is shown that TFD somewhat works well when the exact electron density is used to evaluate it. Burke et al.[72] have shown that the exact electronic ground-state density and external potential can be used to improve the accuracy of approximate density functional by exploiting the fact that exact exchange-correlation energy functional is more local for full-coupling strength than for the coupling-constant average and that exact virial can be used to reduce the exchange energy error by a factor of 2. To apply his 'local model' to the hardness kernel and related reactivity parameters in DFT, Fuentealba[73] used TFD approach to approximate any local functional $F[\rho]$ and also used the electron density (ρ). Using this method, all the calculated reactivity indices

are positive definite since ρ is so. Senet[74] has emphasized that in spite of several loopholes, the TF model has been 'extensively implemented by using an electronic density arising from an independent ab initio calculation.[75,76] But it is warned that TF model only yields fruitful results for a system having a relatively large number of electrons. Some desirable properties are also obtained by using TFDW Euler–Lagrange equation[3] for the ground-state electronic densities of atoms and jellium surfaces.[77-79]

Thomas-Fermi like theories supports the existence of the electrostatic potential component of the hardness kernel. But from the first derivative of Kohn-Sham kinetic energy with respect to the electron density (which emerges out to be the difference between chemical potential and effective Kohn-Sham potential), it can be demonstrated that the electrostatic term as well as exchange correlation term cancel out. Liu and Ayers[80] discussed it while showing that the functional derivative of the non-interacting kinetic energy density functional can unambiguously be represented as the negative of the Kohn–Sham effective potential, arbitrary only to an additive orbital-independent constant. However, while discussing second functional derivative of Kohn-Sham kinetic energy, Ayers has shown[81] that the derivative of the Kohn–Sham potential with respect to the electron density contains a contribution from a coulomb term (Eq. (61) of ref. 81). Here, the explicit coulomb contribution vanishes, but an implicit dependence [which is embedded in the Kohn–Sham potential derivative i. e., the first term in Eq. (61) of ref. 81] exists.

It may also be noticed that hardness potential belongs to the class of derived (arising out of more fundamental response functions and not derived from first principles) chemical reactivity descriptors. There are three types of derived chemical reactivity descriptors.[16] Some of them are derived by rigorous mathematical methods (electrophilicity,[32-35] nucleofugality,[82] electrofugality,[82] point charge response[83,84] etc), some are proposed for their easy-to-compute nature and efficiency to analyze chemical phenomena (relative nucleophilicity and electrophilicty[41,42] and leaving group indicators[85-87] etc) and some lie within these two extremes (which are mentioned as 'intermediate' such as local hardness,[8,38-40] multiphilic descriptor,[88,89] indicators associated with CDASE[90] etc). Hardness potential is also one of the "intermediate" derived chemical reactivity indicators. A close analogy to hardness potential may be found in the recent work by Ayers et. al.,[91] where they showed that local hardness emerges 'naturally' while

using variational approach to define local stability conditions for electronic states. Variational approach is also exploited to optimize the electron density or the electron number in a fixed external potential previously.[29]

Without going into the ambiguity of adopting any particular approach to DFT (i.e., either TFD or Kohn-Sham) if we define $h(\bar{r})$ as in Eq. 3.1 or its approximated form [i.e., $h(\bar{r}) = -V_{el}(\bar{r})$] then these two variants [i.e., $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$] emerge out to be two useful reactivity descriptors in their own merit. Because, then these two variants of $h(k)$ [i.e., when $\bar{r} \to 0$ in $h(\bar{r})$] can represent the reactivity of the concerned reactive atom towards an approaching nucleophile and an electrophile, respectively. Use of the difference of electrostatic potential to explain reactivity is not new in theoretical chemistry but only the new things in $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ is that here the differences of only electronic components of electrostatic potential is used (the details to be discussed in Section 3.2.B.).

Also, it is important to indicate that these two variants of hardness potential are originated (with some approximation) from hardness functional, $H[\rho]$,[66,98] which in turn belongs to grand canonical ensemble (i.e., $-H[\rho] = E - \mu N = \Omega$). Hence, in principle, they have the ability to take care of both intramolecular (i.e., site selectivity) as well as intermolecular reactivity trends, which also have been illustrated with some model systems and real examples.[65]

In the present chapter, an effort is made to rationalize relative contribution of the sum of kinetic energy $[\frac{10}{9}C_F\rho(\bar{r})^{2/3}]$ and exchange energy $[\frac{4}{9}C_X\rho(\bar{r})^{1/3}]$ terms to that of electronic contribution to the molecular electrostatic potential $[V_{el}(\bar{r})]$ while defining the working equations of $[\Delta^{+}h(k)]$ and $[\Delta^{-}h(k)]$. Discussion will also be there for considering only the electronic component, instead of taking the total (i.e., nuclear + electronic) contribution, of molecular electrostatic potential which was exploited in several other approaches.[84,99-102] Several arenes (undergoing electrophilic chlorination, nitration and benzylation) and polycyclic aromatic hydrocarbons (undergoing electrophilic bromination) as well as carboxylic acids and their derivatives have been chosen to carry out the theoretical investigations as mentioned above. Arenes and polycyclic aromatic hydrocarbons have been exploited further to study intramolecular (regioselectivity) as well as intermolecular reactivity (relative reaction rates

compared to that of benzene) using nucleophilic variant of the hardness potential [$\Delta^{-}h(k)$] (evaluated at the nucleus).

3.2. Theoretical Background:

A. Working Equations of $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$:

The analytical equations of $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$ can be written as,

$$\Delta^{+}h(\bar{r}) = N\Delta\eta^{+}(\bar{r}) \tag{3.2}$$

$$\Delta^{-}h(\bar{r}) = N\Delta\eta^{-}(\bar{r}) \tag{3.3}$$

The $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$, when evaluated at the nucleus (i.e., $\Delta^{+}h(\bar{r})\big|_{r\to 0}$ and $\Delta^{-}h(\bar{r})\big|_{r\to 0}$) of atom 'k', and denoted as $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$, respectively, can be formulated (after neglecting the kinetic and exchange energy terms in Eq. (3.1)) as[6]:

$$\Delta^{+}h(k) = -[V_{el}^{N+1}(k) - V_{el}^{N}(k)] \tag{3.4}$$

and,

$$\Delta^{-}h(k) = -[V_{el}^{N}(k) - V_{el}^{N-1}(k)] \tag{3.5}$$

Incidentally, these two approximated forms of $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$ lead, respectively, to,[6]

$$\Delta^{+}h(\bar{r}) = \int \frac{f^{+}(\bar{r}')}{|\bar{r}-\bar{r}'|}d\bar{r}' \tag{3.6}$$

and,

$$\Delta^{-}h(\bar{r}) = \int \frac{f^{-}(\bar{r}')}{|\bar{r}-\bar{r}'|}d\bar{r}' \tag{3.7}$$

where, $\int \frac{f(\bar{r}')}{|\bar{r}-\bar{r}'|}d\bar{r}'$ is Fukui potential.[56,92-97]

The fact that $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$ are related to the electronic contribution of the molecular electrostatic potential (MEP) [i. e., $V_{el}(\bar{r})$] directly (Eqs. (3.4) and (3.5)) and hence to electron density [i. e., $\rho(\bar{r})$] indirectly (Eqs. (3.6) and (3.7)), should be able to interpret reactions where both frontier molecular orbital and electrostatic control play important roles.

Normally, electronic contribution to the molecular electrostatic potential, $V_{el}(\bar{r})$, is the dominant one when compared to the other two terms (i.e., kinetic and exchange energy terms). Also, the negative sign in the exchange energy term cancels out, to some extent, the effect of the kinetic energy term[38,51,52,55,103-107] (see Eq. (3.1)). Thus, Eqs. (3.4) and (3.5) seem to provide reasonably reliable working formula of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$, respectively. Some similar kind of idea (i.e., change of kinetic energy functional equals to the negative of the sum of changes of exchange and correlation energy functionals at isodensity contours of 0.00872) was first invoked by Politzer et al.[108] when they tried to establish the relationships between atomic chemical potentials, electrostatic potentials, and covalent radii. A similar protocol was used by Liu et al.[105] while establishing a simplified model for hardness kernel, $\eta(\bar{r},\bar{r}')$. They stressed that it must be of the form, $\eta(\bar{r},\bar{r}') = \frac{1}{\left|r-r'\right|} + R(r,r')$ where the first term on the right-hand side of the above equation results from the classical Coulomb repulsion term and the second term includes contributions from the kinetic, exchange, and correlation energy functionals. Liu et al.[105] assumed that the contribution from the second term is typically small and hence $\eta(\bar{r},\bar{r}')$ got reduced to $\eta(\bar{r},\bar{r}') \approx \frac{1}{\left|r-r'\right|}$.

Contrary to all these, Jin et al.[109] have argued that the equation $\eta(\bar{r}) = \frac{-V_{el}(\bar{r})}{N}$ or $h(\bar{r}) = -V_{el}(\bar{r})$ cannot be accepted. Because most of their observations were not satisfactory at a surface of 0.001 electrons/Bohr^3 (based on the cancellation of first and third terms in the right hand side of Eq. (3.1)). In our earlier study,[6] we conjectured that the definition of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ as projected by Eqs. (3.4) and (3.5), respectively, seem to be acceptable because electron density differences (of neutral systems and its ions) at the atomic nuclei may be very small (even if not 0.001 a. u.) and thus net contribution of the first and third terms will be almost negligible. Analytically, this can be shown from the original equations[6] of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ taking into account of all three terms as below:

$$\Delta^{+}h(k) = \left[\left\{\frac{10}{9}C_F\rho(k)^{2/3} - \frac{4}{9}C_X\rho(k)^{1/3}\right\}_{N+1} - \left\{\frac{10}{9}C_F\rho(k)^{2/3} - \frac{4}{9}C_X\rho(k)^{1/3}\right\}_{N}\right] - \left[{V_{el}}^{N+1}(k) - {V_{el}}^{N}(k)\right] \tag{3.8}$$

$$\Delta^{-}h(k) = \left[\left\{\frac{10}{9}C_F\rho(k)^{2/3} - \frac{4}{9}C_X\rho(k)^{1/3}\right\}_{N} - \left\{\frac{10}{9}C_F\rho(k)^{2/3} - \frac{4}{9}C_X\rho(k)^{1/3}\right\}_{N-1}\right] - \left[{V_{el}}^{N}(k) - {V_{el}}^{N-1}(k)\right] \tag{3.9}$$

Here, the net contribution of the first four terms (i.e., the differences of kinetic and exchange energy terms) is expected to be negligible when compared to the net contribution of the last two terms (i.e., difference of $V_{el}(k)$ terms) in both the equations. The quantitative scenario will be presented in Section 3.4 (Results and Discussion) based on generated numerical values of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ of the concerned reactive centers in the chosen systems.

B. Total (i. e., $V_T = V_{nu}(\bar{r}) + V_{el}(\bar{r})$) vs electronic [i. e., $V_{el}(\bar{r})$] contribution of Molecular electrostatic potential within the context of $\Delta^{+}h(\bar{r})$ and $\Delta^{-}h(\bar{r})$:

In an earlier work,[66] Parr and Gázquez obtained an important relation,

$$H(\rho) = \frac{1}{2}\int h(\bar{r})\rho(\bar{r})d\bar{r} + \text{higher order terms} \tag{3.10}$$

Where, at large r, $h(\bar{r})$ equalizes to the classical electrostatic potential generated by the electron density ρ. Here, 'higher-order' means terms involving third and higher functional derivatives of $F[\rho]$, the so-called Hohenberg-Kohn functional[9,10] (which is the sum of kinetic energy functional $T[\rho]$ and electron-electron interaction energy functional $V_{ee}[\rho]$). Molecular electrostatic potential (MEP) has been exploited over years in the formulation of DFT-based reactivity indicators. Ayers and collaborators[84,94,95,99] showed that the effective external potential felt by an electrophile due to the presence of a nucleophile can, in principle, be calculated exactly (when the reagents are far apart, electrostatic control dominates) by involving a correction to MEP with a term which involves the nucleophilic Fukui function of the nucleophile (similar case was obtained for nucleophile in presence of an electrophile). Gadre and co-workers exploited MEP for various organic molecules.[110-116] They have developed three dimensional

characterization and topographical approaches towards MEP to explore the molecular reactivities, weak intermolecular interactions, and a variety of chemical phenomena.[110,112,113,115] Langenaeker et al[51] argued that MEP is the best reactivity indicator for comparing reactivity of different mono-substituted benzenes. But according to them, application of MEP is limited to only charge-controlled processes and it cannot be a good indicator of hardness as well. Politzer et al[117,118] showed that MEP of substituted arenes can be used to indicate the activation or deactivation of aromatic rings towards electrophilic attack. MEP is labeled as a rigorous descriptor to predict both Lewis basicity and Brønsted-Lowry basicity[119] in the study of zeolites. Several other use of MEP together with the atomic charges can be found elsewhere.[119-121] Some studies show that electrostatic potential at the nucleus is in good agreement with acidity/pKa.[122-124] More recently, it is presented that electrostatic potential at nuclei (EPN)[125-132] can correlate well to the experimental trends.

However, in almost all the studies in literature, it is a common practice to consider the overall electrostatic potential [i.e., $V_{nu}(\bar{r})+V_{el}(\bar{r})$][84,94,95,99-102,117-121,125-132] to account for different types of interactions that govern chemical reactions. Hence, it raises a question about the working formulation of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ either by using only the difference of electronic contribution to MEP (i.e., Eqns. (3.4) and (3.5)) or the difference of all the three terms (Eqns. (3.8) and (3.9)). It is worthy of mentioning here that the hardness potential arises from the second derivative of the universal Hohenberg-Kohn functional, which by definition does not contain the nuclei repulsion [i.e., the external potential is held constant in the response function, the hardness kernel $\eta(\bar{r},\bar{r}')$, itself]. Hence, only electronic part of the molecular electrostatic potential exists in the definition of hardness potential. It would be interesting to note the effect of the absence of the nuclear contribution of the electrostatic potential term in $\Delta^{+}h(k)$ or $\Delta^{-}h(k)$ in the generated trends of inter and intramolecular reactivity. Incidentally, in a recent paper,[94] *Ca′rdenas* et al. have also favored the idea that the Fukui potential at the nucleus can rationally be computed from differences of the electronic contribution to the molecular electrostatic potential of the neutral atoms and their corresponding ions.

3.3. Computational Details:

To verify quantitatively the approximation [i.e., $h(\bar{r}) = -V_{el}(\bar{r})$] used in the formulation of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ [6] and to elucidate their potency for studying some intra as well as intermolecular reactivity studies, we have chosen several model systems and classified them as Group I, Group II and Group III. Group I consists of several substituted benzenes (i.e., alkylbenznes and halobenznes) (see Table 3.1, 3.2 and 3.3) which undergo electrophilic substitutions (chlorination, nitration and benzylation are discussed here for brevity). Group II contains some polycyclic aromatic hydrocarbons (bromination is discussed in detail, see Table 3.4 and Figure 3.1). Experimental partial rate factors (of different positions of the *Ph* ring and fused rings) and relative reaction rates (of substituted benzenes and polyarenes with respect to unsubstituted benzene) were verified by $\Delta^{-}h(k)$ values. It is a test of the reliability of $\Delta^{-}h(k)$ to study inter as well as intra-molecular reactivity trends. Some electrophiles such as carboxylic acids and their derivatives (Table 3.5) are listed in Group III. Incidentally, these are part of the systems chosen in the last chapter.[6] The three series generated from these systems are given below:

(i) *H**C**OOH, CH$_3$**C**OOH, CH$_3$CH$_2$**C**OOH*

(ii) *H**C**OF, CH$_3$**C**OF, CH$_3$CH$_2$**C**OF*

(iii) *H**C**ONH$_2$, CH$_3$**C**ONH$_2$, CH$_3$CH$_2$**C**ONH$_2$*

Optimizations (neutral systems) for all the systems of the three Groups are carried out at B3LYP[133-135]/6-31G** level while the corresponding single point calculations for cations and anions are carried out at UB3LYP/6-31G** level. Also, calculations for all systems are performed in gas phase and the SCF density is used to evaluate $V_{el}(k)$ and $\rho(k)$. All computations are carried out using Gamess[136] software package.

3.4. Results and Discussion:

A. Group I: Alkylbenzenes and Halobenzenes:

(i) Intramolecular reactivity trends by $\Delta^{-}h(k)$:

To test the reliability of Eq. (3.5) as a proposed definition of $\Delta^{-}h(k)$, positional selectivity and relative rates (compared to that of benzene) of nitration, benzylation and chlorination on halobenzenes and alkylbenzenes are studied here. There are a number of earlier attempts where electrophilic substitutions on arenes are studied using reactivity indices based on density functional reactivity theory (DFRT) and other theoretical approaches.[9,51,117,118,137-149]

Normally, higher the $\Delta^{-}h(k)$ value higher should be the reactivity of that site (here atom) (similar intramolecular studies were done earlier on indolynes and unsymmetrical arynes).[6] From Table 3.1 (third column), it is evident that for chlorination of methylbenzenes, $\Delta^{-}h(k)$ of individual arenes correlated satisfactorily with experimental partial rate factors[132] in all cases. G. Koleva et. al.[132] have recently demonstrated successful use of electrophile affinity and electrostatic potential at nuclei (EPN, denoted by V_c,[150,151] reflecting the electron densities at different ring positions of arenes), which can function as an excellent local reactivity index for charge-controlled chemical interactions.[125-132] But EPN failed to produce exact intramolecular reactivity trends in some cases[132] (shown in bold in Table 3.1). The ortho position of toluene has the higher V_c (electrostatic potential at nuclei) but the reactivity ($\ln f$ value) for the para position is greater. The same irregularities exist between the 3 and 4 positions of 1,2-dimethylbenzene and the 2- and 4-positions of 1,3-dimethylbenzene (Table 3.1). Cause of these irregularities in V_c values are attributed to the ortho steric effects.[132] Because in *Ph*-ring all reactive centers (i.e., atoms) are same (i.e., carbon), V_c values reflect the variations of electron densities at particular sites and more negative the V_c value greater is the electron density, making the site more susceptible to electrophilic attack. As V_c values fail to produce expected intramolecular reactivity trends in the system as mentioned above, it is expected that $\Delta^{-}h(k)$ values will also fail. But surprisingly $\Delta^{-}h(k)$ values produce correct trends in all these systems. Naturally, the question arises why $\Delta^{-}h(k)$ is successful where V_c fails? This may be due to the fact that though $\Delta^{-}h(k)$ also takes care of only electronic effects, it does so in a unique way. It reflects how that particular reactive site responds in the changing electron density scenario in the event of an approaching electrophile, whereas V_c is all about the neutral system only. This

might be the reason why $\Delta^{-}h(k)$ values show superior intramolecular reactivity trends than those by V_c values of the atoms of the neutral system. It is worth to note that similar expected intramolecular reactivity trends are obtained from $\Delta^{-}h(k)$ values for nitration of halobenzenes[152,153] (Table 3.2, third column) and benzylation of halobenzenes[154,155] (Table 3.3, third column). From the V_c values it is obvious that although for nitration intramolecular reactivity trends are as expected (Table 3.2, sixth column), for benzylation it does not match with experimental observation for chlorobenzenes and bromobenzenes (Table 3.3, sixth column).

(ii) Intermolecular reactivity trends by $\Delta^{-}h(k)$:

The grand canonical ensemble origin of $\Delta^{-}h(k)$ [6] approves that it should, in principle, explain the intermolecular reactivity trends also. However, depending on the nature of substituents (e.g., methyl groups are electron-pushing, while halides are electron-withdrawing) interpretation of intermolecular reactivity trends will vary when $\Delta^{-}h(k)$ [or $\Delta^{+}h(k)$] are used as descriptors. Situations are further complicated when the concerned systems have two or more sites of comparatively high reactivity and also if the reactions are not single step concerted ones. In the next few paragraphs, systematic analysis of these trends are carried out.

While studying relative reaction rates[132] of alkylbenzenes compared to that of benzene by using $\Delta^{-}h(k)$), the existence of electron pushing $+I$ effect of several methyl groups (in alkylbenzenes) makes the interpretation different from intramolecular cases. It is argued in our earlier study, that for intermolecular reactivity comparison of this type of systems (where rest part of the system is electron pushing) lower the positive value of $\Delta^{-}h(k)$ higher is the nucleophilicity of the corresponding nucleophilic atom.[6] The reason is that, with increasing number of $-CH_3$ groups, the value of both $V_{el}^{N}(k)$ and $V_{el}^{N-1}(k)$ of the nucleophilic atom on the *Ph*-ring will increase. But what exactly happens is that relative increase of $V_{el}^{N-1}(k)$ is more than that of $V_{el}^{N}(k)$, which in turn, leads to lowering of $\Delta^{-}h(k)$ value. If Eq. (3.5) (or Eq. (3.9)) are examined carefully, it is revealed that the argument is justified.

In the course of studying the relative reaction rates of halobenzenes[155,156] compared to that of benzene, the presence of two opposing forces, i.e., electron-withdrawing $-I$ effect and electron pushing $+R$ effect of halo groups make the interpretation different from that of alkylbenzenes. If again we look at Eq. (3.5) (or Eq. (3.9)), it is evident that if the rest part of the system is not electron pushing (i.e. not compensating for the loss of electron to an incoming electrophile), then higher the absolute value of $\left[V_{el}{}^{N}(k) - V_{el}{}^{N-1}(k)\right]$ or $\Delta^{-}h(k)$, higher is the reactivity towards an electrophile. However, if after the attack of the electrophile the $+R$ effect dominates over the $-I$ effect then the interpretation will be as outlined in the previous paragraph (i.e., lower the positive value of $\Delta^{-}h(k)$, higher is the reactivity or vice versa).

In several earlier studies,[58-60] it was argued that these type of descriptors [e.g., local softness $s(\bar{r})$, philicity $\omega(\bar{r})$ etc, which are originated from grand canonical ensemble] can be used for intermolecular reactivity studies only in limited cases where the systems have only one predominant reactive site or sites of equal reactivity (i.e., chemically equivalent sites). Systems, in which there are more than one sites of comparable reactivity, these descriptors may not be suitable. Thus, from Table 3.1, third column, we get expected reactivity trends for almost all systems of the former type (first, fifth, sixth, seventh and eighth rows) by using Eq. (3.5). There is only one irregularity with 1,3,5-trimethylbenzene which is resolved when Eq. (3.9) is used instead of Eq. (3.5) (Table 3.1, fourth column). Here, it should be noted that discrepancy is also observed in V_c values for 1,3,5-trimethylbenzene and 1,2,4,5-tetramethylbenzene (observed value of V_c is higher for the latter which is actually less reactive, Table 3.1, sixth column).[132]

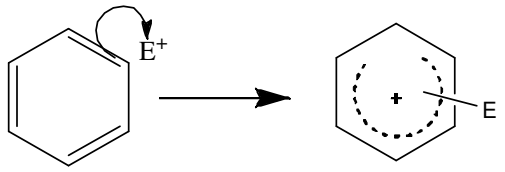
For systems with multiple reactive sites such as toluene, 1,2-dimethylbenzene and 1,3-dimethylbenzene (Table 3.1) expected intermolecular reactivity trends are obtained when the $\Delta^{-}h(k)$ values of the most reactive sites of individual systems are compared (however, trend of reactivity of these three systems cannot be compared with those having only one reactive site, as discussed in the preceding paragraph). If we consider the $\Delta^{-}h(k)$ values of position 4 (most reactive site on the basis of intramolecular study) for toluene, 1,2-dimethylbenzene and 1,3-dimethylbenzene (Table 3.1, third and fourth columns) it is observed that lower is the value, higher is the reactivity (as per discussion in paragraph 2 above in this Section). Here, it is

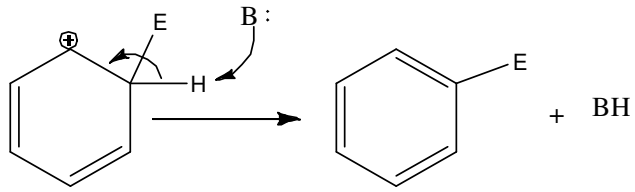
important to note that 1,3-dimethylbenzene (m-xylene) is the highest reactive among all xylenes. Kobe et al.[157] suggested that in m-xylene, the two methyl groups strengthen one another in their activation of the ring. But in 1,2-dimethylbenzene (o-xylene) and 1,4-dimethylbenzene (p-xylene), the methyl groups cancel the ring activation to some extent.

If we look at position 4 (most reactive site on the basis of intramolecular study) of halobenzenes, (Table 3.2 and 3.3, third and fourth columns) expected results are obtained (as per discussion in paragraph 3 above) except for bromobenzene. However, as Br is a heavy atom, use of higher basis set may correct the anomaly. It is worth mentioning here that due to the presence of two opposing forces, i.e., *–I* effect and *+R* effect, reactivity trends of halobenzenes are ambiguous and also depend on the type of reactions.[158] However, what apparently seems from the correlation of $\Delta^{-}h(k)$ values with the experimental relative reaction rate data is that *+R* effect is a stronger operating force than *–I* effect in the process of an electrophilic attack on halobenzenes. That might be the reason why $\Delta^{-}h(k)$ values (of the strongest reactive sites) increase (again except for bromobenzene) as the relative rate of nitration and benzylation decrease. This argument is more justified because electrophilic aromatic substitution is a two-step process and passes through a positively charged σ-complex (see the mechanism below).

It should be stressed that $\Delta^{-}h(\bar{r})$ is based on electrostatic potential (in spite of the fact that only electronic component is present here) and so, hopefully, can take care of long range interactions (intermolecular) more accurately. This may be the probable reason why $\Delta^{-}h(k)$ can predict intermolecular reactivity trends of the systems those are discussed so far.

The general mechanism of electrophilic aromatic substitution is as shown below:[158]

1. 

2. 

where, E^+ is the electrophile involved and B is a nucleophile / base.

Electrophilic aromatic substitution is a two-step reaction. In the first step a π-complex and then a σ-complex formation takes place. As this step involves the loss of aromaticity, it is the slowest, i. e, the rate-determining one. The second step involves the elimination of H^+ from the intermediate σ-complex by a base / nucleophile. In an earlier study, Bagaria and Roy[62] demonstrated that in multistep reactions electrophilicity / nucleophilcity of the starting substrate may not always provide reliable information on the overall rate of the reaction. Similar arguments will hold for intermolecular comparison of reaction rates on the basis of most reactive site of the individual species (when systems have multiple sites of comparable reactivity). However, for the reaction chosen in the present study, the first step is the rate-determining one. Hence higher nucleophilicity of the substrate will favor the first step as well as the overall rate of the reaction. That might be the probable reason why $\Delta^- h(k)$ is able to produce expected trends for reactivity for most of the chosen systems though electrophilic aromatic substitution is not a single-step concerted reaction.

Group II: Polycyclic Aromatic Hydrocarbons (PAHs):

The reactivity of alkylbenzenes and halobenzenes may be solely explained on the basis of resonance theory due to their structural simplicity. To test the efficacy of Eq. (3.5) as a proposed definition of $\Delta^- h(k)$, positional selectivity and relative rates (compared to that of benzene) of bromination of polycyclic aromatic hydrocarbons (which are structurally as well as mechanistically more complex systems compared to simple arenes) are studied here. Some of the earlier theoretical approaches which are exploited to study electrophilic substitution on polycyclic aromatic hydrocarbons, are based on MO reactivity parameters[159-162] and electrophile affinity.[163]

The chosen polycyclic aromatic hydrocarbons have only one predominant reactive site (experimentally found for bromination) except for naphthalene which has two reactive sites (of comparable strength) and reactivity of position 1 is higher than that of position 2. In section 3.4. A. (i) it is discussed that higher the $\Delta^- h(k)$ value higher should be the reactivity of that site (here atom) within a molecule (intramolecular). Here, in case of naphthalene also it is observed

that the $\Delta^{-}h(k)$ value of position 1 is higher than that of position 2 (Table 3.4, third column) i. e., position 1 is more reactive compared to position 2.

Also, as per discussion in section 3.4.A.(ii) (fourth paragraph), $\Delta^{-}h(k)$ can be safely applied to systems with single predominant reactive sites to study relative reaction (in this case bromination) rates (i.e., intermolecular reactivity). But the interpretation will be different from intramolecular cases. Here, five or six membered fused rings adjacent to the reactive sites in polycyclic aromatic hydrocarbons are neither electron-withdrawing nor electron releasing. However, variation of the electron pushing power (after the electrophilic attack) of the rest part of the molecule in different PAHs will be reflected in the generated $\Delta^{-}h(k)$ values. From Table 4, third column, we get expected reactivity trends for almost all systems, except for fluorene, pyrene and acenaphthene (for naphthalene, the value of most reactive site i. e., position 1 is considered). The bromination of PAHs are carried out experimentally in different concentrations of aqueous acetic acid for different systems. In the present study, theoretical calculations are performed in gas phase. This may be one of the probable reasons for the irregular reactivity trends in some cases generated by $\Delta^{-}h(k)$ values. Also, some of the PAHs undergo substantial amount of addition reaction apart from substitution ones. Both the types of reaction involve the same transition state[162] and the ratios of substitution vs. addition reaction also vary from one system to the other. While the experimental values of relative rates are for substitution only the calculated values of $\Delta^{-}h(k)$ represent the overall reactivity. This also makes the comparison of $\Delta^{-}h(k)$ values with experimental relative rates of bromination more complicated and inconclusive.

B. Relative contributions of the sum of kinetic and exchange energy terms to that of the electronic component of the molecular electrostatic potential in $\Delta^{-}h(k)$:

Upto this point, intra and intermolecular reactivity trends of the chosen systems towards electrophilic attacks on them are analyzed. However, the prime objective of the present study is to test the reliability of the approximated forms of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ (Eqs. (4) and (5)). So, the

relative contributions of the sum of kinetic $\left[\frac{10}{9}C_F\rho(\bar{r})^{2/3}\right]$ and exchange energy $\left[\frac{4}{9}C_X\rho(\bar{r})^{1/3}\right]$ terms and electronic part of the molecular electrostatic potential $[V_{el}(\bar{r})]$, as indicated in Eq. (3.9) are shown separately [Table 3.1, 3.2, 3.3 and 3.4]. If the numerical values in the third and fifth columns of these tables are compared, it is evident that the net contribution of the first four terms (i.e., kinetic and exchange energy terms) is negligible when compared to the net contribution of the last two terms in Eq. (3.9). Moreover, if we consider all the three terms (i.e., kinetic energy, $V_{el}(\bar{r})$ and exchange energy, [Eq (3.9)] or only the $V_{el}(\bar{r})$ [Eq. (3.5)] while generating $\Delta^{-}h(k)$ values, in both the cases predicted reactivity trends do not vary much from each other (Table 3.1, 3.2, 3.3 and 3.4, third and fourth columns). It encourages us to argue that Eq. (3.5) is a reasonable approximation to Eq. (3.9) in the formulation of variants of hardness potential.

C. Relative contributions of the sum of kinetic and exchange energy terms to that of the electronic part of the molecular electrostatic potential in $\Delta^{+}h(k)$:

To validate the ability of the approximated form (Eq. (3.4) as a working Eq. of $\Delta^{+}h(k)$, carboxylic acids and their derivatives have been chosen as electrophilic systems (i.e., systems belonging to group III). The relative contributions of the sum of kinetic $\left[\frac{10}{9}C_F\rho(\bar{r})^{2/3}\right]$ and exchange energy $\left[\frac{4}{9}C_X\rho(\bar{r})^{1/3}\right]$ terms and the electronic part of the molecular electrostatic potential $[V_{el}(\bar{r})]$, as formulated in Eq. (3.8), are shown in Table 3.5, (second and fourth columns). If the numerical values are compared, it is clear that the net contribution of the first four terms (i.e., kinetic and exchange energy terms) is not always negligible when compared to the net contribution of the last two terms in Eq. (3.8). However, it is gratifying to note that intermolecular reactivity trends generated by $\Delta^{+}h(k)$ values using Eqs. (3.4) and (3.8) do not vary much from each other (Table 3.5, second and third columns). Here, the strategy adopted to

interpret intermolecular reactivity trends using $\Delta^{+}h(k)$ is that, higher is the value of $\Delta^{+}h(k)$, higher is the reactivity.[6]

3.5. Conclusion:

The primary theme of the present chapter is to assess formally, as well as computationally, the relative contribution of the sum of kinetic and exchange energy terms to that of the electronic part of molecular electrostatic potential in the working equations of the variants of hardness potential [i.e., $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$]. The reason behind considering only the electronic part of molecular electrostatic potential, unlike many other approaches where total electrostatic potential i.e., both electronic and nuclear components are used, is also addressed. It is worth mentioning here that reactivity trends generated by $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ are in good agreement with experimental ones, even though $V_{nu}(\bar{r})$ part is absent in the definition (i.e., Eqs. (3.4) and (3.5) or Eqs. (3.8) and (3.9) of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$.

While, the net contribution of the sum of kinetic [$\frac{10}{9}C_F\rho(\bar{r})^{2/3}$] and exchange energy [$\frac{4}{9}C_X\rho(\bar{r})^{1/3}$] terms is found to be negligible when compared to that of electronic contribution to the molecular electrostatic potential [$V_{el}(\bar{r})$] [Eq. (9) and Table 3.1, 3.2, 3.3 and 3.4] for systems like substituted benzenes and polycyclic aromatic hydrocarbons, this is not the case for systems like carboxylic acids and their derivatives (Eq. (3.8) and Table 3.5). So, it may be broadly concluded that depending on the type of systems, the net contribution of the sum of the kinetic and exchange energy terms may or may not be negligible when compared to that of $V_{el}(\bar{r})$. Thus, to be on the safer side, it is better to use all the three terms i.e., Eqs. (3.8) and (3.9) in place of Eqs. (3.4) and (3.5), respectively. Incidentally the values of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ (wherever applicable), generated by the two approaches on the chosen systems maintain mostly identical trends which again are as per experimental observation in majority of cases.

While $\Delta^{-}h(k)$ is able to reproduce experimental trends for site-selectivity for almost all alkylbenzenes, halobenzenes and polycyclic aromatic hydrocarbons in electrophilic aromatic

substitution, it is observed that intramolecular reactivity trends for toluene, 1,2-dimethylbenzene and 1,3 dimethylbenzene (where ortho steric effects should be dominant) were also satisfactorily predicted by $\Delta^{-}h(k)$. This latter observation is particularly encouraging because earlier study using total electrostatic potential at the nucleus (EPN) could not produce experimental trends.[132] The success of $\Delta^{-}h(k)$ in generating expected reactivity trends is attributed to the fact that it can take care of the changing electron density scenario when the electrophile approaches towards the nucleophilic system of interest.

In an earlier study,[62] it was also argued that these type of descriptors can be reliably used only for reactions which are single step concerted ones and not always for multi-step ones. Similar logic can be applied to intermolecular comparison of reaction rates on the basis of reactivity of the most reactive site in individual species (when systems have multiple sites of comparable, but not equal reactivity). Although electrophilic aromatic substitutions are multistep processes, the first step itself is the rate-determining one. Hence, $\Delta^{-}h(k)$ can predict expected reaction rates.

Finally, on the basis of 'the most reactive site' model of the individual species, $\Delta^{-}h(k)$ and $\Delta^{+}h(k)$ can generate satisfactory intermolecular reactivity trends for most of the chosen systems having multiple sites of comparable (but not equal) reactivity. The probable reason of this success is that these descriptors are based primarily on electrostatic potential, which can take care of large distance effects and so the intermolecular reactivity.

References and Notes

1. R. G. Parr and J. L. Gázquez, *J. Phys. Chem*., **1993,** *97*, 3939.
2. M. Berkowitz, S. K. Ghosh and R. G. Parr, *J. Am. Chem. Soc*., **1985,** *107*, 6811.
3. S. K. Ghosh and M. Berkowitz, *J. Chem. Phys*., **1985,** *83*, 2976.
4. R. G. Parr, R. A. Donnelly, M. Levy and W. E. Palke, *J. Chem. Phys*., **1978,** *68,* 3801.
5. P. Geerlings, F. De Proft and W. Langenaeker, *Chem. Rev*., **2003,** *103,* 1793.
6. S. Saha, R. Bhattacharjee and R. K. Roy, *J. Comp. Chem.,* **2013,** *34***,** 662.
7. J. L. Gázquez, *J. Mex. Chem. Soc*., **2008,** *52*, 3.
8. R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc*., **1983**, *105*, 7512.
9. P. Hohenberg and W. Kohn, *Phys. Rev. B, **1964**, 136,* 864.
10. W. Kohn and L. Sham, *Phys. Rev. A,* **1965,** *140,* 1133.
11. R. G. Parr and W. Yang, *J. Am. Chem. Soc*., **1984,** *106*, 4049.
12. W. Yang, R. G. Parr, and R. Pucci, *J. Chem. Phys*., **1984,** *81,* 2862.
13. R. G. Parr, *Annu. Rev. Phys. Chem*., **1983**, *34*, 631.
14. W. Yang and R. G. Parr, *Proc. Natl. Acad. Sci. U.S.A*. **1985,** *82*, 6723.
15. R. G. Parr and W. Yang, Density–Functional Theory of Atoms and Molecules; Oxford University Press: New York, **1989**.
16. P. A. Johnson, L. J. Bartolotti, P.W. Ayers, T. Fievez and P. Geerlings, Charge Density and Chemical Reactivity: A Unified View from Conceptual DFT". In Modern Charge Density Analysis. Gatti, C.; Macchi, P., Eds. Springer: New York, **2012**; pp 715.
17. S. B Liu., *Acta Physico-Chimica Sinica,* **2009**, *25*, 590.
18. R. T. Sanderson, *Science.,* **1951**, *114,* 670.
19. R. G. Pearson, Hard and Soft Acids and Bases. *J. Am. Chem. Soc.,* **1963,** *85,* 3533.
20. R. G. Pearson, *J. Chem. Educ.,* **1987,** *64,* 561.
21. R. G. Pearson, *Chemical Hardness:Applications from Molecules to Solid;* Wiley-VCH, Oxford, **1997**.
22. P. K. Chattaraj, H. Lee, and R. G. Parr, *J. Am. Chem. Soc*., **1991**, *113*, 1855.
23. P. W. Ayers, Faraday Discuss., **2007**, *135*, 161.
24. P. W. Ayers, R. G. Parr and R. G. Pearson, *J. Chem. Phys*., **2006**, *124*, 194107.

25. P. W. Ayers, *J. Chem. Phys*., **2005**, *122*, 141102.

26. R. G. Parr and P. K. Chattaraj, *J. Am. Chem. Soc.*, **1991,** *113,* 1854.

27. M. Torrent-Sucarrat, J. M. Luis, M. Duran and M. Solà, *J. Am. Chem. Soc.*, **2001,** *123,* 7951.

28. R. G. Pearson, *J. Chem. Educ*., **1999,** *76,* 267.

29. P. W. Ayers and R. G. Parr, *J. Am. Chem. Soc*., **2000**, *122*, 2010.

30. P. K. Chattaraj, P. W. Ayers and J. Melin, *Phys. Chem. Chem. Phys*., **2007**, *9*, 3853.

31. P. K. Chattaraj and P. W. Ayers, *J. Chem. Phys*., **2005**, *123*, 086101.

32. R. G. Parr, L. Szentpàly and S. Liu, *J. Am. Chem. Soc*., **1999,** *121,* 1922.

33. A. T. Maynard, M. Huang, W. G Rice and D. G. Covell, *Proc. Natl. Acad. Sci. U. S. A*., **1998,** *95,* 11578.

34. P. Pérez*,* A. Torro-Labbé, A. Aizman *and* R. Contreras, *J. Org. Chem.* **2002**, *67*, 4747.

35. P. K. Chattaraj, U. Sarkar and D. R. Roy, *Chem. Rev*., **2006**, *106*, 2065.

36. W. Yang and W. Mortier, *J. Am. Chem. Soc.,* **1986**, *108*, 5708.

37. P. W. Ayers and M. Levy, *Theor. Chem. Acc*., **2000**, *103*, 353.

38. S. K. Ghosh and M. Berkowitz, J. Chem. Phys., **1985**, *83*, 2976.

39. P. K. Chattaraj, D. R. Roy, P. Geerlings, and M. Torrent-Sucarrat, Theor. Chem. Acc., **2007**, *118*, 923.

40. P. W. Ayers and R. G. Parr, J. Chem. Phys., **2008**, *128*, 184108.

41. R. K. Roy, S. Krishnamurti, P. Geerlings and S. Pal, *J. Phys. Chem. A,* **1998**, *102*, 3746.

42. R. K. Roy, F. De Proft and P. Geerlings, *J. Phys. Chem. A,* **1998,** *102,* 7035.

43. P. K. Chattaraj, B. Maiti and U. Sarkar, *J. Phys. Chem. A,* **2003***, 107*, 4973.

44. M. Berkowitz and R. G. Parr, *J. Chem. Phys*., **1988,** *88*, 2554.

45. R. F. Nalewajski, *J. Phys. Chem.,* **1985,** *89,* 2831.

46. H. Hirao, T. Ohwada, *J. Phys. Chem. A,* **2005,** *109,* 816.

47. C. Morell, A. Grand and A. Toro-Labbé, *J. Phys. Chem. A,* **2005,** *109,* 205.

48. S. Damoun, G. Van de Woude, F. Méndez and P. Geerlings, *J. Phys. Chem. A,* **1997**, *101*, 886.

49. F. A. Bulat, E. Chamorro, P. Fuentealba and A. Toro-Labbé, *J. Phys. Chem. A,* **2004**, *108*, 342.

50. F. Gilardoni, J. Weber, H. Chermette and T. R. Ward, *J. Phys. Chem. A,* **1998,** *102,* 3607.

51. W. Langenaeker, F. De Proft and P. Geerlings, *J. Phys. Chem,* **1995**, *99,* 6424.

52. M. Torrent-Sucarrat, P. Salvador, P. Geerlings and M. Solà, *J. Comput. Chem*., **2007,** *28*, 574.

53. P. Mignon, S. Loverix, F. De Proft and P. Geerlings, *J. Phys. Chem. A,* **2004,** *108,* 6038.

54. M Torrent–Sucarrat, J. M. Luis, M. Duran and M. Solà, *J. Mol. Struct. (Theochem),* **2005,** *727,* 139.

55. M. Torrent-Sucarrat and P. Geerlings, *J. Chem. Phys*., **2006,** *125,* 244101.

56. M. Torrent-Sucarrat, F. De Proft, P. Geerlings, P. W. Ayers, *Phys. Chem. Chem. Phys.,* **2010**, *12*, 1072.

57. P. W. Ayers, C. Morell, F. De Proft and P. Geerlings, *Chem.–Eur. J*., **2007,** *13,* 8240.

58. R. K. Roy, *J. Phys. Chem. A,* **2004,** *108,* 4934.

59. R. K. Roy, V. Usha, J. Paulovic and K. Hirao, *J. Phys. Chem. A,* **2005,** *109,* 4601.

60. R. K. Roy, V. Usha, B. K. Patel and K. Hirao, *J. Comput. Chem*., **2006,** *27,* 773.

61. R. K. Roy, P. Bagaria, S. Naik, V. Kavala and B. K. Patel, *J. Phys. Chem. A,* **2006,** *110,* 2181.

62. P. Bagaria and R. K. Roy, *J. Phys. Chem. A,* **2008,** *112,* 97.

63. G.Klopman, *J. Am. Chem. Soc*., **1968,** *90,* 223.

64. S. Saha and R. K. Roy, *Phys. Chem. Chem. Phys*., **2008**, *10*, 5591.

65. R. Bhattacharjee and R. K. Roy, *J. Phys. Chem. A.*, 2013, **117**, 11528.

66. R. G. Parr and J. L. Gázquez, *J. Phys. Chem.*, 1993, **97,** 3939.

67. L. H. Thomas, *Proc. Cambridge Philos. Soc*., **1927**, *23*, 542.

68. E. Z. Fermi, Z. *Phys*., **1928**, *48*, 73.

69. P. A. M. Dirac, *Proc Cambridge Philos*. Soc., **1930**, *26*, 376.

70. E. H. Lieb, *Rev. Mod. Phys.,* **1981**, *53*, 603.

71. C. F. von Weizsäcker, *Z. Physik,* **1935**, *96*, 431. In German

72. K. Burke, J. P. Perdew and M. Levy, *Phys Rev. A,* **1996,** *53*, 2915.

73. P. Fuentealba, *J. Chem. Phys*., **1995,** *103*, 6571.

74. P. Senet, *J. Chem. Phys*., **1996,** *105*, 6471.

75.Y. S. Kim and R. G. Gordon, *J. Chem. Phys*., **1974,** *60,* 1842.

76. R. K. Pathak, B.S. Sharma and A. J. Thakkar, *J. Chem. Phys*., **1986**, *85,* 958.

77. A. Scheidmann and R. M. Dreizler, *Z. Phys.,* **1986,** *D 2,* 43**.** see references therein.

78. J. R. Smith, *Phys. Rev*., **1969,** *181,* 522.

79. A. Chizmeshya and E.Zaremba, *Phys. Rev. B.,* **1988***, 37*, 2805.

80. S. Liu and P. W. Ayers, *Phys Rev. A.,* **2004,** *70*, 022501.

81. P. W. Ayers, *Theor. Chem. Acc.,* **2001,** *106*, 271.

82. P. W. Ayers, J. S. M. Anderson, J. I. Rodriguez and Z. Jawed, Z., *Phys Chem Chem Phys.,* **2005**, *7*, 1918.

83. A. Cedillo, R. Contreras, M. Galvan, A. Aizman, J. Andres and V. S. Safont, *J. Phys Chem A.,* **2007,** *111,* 2442.

84. P. W. Ayers and R. G. Parr, *J. Am. Chem. Soc,* **2001**, *123,* 2007.

85. P. R. Campodonico, A. Aizman and R. Contreras, *Chem Phys Lett.,* **2006,** *422*, 340.

86. P. R. Campodonico, J. Andres, A. Aizman and R. Contreras, *Chem Phys Lett.,* **2007,** *439*, 177.

87. P. R. Campodonico, C. Perez, M. Aliaga, M. Gazitua, and R. Contreras, *Chem Phys Lett.,* **2007,** *447*, 375.

88. J. Padmanabhan, R. Parthasarathi, M. Elango, V. Subramanian, B. S. Krishnamoorthy, S. Gutierrez-Oliva, A. Toro-Labbé, D. R. Roy and P. K. Chattaraj, *J. Phys. Chem. A.,* **2007,** *111*, 9130.

89. J. Padmanabhan, R. Parthasarathi, V. Subramanian, and P. K. Chattaraj, *J. Phys. Chem. A.,* **2006,** *110*, 2739.

90. P. Bagaria, S. Saha, S. Murru, V. Kavala, B. K. Patel and R. K. Roy, *Phys Chem. Chem. Phys.,* **2009,** *11*, 8306.

91. P. W. Ayers, S. B. Liu and T. L. Li, *Phys. Chem. Chem. Phys.,* **2011**, *13*, 4427.

92. M. Berkowitz, *J. Am. Chem. Soc*., **1987,** *109*, 4823.

93. M. Torrent-Sucarrat, F. De Proft, P. Geerlings and P. W. Ayers, *Chem. - Eur. J*., **2008,** *14*, 8652.

94. C. Cárdenas, W. Tiznado, P. W. Ayers and P. Fuentealba, *J. Phys. Chem. A.,* **2011,** *115*, 2325.

95. C. Cárdenas, *Chem. Phys. Lett*., **2011,** *513*, 127.

96. P. Senet, *J. Chem. Phys.,* **1997**, *107*, 2516.

97. P. Senet, *Chem. Phys. Lett.,* **1997,** *275*, 527.

98. J. L. Gázquez,. in Struct. Bonding; K. D. Sen, Ed.; Springer Verlag: Berlin, Vol. *80* pp. 27. **1993.**

99. P. W. Ayers, *J. Chem. Phys*., **2000,** *113,* 10886.

100. J. S. M. Anderson and P. W Ayers, *Phys. Chem. Chem.Phys*., **2007,** *9,* 2371.

101. J. S. M. Anderson, J. Melin and P. W Ayers, *J. Chem. Theory Comput*., **2007,** *3*, 358.

102. J. S. M. Anderson, J. Melin and P. W. Ayers, *J. Chem. Theory Comput*., **2007,** *3,* 375.

103. In the literature several authors have shown that the Coulomb term is usually dominant[38,51,104-106] in the evaluation of local hardness, although the kinetic term is not negligible and can be compared to Coulomb term.[52,55]

104. P. K. Chattaraj, A. Cedillo and R. G. Parr, *J. Chem. Phys.,* **1995,** *103*, 10621.

105. S. Liu, F. De Proft and R. G. Parr, *J. Phys. Chem. A ,* **1997,** *101*, 6991.

106. L. F. Pacios, *Chem. Phys. Lett.,* **1997,** *276*, 381.

107. A. Borgoo, M. Torrent-Sucarrat, F. De Proft and P. Geerlings, *J. Chem. Phys*., **2007,** *126*, 234104.

108. P. Politzer, R. G. Parr and D. R. Murphy, *J. Chem. Phys*., **1983,** *79*, 3859.

109. P. Jin, J. S. Murray and P. Politzer, *Comp Lett*., **2007,** *3,* 373.

110. S. R. Gadre and C. H. Suresh, *J. Org. Chem.,* **1997,** *62,* 2625.

111. C. H. Suresh, N. Koga and S. R. Gadre, *J. Org. Chem.,* **2001,** *66,* 6883.

112. S. R. Gadre, S. A. Kulkarni and I. H. Shrivastava, *J. Chem. Phys.,* **1992,** *96*, 5253.

113. R. N. Shirsat, S. V. Bapat and S. R. Gadre, *Chem. Phys. Lett*., **1992**, *200*, 373.

114. G. Mehta, G. Gunasekaran, S. R. Gadre, R. N. Shirsat, B. Ganguly and J. Chandrasekhar, *J. Org. Chem.*. **1994,** *59,* 1953.

115. S. R. Gadre and S. S. Pundlik, *J. Am. Chem. Soc*., **1995,** *117,* 9559.

116. S. P. Gejji, C. H. Suresh, L. J. Bartolotti and S. R. Gadre, *J. Phys. Chem. A,* **1997**, *101,* 5678.

117. P. Politzer, L. Abrahmsen and P. Sjoberg, *J. Am. Chem. Soc*., **1984,** 106, 855.

118. P. Politzer, K. Jayasuriya, P. Sjoberg, P and P. R. Laurence, *J. Am. Chem. Soc*., **1985,** *107*, 1174.

119. P. Mignon, P. Geerlings and R. A. Schoonheydt, *J. Phys. Chem. C,* **2007,** *111,* 12376.

120. P. Geerlings, A. M. Vos and R. A. Schoonheydt, *J. Mol. Struct (THEOCHEM),* **2006,** *762*, 69.

121. P. Mignon, P. Geerlings and R. A. Schoonheydt, *J. Phys. Chem. B,* **2006,** *110,* 24947.

122. S. B.Liu, C. K. Schauer and L. G. Pedersen, *J. Chem. Phys*., **2009**, *131*, 164107.

123. S. B. Liu and L. G. Pedersen, *J. Phys. Chem. A.,* **2009**, *113*, 3648.

124. S. K. Burger, S. B. Liu and P. W. Ayers, *J. Phys. Chem. A.* ,**2011**, *115*, 1293.

125. P. Bobadova-Parvanova and B. Galabov, *J. Phys. Chem. A,* **1998**, *102,* 1815.

126. B. Galabov and P. Bobadova-Parvanova, *J. Phys. Chem. A,* **1999,** *103,* 6793.

127. V. Dimitrova, S. Ilieva and B. Galabov, *J. Phys. Chem. A,* **2002,** *106,* 11801.

128. B. Galabov, D. Cheshmedzhieva, S. Ilieva and B. Hadjieva, *J. Phys. Chem. A,* **2004,** *108,* 11457.

129. B. Galabov, S. Ilieva, B. Hadjieva, Y. Atanasov and H. F. Schaefer, *J. Phys. Chem. A,* **2008,** *112,* 6700.

130. B. Galabov, V. Nikolova, J. J. Wilke, H. F. Schaefer and W. D. Allen, *J. Am. Chem. Soc.,* **2008,** *130*, 9887.

131. B. Galabov, S. Ilieva and H. F. Schaefer, *J. Org. Chem.,* **2006,** *71,* 6382.

132. G. Koleva, B. Galabov, J. I. Wu, J., H. F. Schaefer and P. von R. Schleyer, *J. Am. Chem. Soc.,* **2009**, *131,* 14722.

133. A. D. Becke, *J. Chem. Phys.,* **1993,** *98*, 5648.

134. A. D. Becke, *Phys. ReV. A,* **1988**, *38,* 3098.

135. C. Lee, W. Yang and R. G. Parr, *Phys. ReV. B* ,**1988**, *37,* 785.

136. M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Natsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem.,* **1993**, *14*, 1347.

137. N. D. Epiotis and S. Shaik, *J. Am. Chem. Soc.,* **1978**, *100*, 29.

138. A. Streitwieser, A. Lewis, A. Schwager, R. W. Fish and S. Labana, *J. Am. Chem. Soc.,***1970**, *92*, 6525.

139. D. Z. Wang and A. Streitwieser, *Theor. Chem. Acc.,* **1999**, *102*, 78.

140. A. M. Vos, K. H. L. Nulens, F. De Proft, R. A. Schoonheydt and P. Geerlings, *J. Phys. Chem. B,* **2002**, *106*, 2026.

141. W. J. Hehre and P. C. Hiberty, *J. Am. Chem. Soc.,* **1974**, *96*, 7163.

142. J. M. McKelvey, S. Alexandratos, A. Streitwieser, J. L. M. Abboud and W. J. Hehre, *J. Am. Chem. Soc.,* **1976**, *98*, 244.

143. R. F. W. Bader and C. Chang, *J. Phys. Chem.,* **1989**, *93*, 2946.

144. Z. Zhou and R. G. Parr, *J. Am. Chem. Soc.,* **1990**, *112*, 5720.

145. Y. Osamura, K. Terada, Y. Kobayashi, R. Okazaki and Y. Ishiyama, *J. Mol. Struct.,* **1999**, *461*, 399.

146. F. Fuster, A. Sevin and B. Silvi, *J. Phys.Chem. A,* **2000**, *104*, 852.

147. H. Hirao and T. Ohwada, *J. Phys. Chem. A,* **2003**, *107*, 2875.

148. A. R. Reddy, G. Fridman-Marueli and M. Bendikov, *J. Org. Chem.,* **2007**, *72*, 51.

149. K. Fukui, T. Yonezawa and H. Shingu, *J. Chem. Phys.,* **1952**, *20*, 722.

150. E. B. Wilson, *J. Chem. Phys*., **1962,** *36,* 2232.

151. P. Politzer, In Chemical Applications of Atomic and Molecular Electrostatic Potentials; P. Politzer, P., D. G. Truhlar, Eds.; Plenum Press: New York, **1981**; pp 7.

152. H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.,* **1962,** *84,* 3298.

153. A. D. Mésure and J. G Tillett,. *J. Chem. Soc. (B),* **1966,** 669.

154. G. A. Olah, S. J. Kuhn and S. H. Flood, *J. Am. Chem. Soc*., **1962,** *84*, 1688.

155. G. A. Olah, S. J. Kuhn and S. H. Flood, *J. Am. Chem. Soc*., **1962,** *84,* 1695.

156. G. A. Olah, S. J. Kuhn and S. H. Flood, *J. Am. Chem. Soc.,* **1961,** *83,* 4581.

157. K. A. Kobe and H. M. Brennecke, *Ind. Eng. Chem.,* **1954,** *4*6, 728.

158. J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry;* 2nd Ed, Oxford University Press: New York, **2012**.

159. M. J. S Dewar, T. Mole and E. W. T. Warford, *J. Chem. Soc.,* **1956,** 3581.

160. M. J. S Dewar and T. Mole, *J. Chem. Soc.,* **1957**, 342.

161. S. F. Mason, *J. Chem. Soc.,* **1959,** 1233.

162. L. Altschuler and E. Berliner *J. Am. Chem. Soc*., **1966**, *88,* 5837.

163. B. Galabov, G. Koleva, G.; H. F. Schaefer and P. von. R. Schleyer, *J. Org. Chem*., **2010**, *75,* 2813.

Table 3.1: Values of $\Delta^{-}h(k)$ (using Eg. (3.5)), $\Delta^{-}h(k)$ (using Eq. (3.9)), sum of (kinetic and exchange) energy terms, V_c, $\ln f$ and rates of chlorination (relative to that of benzene) for Methyl Arenes at B3LYP/6-31G(D,P) level.

Systems for Chlorination	Position of attachment of electrophile	$\Delta^{-}h(k)$ (a. u.) using, $V_{el}(\bar{r})$ (Eq. 5)	$\Delta^{-}h(k)$ (a. u.) using, three terms (Eq. 9)	(Kinetic + Exchange) energy terms (a. u.)	V_c [a] (volts)	$\ln f$ [b]	Relative Rate[c]
1. benzene	1	0.258	0.242	-0.016	-1.069	0.0	1
2. toluene[d]	2 4	0.214 0.258	0.197 0.209	-0.017 -0.049	-1.225 -1.210	6.4 6.7	340
3. 1,2-dimethyl-benzene[d]	3 4	0.207 0.229	0.196 0.208	-0.011 -0.021	-1.310 -1.298	7.9 8.2	2030
4. 1,3-dimethyl-benzene[d]	2 4	0.154 0.199	0.194 0.205	0.040 0.006	-1.372 -1.359	12.6 12.9	180000
5. 1,4-dimethyl-benzene	2	0.215	0.201	-0.014	-1.307	8.0	2000
6. 1,3,5-trimethyl-benzene	2	0.238	0.188	-0.052	-1.500	17.9	30000000
7. 1,2,4,5-tetramethyl-benzene	3	0.194	0.195	0.001	-1.521	15.4	1580000
8. pentamethyl-benzene	6	0.191	0.192	0.001	-1.686	20.5	134000000

a. V_c is the electrostatic potential at the reacting carbon atom.[132]

b. Logarithm of partial rate factors ' f '(i.e., $\ln f$) values were taken from Ref. 132. The positive values indicate that the ring is activated (due to the presence of methyl groups) in alkylbenzenes w.r.t benzene.

c. Taken from Ref.132.

d. Systems where EPN failed but $\Delta^{-}h(k)$ produced correct reactivity trends are shown in bold.

Table 3.2: Values of $\Delta^{-}h(k)$ (using Eq. (3.5)), $\Delta^{-}h(k)$ (using Eq. (3.9)), sum of (kinetic and exchange) energy terms, V_c, $\ln f$ and rates of nitration (relative to that of benzene) for halobenzenes at B3LYP/6-31G(D,P) level.

Systems for Nitration	Position of attachment of electrophile	$\Delta^{-}h(k)$ (a. u.) using, $V_{el}(\bar{r})$ (Eq. 5)	$\Delta^{-}h(k)$ (a. u.) using, three terms (Eq. 9)	(Kinetic +Exchange) energy terms (a. u.)	V_c [a] (volts)	$\ln f$ [b]	Relative Rate[c]
1. benzene	1	0.258	0.242	-0.016	-1.069	0.0	1
2. fluorobenzene	4	0.264	0.227	-0.037	-0.869	-0.3	0.45
3. chlorobenzene	3	0.193	0.203	0.010	-0.672	-7.1	0.14
	4	0.269	0.227	-0.042	-0.768	-2.0	
4. bromobenzene	3	0.203	0.193	-0.010	-0.699	-6.9	0.12
	4	0.230	0.197	-0.033	-0.817	-2.3	

a. V_c is the electrostatic potential at the reacting carbon atom.[132]

b. Logarithm of partial rate factors 'f' (i.e., $\ln f$) values were taken from Ref 132. The negative values in halobenzenes (due to the presence of halides) indicate that the ring is deactivated w.r.t. benzene.

c. Taken from Ref.156.

Table 3.3: Values of $\Delta^{-}h(k)$ (using Eq. (3.5)), $\Delta^{-}h(k)$ (using Eq. (3.9)), sum of (kinetic and exchange) energy terms, V_c, $\ln f$ and rates of benzylation (relative to that of benzene) for halobenzenes at B3LYP/6-31G(D,P) level.

Systems for benzylation	Position of attachment of electrophile	$\Delta^{-}h(k)$ (a. u.) using, $V_{el}(\bar{r})$ (Eq. 5)	$\Delta^{-}h(k)$ (a. u.) using, three terms (Eq. 9)	(Kinetic + Exchange) energy terms (a. u.)	V_c [a] (volts)	$\ln f$ [b]	Relative Rate[c]
1.benzene	1	0.258	0.219	-0.016	-1.069	0.0	1
2.fluorobenzene	2	0.237	0.219	-0.018	-0.767	-1.6	0.46
	3	0.230	0.217	-0.013	-0.694	-5.9	
	4	0.264	0.227	-0.037	-0.869	0.9	
3.chlorobenzene	2	0.217	0.217	-0.000	-0.653	-1.4	0.24
	3	0.193	0.203	0.010	-0.672	-5.4	
	4	0.269	0.227	-0.042	-0.768	0.0	
4.bromobenzene	2	0.210	0.195	-0.015	-0.554	-1.7	0.18
	3	0.203	0.193	-0.010	-0.699	-5.6	
	4	0.230	0.197	-0.033	-0.817	-0.3	

a. V_c is the electrostatic potential at the reacting carbon atom.[132]

b. Logarithm of partial rate factors ' f '(i.e., $\ln f$) values were taken from Ref 132. The negative values indicate that the ring is deactivated (due to the presence of halides) in halobenzenes w.r.t. benzene.

c. Taken from Ref. 155.

Table 3.4: Values of $\Delta^{-}h(k)$ (using Eq. (3.5)), $\Delta^{-}h(k)$ (using Eq. (3.9)), sum of (kinetic and exchange) energy terms, $\ln f$ and rates of bromination (relative to that of benzene) for polynuclear aromatic hydrocarbons at B3LYP/6-31G(D,P) level.

Hydrocarbon	Position of reaction	$\Delta^{-}h(k)$ (a.u.) using, $V_{el}(\bar{r})$ (Eq. 5)	$\Delta^{-}h(k)$ (a. u.) using,three terms (Eq. 9)	(Kinetic +Exchange) energy terms (a. u)	$\ln f$ [b]	Relative Rate[c]
1. benzene	1	0.258	0.242	-0.016	0.0	1
2. naphthalene	1 2	0.206 0.193	0.178 0.179	-0.027 -0.014	5.3 3.3	1.24×10^{5}
3. phenanthrene	9	0.189	0.166	-0.024	6.3	7.43×10^{5}
4. fluoranthene	3	0.170	0.151	-0.019	6.8	2.30×10^{6}
5.fluorene[a]	2	0.183	0.154	-0.029	7.0	3.53×10^{6}
6. chrysene	6	0.167	0.145	-0.022	7.6	1.25×10^{7}
7. 1,2 benzanthracene	7	0.152	0.140	-0.012	11.2	2.44×10^{10}
8. pyrene[a]	1	0.167	0.155	-0.012	10.6	2.84×10^{10}
9. acenaphthene[a]	5	0.195	0.168	-0.027	11.2	5.49×10^{10}
10. anthracene	9	0.187	0.161	-0.026	12.4	7.87×10^{11}

a. Systems where $\Delta^{-}h(k)$ produced irregular reactivity trends are shown in bold.

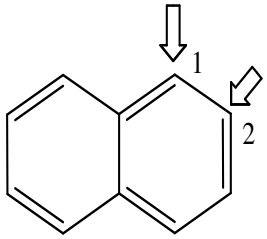
b. Logarithm of partial rate factors ' f ' (i.e., $\ln f$) values were taken from Ref 163.

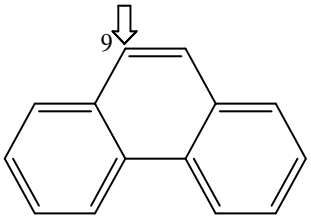
c. Taken from Ref. 162.

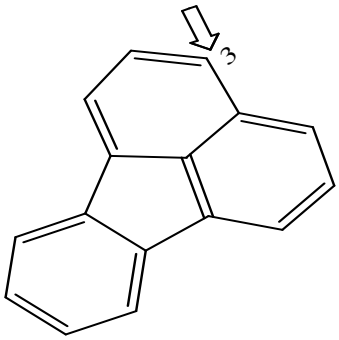
Table 3.5: Values of $\Delta^{+}h(k)$ (using Eq. (3.4)), $\Delta^{+}h(k)$ (using Eq. (3.8)) and sum of (kinetic and exchange) energy terms for carboxylic acid and its derivatives at B3LYP/6-31G(D,P) level. Electrophilic centres are shown in bold.

Systems for Nucleophilic Attack	$\Delta^{+}h(k)$ (a. u.) using, $V_{el}(\bar{r})$ (Eq. 4)	$\Delta^{+}h(k)$ (a. u.) using, three terms (Eq. 8)	(Kinetic +Exchange) energy terms (a. u.)
1. H**C**OF	0.409	0.298	-0.112
1. H**C**OOH	0.393	0.286	-0.108
3. H**C**ONH$_2$	0.374	0.275	-0.099
4. CH$_3$**C**OOH	0.360	0.255	-0.106
5.CH$_3$CH$_2$**C**OOH	0.329	0.237	-0.092
6.CH$_3$**C**ONH$_2$	0.320	0.241	-0.079
7.CH$_3$CH$_2$**C**ONH$_2$	0.226	0.231	0.005
8.CH$_3$**C**OF	0.375	0.264	-0.110
9.CH$_3$CH$_2$**C**OF	0.250	0.257	0.007

Figure 3.1: Chosen Polycyclic Aromatic Hydrocarbons:

<table>
<tr>
<td> 

2. Naphthalene</td>
<td> 

3. Phenanthrene</td>
<td> 

4. Fluoranthene</td>
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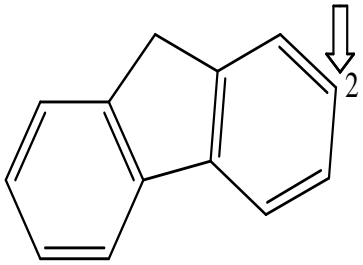
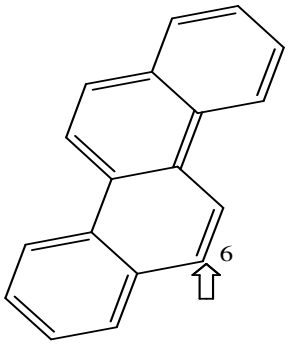
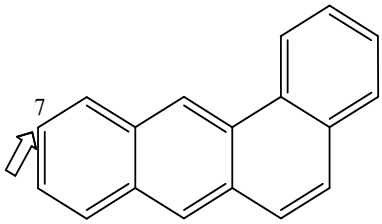
<td> 

5. Fluorene</td>
<td> 

6. Chrysene</td>
<td> 

7. 1,2-benzanthracene</td>
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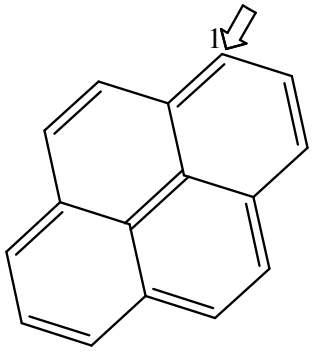
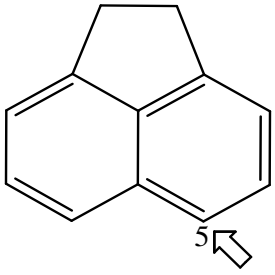
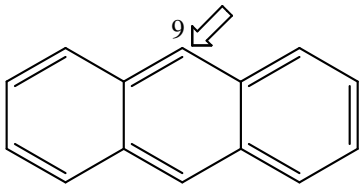
<td> 

8. Pyrene</td>
<td> 

9. Acenaphthene</td>
<td> 

10.Anthracene</td>
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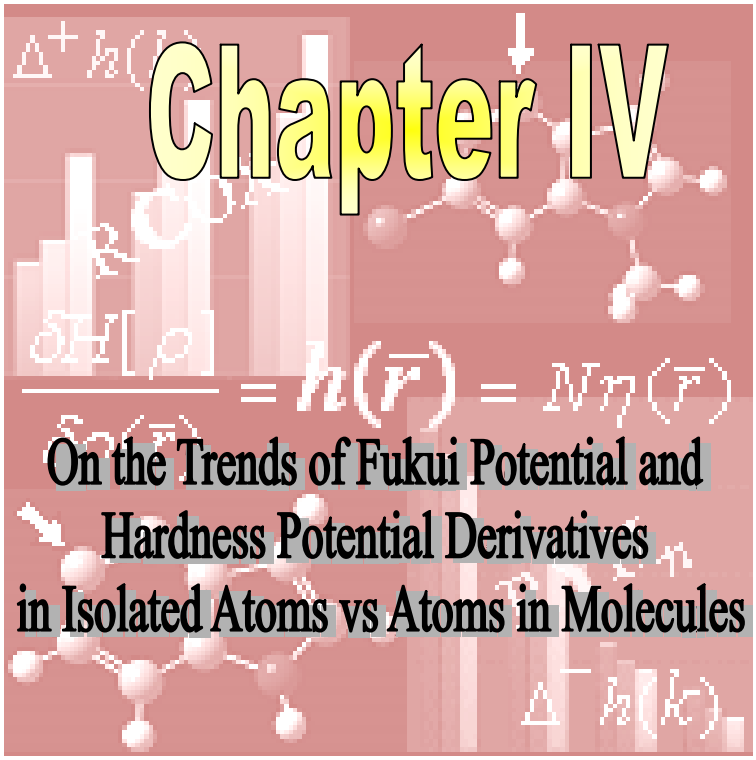
⇨ **Preferred Site of electrophilic attack**


Chapter IV
On the Trends of Fukui Potential and Hardness Potential Derivatives in Isolated Atoms vs Atoms in Molecules

4.1. Introduction:

'Chemical Reactivity Theory' (CRT) or 'Density Functional Reactivity Theory (DFRT) exploits the electron density and its various response functions to understand and predict chemical reactivity.[1-41] In the previous chapter, the relative contribution of the sum of kinetic [$\frac{10}{9}C_F\rho(\bar{r})^{2/3}$] and exchange energy [$\frac{4}{9}C_X\rho(\bar{r})^{1/3}$] terms to that of the electronic part of the molecular electrostatic potential [$V_{el}(\bar{r})$] in the variants of hardness potential is investigated to evaluate the proposed definition of $\Delta^{+}h(k) = -[V_{el}^{N+1}(k) - V_{el}^{N}(k)]$ and $\Delta^{-}h(k) = -[V_{el}^{N}(k) - V_{el}^{N-1}(k)]$. Some substituted benzenes and polycyclic aromatic hydrocarbons (PAHs) (undergoing electrophilic aromatic substitution), carboxylic acids and their derivatives are chosen to carry out the theoretical investigation as stated above. In the present chapter, trends of electronic contribution to molecular electrostatic potential [$V_{el}(\bar{r})_{r=0}$], Fukui potential [$v_f^{+}\big|_{r=0}$ and $v_f^{-}\big|_{r=0}$] and hardness potential derivatives [$\Delta^{+}h(k)$ and $\Delta^{-}h(k)$] for isolated atoms as well as atoms in molecules are studied.[32] The generated numerical values of these three reactivity descriptors in these two electronically different situations are critically analyzed through the relevant formalism. Chemical consequence of the observed trends of these descriptors in interpreting electron delocalization, electronic relaxation and non-negativity of atomic Fukui function indices is also touched upon. Several commonly used molecules containing carbon as well as hetero atoms (where reactivities are known experimentally)[42-52] are chosen to make the investigations more insightful.

4.2. Theoretical Background:

I. Working Equations of Fukui Potential:

The approximated analytical form of hardness potential [$h(\bar{r})$] is given as,[30]

$$h(\bar{r}) = \frac{10}{9}C_F\rho(\bar{r})^{2/3} - V^{el}(\bar{r}) - \frac{4}{9}C_X\rho(\bar{r})^{1/3} \qquad (4.1)$$

where, $V_{el}(\bar{r})$ is the electronic contribution to the molecular electrostatic potential, $\frac{10}{9}C_F\rho(\bar{r})^{2/3}$ and $\frac{4}{9}C_X\rho(\bar{r})^{1/3}$ are the kinetic energy and exchange exchange energy terms, respectively. Then it was approximated further as,

$$h(\bar{r}) = -V_{el}(\bar{r}) \tag{4.2}$$

The expression of $h(\bar{r})$ [i. e., Eq. (4.1)] contains nonlinear functions of $\rho(\bar{r})$ (the first and the third terms) and hence the condensation of $h(\bar{r})$ [as it is in Eq. (4.1)] is mathematically inexact.[33] So, for evaluating $V_{el}(\bar{r})$ and $\rho(\bar{r})$, the values at the nucleus (i.e., at $\vec{r} = 0$) of a particular atom k are considered while developing two variants of hardness potential [$\Delta^{+}h(k)$] and [$\Delta^{-}h(k)$] to explain both intermolecular and intramolecular reactivity trends of systems having variation of atom types of the reactive centres, different sizes (i.e., number of electrons) and characteristics.[30] The ability of those two descriptors to take care of both intramolecular (i.e., site selectivity) as well as intermolecular reactivity trends seems to be promising so far. As these two descriptors belong to grand canonical ensemble (i.e., $-H[\rho] = E - \mu N = \Omega$), in principle, they have the ability to do so. The main advantage of taking the left and right derivative of $h(\bar{r})$ is to make a difference between the processes of gaining or loosing electron density and when this is applied to Eq. (4.2), they lead to the left and right derivatives of Fukui potential.[34-41]

Fukui Potentials are defined as,[30, 35, 37,41]

$$v_f^{+}|_{r=0} = \int \frac{f^{+}(\bar{r})}{|r - r'|}dr' = -[V_{el}^{N+1}(\bar{r}) - V_{el}^{N}(\bar{r})] \tag{4.3}$$

$$v_f^{-}|_{r=0} = \int \frac{f^{-}(\bar{r})}{|r - r'|}dr' = -[V_{el}^{N}(\bar{r}) - V_{el}^{N-1}(\bar{r})] \tag{4.4}$$

Ca′rdenas et. al.[37] have asserted that Fukui potential at the position of the nuclei (i. e., $r \to 0$) is equal to the variation of the chemical potential with the nuclear charge and thus it can measure the sensitivity of the system to changes in atom type. They concluded that Fukui potential attains its maximum close to the nuclear position and collapses with the distance for the atoms of the second period. They also inferred that the shape of the Fukui potential leads the incoming distant reagent toward the site within an electrophile or nucleophile where the propensity of acceptance

or donation of charge is the highest. In another study[53] Ayers et al. have shown that the asymptotic decay of the exchange correlation potential is governed by the Fukui potential.

II. Working Equations of Electronic Contribution to the Molecular Electrostatic Potential:

Molecular electrostatic potential (MEP)[54] has played a pivotal role over years in the development of DFT-based reactivity indicators. It is also known as the expectation value of the operator $\hat{r}^{-1}$ [i. e., $\phi|\hat{r}^{-1}|\phi$] where ϕ stands for the unperturbed molecular wave function].

The expression for MEP (Φ) is as follows :

$$\Phi = V_{Nu}(\dot{r}) + V_{el}(\dot{r}) = \sum_A \frac{Z_A}{|\bar{r} - \bar{r}'|} - \sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(\bar{r})\chi_\nu(\bar{r})}{|\bar{r} - \bar{r}'|} d\bar{r}' \tag{4.5}$$

where, Z_A stands for the nuclear charge of atom A, which is placed at r'; $P_{\mu\nu}$ is the first-order density matrix; and χ denotes the basis of AO within MO-LCAO framework.

Fukui potential (evaluated at the nucleus) deals with the differences of the electronic contribution to the molecular electrostatic potential of the neutral systems and their corresponding ions. Hence, from Eqs. (4.3) and (4.4) we get two new expressions,

$$v_f^+ \,|_{r=0} = -\left[\left(\sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(\bar{r})\chi_\nu(\bar{r})}{|\bar{r} - \bar{r}'|} dr' \right)_{N+1} - \left(\sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(\bar{r})\chi_\nu(\bar{r})}{|\bar{r} - \bar{r}'|} dr' \right)_N \right] \tag{4.3a}$$

$$v_f^- \,|_{r=0} = -\left[\left(\sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(\bar{r})\chi_\nu(\bar{r})}{|\bar{r} - \bar{r}'|} dr' \right)_{N} - \left(\sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(\bar{r})\chi_\nu(\bar{r})}{|\bar{r} - \bar{r}'|} dr' \right)_{N-1} \right] \tag{4.4a}$$

III. Working Equations of Hardness Potential Derivatives:

Hardness Potential Derivatives are expressed as (evaluated at the nucleus of the atom 'k', i. e., when, $r \to 0$),

$$\Delta^+ h(k) = \frac{10}{9} C_F \left[\rho_{N+1}(k)^{2/3} - \rho_N(k)^{2/3} \right] - \left[V_{el}{}^{N+1}(k) - V_{el}{}^{N}(k) \right] - \frac{4}{9} C_X \left[\rho_{N+1}(k)^{1/3} - \rho_N(k)^{1/3} \right] \tag{4.6}$$

$$\Delta^- h(k) = \frac{10}{9} C_F \left[\rho_N(k)^{2/3} - \rho_{N-1}(k)^{2/3} \right] - \left[V_{el}{}^{N}(k) - V_{el}{}^{N-1}(k) \right] - \frac{4}{9} C_X \left[\rho_N(k)^{1/3} - \rho_{N-1}(k)^{1/3} \right] \tag{4.7}$$

Earlier studies,[55-60] have already shown that in hardness potential electronic contribution to the molecular electrostatic potential, $V_{el}(\bar{r})$, is the dominant one when compared to the other two terms (i.e., the kinetic and the exchange energy terms). It is also demonstrated that in hardness potential derivatives the net contribution of the first and the third square-bracketed terms [i.e., kinetic and exchange energy terms in Eqs. (4.6) and (4.7)] is negligible when compared to the contribution of the terms within the second square-bracket.

It is worth mentioning here that hardness potential derivatives are evolved using the approximated form [based on Thomas–Fermi–Dirac (TFD)[61-63] approach plus the Weizsäcker[64] term] of Hohenberg–Kohn functional $F[\rho]$.[65,66] The presence of the Weizsäcker term in the kinetic energy description nullifies several deficiencies of the Thomas–Fermi–Dirac functional.[19,33, 64] It is also revealed that TFD works well when the exact electron density is used to assess it.[67-74] Besides, it can be argued from the first derivative of Kohn-Sham kinetic energy with respect to the electron density, that the electrostatic term as well as exchange correlation term cancel out.[75] However, while discussing about the second functional derivative of Kohn-Sham kinetic energy, Ayers[76] has shown that the derivative of the Kohn–Sham potential with respect to the electron density bears a contribution from a coulomb term [Eq. (61) of Ref. 76]. Here, the explicit coulomb contribution extinguishes, but an implicit dependence (which is embedded in the Kohn–Sham potential derivative i. e., the first term in Eq. (61) of Ref. 76) prevails.

IV: Orbital relaxation effects in Fukui potential:

Fukui function may be expanded in terms of Kohn-Sham spin-orbitals and the expressions are given as,[13,77]

$$f_N^+(r) = |\phi_{N+1}(r)|^2 + \sum_{i=1}^{N} \left(\frac{\partial |\phi_i(r)|^2}{\partial N}\right)^+_{v(r)} \tag{4.8}$$

$$f_N^-(r) = |\phi_N(r)|^2 + \sum_{i=1}^{N} \left(\frac{\partial |\phi_i(r)|^2}{\partial N}\right)^-_{v(r)} \tag{4.9}$$

where, $\phi_i(r)$ represents all occupied molecular orbitals, $\phi_N(r)$ is the HOMO and $\phi_{N+1}(r)$ is the LUMO. The second term in Eqn. (4.8) and (4.9) clearly indicates that Fukui function provides information about frontier molecular orbitals and also orbital relaxation effects [i. e., the change in the shape of an orbital, when an electron is added (Eq. (4.8)) or removed (Eq. (4.9)]. For some

systems, if the first term is reasonably higher compared to the second term, then the latter may be neglected.[78] In literature,[78,79,80] several examples are found where orbital relaxation plays important role in determining the reactivity. As Fukui potential is directly related to Fukui function (Eqs. (4.3) and (4.4)), it may be interesting to notice the effect of orbital relaxation on the left and right derivatives of Fukui potential for the systems chosen by us.

4.3. Computational Details:

To obtain some qualitative trends of $V_{el}(\bar{r})$, hardness potential derivatives (Eqs. (4.6) and (4.7)) and Fukui potential (Eqs. (4.3) and (4.4)) in isolated atoms vs atoms within a molecule, various types of molecules and some of their constituent atoms are chosen. All molecules are optimized at B3LYP[81-83]/6-311G+(2d,2p) level and their corresponding single point calculations for cations and anions are carried out at UB3LYP/6-311G+(2d,2p) level. It is worth noting here that Soliva et. al.[84] also vouched for the use of large basis sets, including at least a double set of d polarization functions on heavy atoms, for accurate representation of electrostatic properties. The absence of imaginary frequency is confirmed for each of the optimized geometries. Calculations for isolated atoms and their corresponding cations and anions are done at B3LYP[81-83]/6-311G+(2d,2p) and UB3LYP/6-311G+(2d,2p) levels (depending on the type of atoms and their corresponding ions, as some of them have closed-shell structure and some are open-shell one). Similarly, to verify our interpretation of hardness potential derivatives and Fukui potential for isolated atoms, calculations are performed at B3LYP or UB3LYP level with three different basis sets: 6-31G(d,p). 6-311G(2d,2p) and 6-311G+(2d,2p). The SCF density is used to evaluate $V_{el}(k)$ and $\rho(k)$. All calculations are performed in gas phase using Gaussian03[85,86] software package.

4.4. Results and Discussions:

A comparative analysis of $V_{el}(\bar{r})$, hardness potential derivatives and Fukui potential in isolated atoms vs atoms within a molecule may be useful for exploiting them to study intra and intermolecular reactivities. In order to do that, different types of molecules are chosen (which are usually involved in chemical and biological reactions) containing carbon atoms as well as hetero atoms. They can be broadly grouped as:

1) Substituted Benzenes
2) Amino Acids
3) Indolynes
4) Polycycles

Among these major groups, polycycles are made up of only carbon atoms, but rest all contain hetero atoms also. The atoms, which are chosen here (shown in the second column in different Tables.), are of reasonably high reactivity (as already determined experimentally[42-52] and some of them are verified by theoretical methods also[30,32,43,49]). Numbering of atoms in most of the systems chosen is as per standard numbering convention. However, for amino acids the numbering of atoms are given in Figure 4.1.

I. Trends of $V_{el}(\bar{r})$ in isolated atoms vs atoms in molecules:

As evident from Table 4.1.a. and 4.1.b. the values of $V_{el}(\bar{r})\big|_{r=0}$ are higher for atoms in molecules compared to those of isolated atoms. The probable reason for that can be derived from the expression of $V_{el}(\bar{r})$ (second term) in Eq. (4.5). For an isolated atom, given a known set of basis functions, first-order density matrix specifies the charge density centered on that particular atom (evaluated at $r \to 0$). For an atom in a molecule, the value of $V_{el}(\bar{r})$ is not an atomic contribution of that atom to the electronic part of molecular electrostatic potential, but the value of electronic contribution to molecular electrostatic potential measured at the point in space that coincides with the coordinates of the nucleus of that particular atom. $V_{el}(\bar{r})$ for a molecule is well-defined if the electronic charge distribution is known. χ_μ and χ_υ terms of Eq. (4.5) are the diagonal elements of the first order electron density matrix which represents the electron charge distribution within SCF and MO-LCAO approximation. In case of an atom within a molecule, electronic contribution from neighboring atoms probably enhances the charge density on that particular atom, which finally yields higher value of $V_{el}(\bar{r})$ compared to that of the isolated atom. As the picture of electronic charge distribution (which varies from one molecule to the other), is not so vivid within a molecule, it is difficult to make any strong comment on it, at this point of time (some elaborate discussions related to this area is well known in the literature).[54,87-89]

II. Trends of Fukui potential in isolated atoms vs atoms in molecules:

From Table 4.2.a. and 4.2.b., it is observed that the values of $v_f{}^+\big|_{r=0}$ and $v_f{}^-\big|_{r=0}$ are higher in isolated atoms compared to those of atoms in molecules. It can be argued that when an extra electron is added (i. e., $N+1$ electron system) to the neutral isolated atom (i. e., N electron system), the net value of the two terms in the right hand side (R. H. S.) of Eq. (4.3) (or 4.3.a.) will be much higher than when the same atom is in a molecule. This is because, in a molecule, the extra electron is distributed through the whole system and so the net increase of the first term in the R. H. S. of Eq. (4.3) (or 4.3.a.) will be much lower. This explains why $v_f{}^+\big|_{r=0}$ for isolated atoms are much higher than when those atoms are in a molecule. Similarly, when an electron is removed (i. e., $N-1$ electron system) from a neutral system the loss in electron density of the concerned atom will be much less when it is in a molecule as other atoms in the molecule also share the loss to some extent. So, from Eq. (4.4) (or 4.4.a.), it can be argued that the second term in the R. H. S. will be much smaller than the first term when the concerned atom is isolated. This explains why $v_f{}^-\big|_{r=0}$ values are much higher in isolated atoms than for the same atom in a molecule.

III. Trends of hardness potential derivatives in isolated atoms vs atoms in molecules:

Normally, $\Delta^-h(k)$ values (in Table 4.2.c.) are higher for carbon atoms in molecules than when it is isolated. However, trends of $\Delta^+h(k)$ values (in Table 4.2.c.) of isolated carbon atoms vs carbon atoms in molecules, is not regular. Higher $\Delta^-h(k)$ values for nitrogen atoms in molecules (compared to that when it is isolated) are observed in some systems, but the trend is opposite in some other cases. But $\Delta^+h(k)$ values for N atoms (in Table 4.2.d.), are usually lower for atoms in molecules (compared to that of isolated atom). For oxygen, fluorine, chlorine and sulphur atoms, $\Delta^+h(k)$ and $\Delta^-h(k)$ (in Table 4.2.d.) values are normally lower for atoms within molecules than when these atoms are isolated.

An effort to find out the reason of the above observation is made by first comparing the relative magnitudes of the Fukui potentials and hardness potential derivatives. Here, it is worth to note that values of Fukui potentials (i. e., $v_f{}^+\big|_{r=0}$ and $v_f{}^-\big|_{r=0}$) are higher compared to the values of hardness potential derivatives [i. e., $\Delta^+h(k)$ and $\Delta^-h(k)$, evaluated at $r \to 0$, Table

4.4.2.a., 4.4.2.b., 4.4.2.c. and 4.4.2.d.] for isolated atoms (as well as for atoms in molecules). On performing calculations with three different basis sets 6-31G(d,p) (Table 4.3.a.), 6-311G(2d,2p) (Table 4.3.b.) and 6-311G+(2d,2p) (Table 4.3.c.) and all using the B3LYP method for isolated atoms, it is found that the order of electron densities is as follows (Table 4.3.a., 4.3.b. and 4.3.c.),

$$\rho^{N-1} > \rho^{N} > \rho^{N+1}$$

Hence, negative Fukui function (FF) arises for each concerned atom (at $r \to 0$). This distinct observation may be explained by stating that when an electron is lost from a neutral atom, i. e., in a cation, electron-electron repulsion decreases and the effective nuclear charge increases. The consequence is that the protons in the nucleus can more ably pull the remaining electrons towards the nucleus. Hence, the cations possess highest electron density at the nucleus. Similarly, in case of anions, an electron is added to the neutral atom resulting in higher electron-electron repulsion and decreasing effective nuclear charge. The protons in the nucleus cannot efficiently drag electrons towards the nucleus as these used to do in the neutral atom. As a result, anions exhibit lowest electron density at the nucleus. However, the above explanation is highly qualitative and it needs an extensive analysis. It is inappropriate to make any assertive comment at this point of time. Now, if we look at Eqs. (4.6) and (4.7), it can be clearly understood that the net contribution of the first and the third square bracketed terms (the net contribution of the exchange energy terms will be positive and the kinetic energy terms will be negative) substantially reduces the values of $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ compared to those of $v_f{}^{+}\big|_{r=0}$ and $v_f{}^{-}\big|_{r=0}$. The scenario in a molecule is far more complicated due to the presence of several other factors such as multidirectional force etc. and FF values for atoms in a molecule may not always be negative. Hence we restrict our interpretation to isolated atoms. The negativity of Fukui function is argued over years. [90-93] FF indices may turn out to be negative due to the partitioning technique (Mulliken population analysis (MPA) [94] is used here) also. Negative condensed FF values have also been observed[95] with the use of Löwdin partitioning scheme and it is more prominent within the finite difference approximation involving change of one electron. On the other hand, the negativity of molecular FF is attributed to orbital relaxation by Melin et al.[96]

Now from Eqs. (4.3) and (4.4) it is obvious that Fukui potential values [i.e., the net values within the second square bracket of Eqs. (4.6) and (4.7)] of isolated atoms are higher than the

corresponding values of atoms within a molecule. However, there is no straightforward way to predict whether the net contribution of the terms in the first and the third square brackets [in Eqs. (4.6) and (4.7)] will be positive or negative (this is analogous to say whether Fukui function will be positive or negative) for atoms within a molecule. This makes *a priori* prediction of the trends of hardness potential derivatives in isolated atoms vs atoms in molecules complicated.

IV. Sum of Fukui potential and hardness potential derivatives in molecules:

If we closely observe the values of [$v_f^+\big|_{r=0}$ and $v_f^-\big|_{r=0}$] (in Table 4.2.a., 4.2.b., 4.2.c. and 4.2.d.) of constituent atoms of a molecule (or isolated atoms), it is revealed that the value of $v_f^-\big|_{r=0}$ is always substantially higher than that of $v_f^+\big|_{r=0}$ (this is true for either carbon atom or any other hetero atoms). Although, the values of $v_f^+\big|_{r=0}$ and $v_f^-\big|_{r=0}$ of only the reactive carbon atoms are reported here for clarity, the trend is not altered for other carbon atoms as well (in a molecule) in most cases. Incidentally, *Ca´rdenas* et al.[37] have also encountered similar observation (Figure 1 in Ref. 37) for isolated atoms of second period. The suitable explanation may be derived from the fact that ionization potential is more responsive to a change in the nuclear charge than the electron affinity because the HOMO is closer to the nucleus than the LUMO and hence it is less screened. A different perspective suggests that removing an electron from an atom changes the electron density, which in turn changes Fukui function (and hence Fukui potential) near the nucleus more compared to the removal of an electron from the atomic anion. It is because the electron in the neutral atom penetrates deeper into the atomic core and it actuates larger orbital relaxation effects in the near-nucleus region. As a result, the overall sum of $v_f^-\big|_{r=0}$ is higher compared to that of $v_f^+\big|_{r=0}$ for all the chosen molecules [which are mostly comprised of atoms of second period (C, N, F, O)] as evident from Table 4.4.a.

Now, if we look at the sum of hardness potential derivatives, we also observe the same trend (Table 4.4.b.), i. e., sum of $\Delta^- h(k)$ is always higher compared to that of $\Delta^+ h(k)$. On the basis of the expressions of $\Delta^+ h(k)$ and $\Delta^- h(k)$ [Eqs. (4.6) and (4.7)], it is already established that the contribution of the second term [i. e., the differences of the two $V_{el}(\bar{r})$ terms] is dominant when compared to the net contribution of the first and third terms and therefore it can influence the overall value of $\Delta^+ h(k)$ and $\Delta^- h(k)$ for a particular atom.[32] As $v_f^-\big|_{r=0}$ values are higher compared to those of $v_f^+\big|_{r=0}$ (as discussed above), observed values of $\Delta^- h(k)$ are higher

than those of $\Delta^{+}h(k)$ for an atom (isolated or in a molecule, Table 4.2.c. and 4.2.d.). Naturally, the sum of $\Delta^{-}h(k)$ values is also higher compared to the sum of $\Delta^{+}h(k)$ values for a molecule (Table 4.4.b.).

4.5. Conclusion:

The main objective of the present chapter is to gain an insight into the trends of electronic contribution to molecular electrostatic potential [$V_{el}(\bar{r})$], Fukui potential and hardness potential derivatives in isolated atoms and atoms in molecules. It is observed that values of $V_{el}(\bar{r})$ are higher for atoms in molecules than those of isolated atoms. The observation was justified on the basis of differences in the scenario of charge density (as given in Eq. (4.5)) for isolated atoms and atoms in a molecule. As Fukui potential and hardness potential derivatives are significantly dependent on the differences of $V_{el}(\bar{r})$ (Eqs. (4.3), (4.4), (4.6) and (4.7)) the effect of electronic environment on $V_{el}(\bar{r})$ should also be kept in mind while evaluating those descriptors.

Secondly, systematic trends of higher values of $v_f^{+}\big|_{r=0}$ and $v_f^{-}\big|_{r=0}$ for isolated atoms, compared to those of atoms in molecules, are observed. It is explained by difference in electron density distribution (while addition or removal of an electron takes place) in isolated atom and atom in a molecule. Interpretation of the trends of hardness potential derivatives [$\Delta^{+}h(k)$ and $\Delta^{-}h(k)$] are not straightforward, as such, for isolated atoms and atoms in molecules. Plausible explanations are found on the basis of negative Fukui function for isolated atoms (not for molecules, due to their electronic complexity).

Analysis of the trends of the sum of Fukui potential and hardness potential derivatives are also touched upon, which demonstrates the importance of orbital relaxation effects in near-nucleus region.

Finally, the physico-chemical implications of the observations made in the present study can be summarized as follows:

(i) Merits of using Fukui potential as an "alternative definition of chemical hardness" is discussed in details by Cardenas et al.[37,38] The present study demonstrates that the differences of the values of Fukui potentials as well as hardness potential derivatives in isolated atom and the same atom in a molecule provide information about the

extent of electron delocalization in the molecule. More the difference more is the electron delocalization. As electron delocalization plays a major role in chemical reactivity (when an electrophile or nucleophile approaches towards a substrate, there is change in electron density within a molecule) the above findings may be useful in intra and intermolecular reactivity studies by these two descriptors.

(ii) The values of $\sum_K v_f^-(\bar{r})|_{r=0}$ - $\sum_K v_f^+(\bar{r})|_{r=0}$ as well as $\sum_K \Delta^- h(K)$ - $\sum_K \Delta^+ h(K)$ for a polyatomic molecule provide more prominent information about the relaxation effects. This is because, by definition, these values are evaluated at the positions of the atomic nuclei where orbital relaxation effects are more causing large differences between the values of $\sum_K v_f^-(\bar{r})|_{r=0}$ and $\sum_K v_f^+(\bar{r})|_{r=0}$ as well as between $\sum_K \Delta^- h(K)$ and $\sum_K \Delta^+ h(K)$. Orbital relaxation is important for 'Fukui-function-controlled reactions.'[78] These are a class of reactions where not only frontier molecular-orbital and orbital-relaxation control are important, but collaborative effects between the suitable frontier orbitals and orbital relaxation can ably determine chemical reactivity as well.[78] As conventional evaluation of condensed Fukui indices are based on condensed atomic population, information about relaxation effect is missing.

(iii) As these two descriptors are more sensitive to the electronic environment of an atom in a molecule they can, potentially, be implemented in the 'One-into-Many' model[27] to locate the most reactive site in large chemical and biological systems.

(iv) Finally, the striking observation, i. e., cations have higher electron densities compared to those of anions (for isolated atoms) is qualitatively explained on the basis of 'higher electronic repulsion and lower effective nuclear charge' (for anions) and vice versa (for cations).

References and Notes

1. R. G. Parr, R. A. Donnelly, M. Levy, and W. E. Palke, *J. Chem. Phys.,* 1978, **68***,* 3801.
2. R. G. Parr and W. Yang, Density–Functional Theory of Atoms and Molecules, Oxford University Press: New York, 1989.
3. P. Geerlings, F. De Proft, and W. Langenaeker, *Chem. Rev*., 2003, **103,** 1793.
4. P. A. Johnson, L. J. Bartolotti, P. W. Ayers, T. Fievez and P. Geerlings, Gatti, C., Macchi, P., Eds. Springer: New York, 2012, pp 715.
5. P. Senet, *J. Chem. Phys.*, 1996, **105,** 6471.
6. P. W. Ayers, J. S. M. Anderson, and L. J. Bartolotti, *Int. J. Quantum Chem.*, 2005, **101***,* 520.
7. R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc.*, 1983, **105,** 7512.
8. W. Yang and R. G. Parr, *Proc. Natl. Acad. Sci. U.S.A.*, 1985, **82,** 672.
9. R. G. Parr, L. Szentpàly, and S. Liu, *J. Am. Chem. Soc*., 1999, **121,** 1922.
10. S. B. Liu, Electrophilicity. P. K. Chattaraj, Ed. Taylor and Francis: Boca Raton. 2009, p 179.
11. P. K. Chattaraj, U. Sarkar, and D. R. Roy, *Chem. Rev.*, 2006, **106,** 2065.
12. R. G. Parr and W. Yang, *J. Am. Chem. Soc*., 1984, **106,** 4049.
13. W. Yang, R. G. Parr, and R. Pucci, *J. Chem. Phys*., 1984, **81,** 2862.
14. W. Yang and W. Mortier, *J. Am. Chem. Soc.,* 1986, **108,** 5708.
15. P. W. Ayers and M. Levy, *Theor. Chem. Acc.*, 2000, **103,** 353.
16. M. Berkowitz, S. K. Ghosh, and R. G. Parr, *J. Am. Chem. Soc*., 1985, **107,** 6811.
17. P. W. Ayers and R. G. Parr, *J. Am. Chem. Soc*., 2000, **122**, 2010.
18. S. K. Ghosh and M. Berkowitz, *J. Chem. Phys.,* 1985, **83,** 2976.
19. P. K. Chattaraj, D. R. Roy, P. Geerlings, and Torrent-Sucarrat, *Theor. Chem. Acc.***,** 2007, **118,** 923.
20. P. W. Ayers and R. G. Parr, *J. Chem.Phys.*, 2008, **128,** 184108.
21. R. K. Roy, S. Krishnamurti, P. Geerlings, and S. Pal, *J. Phys. Chem. A.*, 1998, **102,** 3746.
22. R. K. Roy, F. De Proft, and P. Geerlings, *J. Phys. Chem. A***.,** 1998, **102**, 7035.
23. P. K. Chattaraj, B. Maiti, and U. Sarkar, *J. Phys. Chem. A.*, 2003, **107,** 4973.
24. M. Berkowitz and R. G. Parr, *J. Chem. Phys*., 1988, **88,** 2554.
25. R. F. Nalewajski, *J. Phys. Chem.*, 1985, **89***,* 2831.
26. G. Klopman, *J. Am. Chem. Soc.***,** 1968, **90,** 223.

27. S. Saha and R. K. Roy, *J. Phys. Chem. B.,* 2007, **111**, 9664.

28. S. Saha and R. K. Roy, *J. Phys. Chem. B*., 2008, **112,** 1884.

29. S. Saha and R. K. Roy, *Phys. Chem. Chem. Phys*., 2008, **10,** 5591.

30. S. Saha, R. Bhattacharjee, and R. K. Roy, *J. Comp. Chem.,* 2013, **34,** 662.

31. R. G. Parr and J. L. Gázquez, *J. Phys. Chem.*, 1993, **97,** 3939.

32. R. Bhattacharjee and R. K. Roy, *J. Phys. Chem. A.*, 2013, **117**, 11528.

33. P. K. Chattaraj and S. Giri, *Annual Reports Sec. C. (Physical Chemistry),* 2009, **105**, 13.

34. M. Torrent-Sucarrat, F. De Proft, P. Geerlings, and P. W. Ayers, *Phys. Chem. Chem. Phys.*, 2010, **12,** 1072.

35. M. Berkowitz, *J. Am. Chem. Soc.*, 1987, **109,** 4823.

36. M. Torrent-Sucarrat, F. De Proft, P. Geerlings, and P. W. Ayers, *Chem. Eur. J.*, 2008, **14,** 8652 .

37. C. Cárdenas, W. Tiznado, P. W. Ayers, and P. Fuentealba, *J. Phys. Chem. A.,* 2011, **115,** 2325.

38. C. Cárdenas, *Chem. Phys. Lett*., 2011, **513**, 127.

39. P. Senet, *J. Chem. Phys*.,1997, **107,** 2516.

40. P. Senet, *Chem. Phys. Lett***., 275,** 527 1997.

41. P. W. Ayers and M. Levy, *Theor. Chem. Acc.,* 2000, **103**, 353.

42. G.-Y. J. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, and N. K. Garg, *J. Am. Chem. Soc*., 2010, **132**, 17933.

43. P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G.-Y. J. Im, N. K. Garg, and K. N. Houk, *J. Am. Chem. Soc*., 2010, **132**, 1267.

44. Z. Liu and R. C. Larock, *J. Org. Chem*., 2006**, 71**, 3198.

45. S. M. Bronner, A. E. Goetz, and N. K. Garg, *J. Am. Chem. Soc.,* 2011, **133**, 3832**.**

46. L. Altschuler and E. Berliner, *J., Am. Chem. Soc.,* 1966, **88***,* 5837.

47. G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc*., 1962, **84,** 1695.

48. G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.,* 1961, **83***,* 4581.

49. G. Koleva, B. Galabov, I. Wu. Judy, H. F. Schaefer, and P. von R. Schleyer, *J. Am. Chem. Soc.,* 2009, **131***,* 14722.

50. J. E. Dubois, J. J. Aaron, P. Alcais, J. P.Doucet, F. Rothenberg, and R. Uzan, *J. Am. Chem. Soc.*, 1972, **94**, 6823.

51. F. Rothenberg, P. Alcais, and J. E. Dubois, *Bull. Soc. Chim. Fr.,* 1971, 592.

52. J. J. Aaron and J. E. Dubois, *Bull. Soc. Chim. Fr.,* 1971, 603.

53. P. W. Ayers, R. C. Morrison, and R. G. Parr, *Mol. Phys.*, 2005, **103**, 2061.

54. R. Bonaccorsi, E. Scrocco and J. Tomasi, *J. Chem. Phys*. 1970, **52***,* 5270.

55. W. Langenaeker, F. De Proft, and P. Geerlings, *J. Phys. Chem*., 1995, **99***,* 6424.

56. M. Torrent-Sucarrat, P. Salvador, P. Geerlings, and M. Solà, *J. Comput. Chem*., 2007, **28**, 574.

57. M. Torrent-Sucarrat and P. Geerlings, *J. Chem. Phys.,* 2006, **125***,* 244101.

58. P. K Chattaraj, A. Cedillo, and R. G. Parr, *J. Chem. Phys.,* 1995**, 103**, 10621.

59. S. Liu, F. De Proft, and R. G. Parr, *J. Phys. Chem. A.,* 1997. **101**, 6991.

60. A. Borgoo, M. Torrent-Sucarrat, F. De Proft, and P. Geerlings, *J. Chem. Phys.*, 2007, **126**, 234104.

61. L. H. Thomas, *Proc. Cambridge Philos. Soc.,* 1927, **23**, 542.

62. E. Z. Fermi, *Z. Phys.,* 1928, **48**, 73.

63. P. A. M. Dirac, *Proc Cambridge Philos. Soc.,* 1930, **26**, 376.

64. C. F. von Weizsäcker, *Z. Physik.,* 1935, **96,** 431

65. P. Hohenberg and W. Kohn, *Phys. Rev. B.,* 1964, **136,** 864

66. W. Kohn and L. J. Sham, *Phys. Rev. A*., 1965, **140***,* 1133.

67. K. Burke, J. P. Perdew, and M. Levy, *Phys Rev. A*., 1996, **53,** 2915.

68. P. Fuentealba, *J. Chem. Phys.*, 1995, **103,** 6571

69. P. Senet, J. Chem. Phys., 1996, **105,** 6471.

70. Y. S. Kim and R. G. Gordon, *J. Chem. Phys.*, 1974, **60,** 1842.

71. R. K. Pathak, B. S. Sharma and A. J. Thakkar, *J. Chem. Phys.*, 1986, **85,** 958.

72. A. Scheidmann and R. M. Dreizler, *Z. Phys.,* 1986, **D 2,** 43 see references therein.

73. J. R. Smith, *Phys. Rev.,* 1969, **181***,* 522.

74. A. Chizmeshya and E. Zaremba, *Phys. Rev. B.,* 1988, **37,** 2805.

75. S. Liu and P. W. Ayers, *Phys Rev. A*., 2004, **70,** 022501.

76. P. W. Ayers, *Theor. Chem. Acc.,* 2001, **106**, 271.

77. M. H. Cohen, M. V. Ganduglia Pirovano, and J. Kudrnovský, *J. Chem. Phys.*, 1994, **101**, 8988.

78. L. J. Bartolotti and P. W. Ayers, *J. Phys. Chem. A*., 2005, **109**, 1146.

79. K. Flurchick and L. Bartolotti, *J. Mol. Graphics.*, 1995, **13**, 10.

80. W. Langenaeker, K. Demel, and P. Geerlings, *THEOCHEM.*, 1991, **80**, 329.

81. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.

82. A. D. Becke, *Phys. Rev. A.*, 1988, **38***,* 3098.

83. C. Lee, W. Yang, and R. G. Parr, *Phys. Rev. B.*, 1988, **37***,* 785.

84. R. Soliva, F. J. Luque, and M. Orozco, *Theor. Chem. Acc.*, 1997, **98**, 42.

85. M. J. Frisch, et al. Gaussian 03, Revision E.01; Gaussian, Inc. Wallingford, CT 2004.

86. help@gaussian.com, private communication.

87. E.Scrocco and J. Tomasi, *J. Comput. Chem.*, 1973, **2,** 95.

88. J. Tomasi, G. Alagona, R. Bonaccorsi, C. Ghio, and R. Cammi, In Theoretical Models in Chemical Bonding, Part IV, Z. B. Maksic, Ed., Springer-Verlag, Berlin, 1991, p. 229

89. J. Tomasi, B. Menucci, and R. Cammi, In Molecular Electrostatic Potentials: Concepts and Applications, Theoretical and Computational Chemistry, Vol. 3, J. S. Murray and K. Sen, Eds., Elsevier, Amsterdam, 1996, p. 1.

90. R. K. Roy, S. Pal, and K. Hirao, *J. Chem. Phys.*, 1999, **110**, 8236.

91. R. K. Roy, K. Hirao, and S. Pal, *J. Chem. Phys.*, 2000, **113**, 1372.

92. P. Fuentealba, P. Pe´rez, and R. Contreras, *J. Chem. Phys*., 2000, **113**, 2544.

93. P. Bultinck, R. Carbo´-Dorca, and W. Langenaeker, *J. Chem. Phys.,* 2003, **118**, 4349.

94. R. S. Mulliken, *J. Chem. Phys*., 1955, **23**, 1833.

95. R. K. Roy, S. Krishnamurty, K. Hirao and S. Pal, *J. Chem. Phys.*, 2001, **115**, 2901.

96. J. Melin, P. W. Ayers, and J. V. Ortiz, *J. Phys. Chem. Lett.*, 2007, **111**, 10017.

Table 4.1.a. Trend of $V_{el}(\bar{r})$ for reactive atoms in molecules vs. isolated atoms at B3LYP/6-311+G(2d, 2p) level. Numbering of atoms is as per standard numbering convention.

Systems	**Reactive Position**	$V_{el}(\bar{r})$ **in isolated atom (in a. u.)**	$V_{el}(\bar{r})$ **in molecule (in a. u.)**
1. Benzene	C1	-14.669	-24.544
2. Toluene	C2 C4	-14.669	-26.090 -25.467
3. 1,2-dimethylbenzene	C3 C4	-14.669	-27.156 -26.523
4. 1,3-dimethylbenzene	C2 C4	-14.669	-27.641 -27.018
5. 1,4-dimethylbenzene	C2	-14.669	-27.143
6. 1,2,4,5-tetramethyl-benzene	C3	-14.669	-29.768
7. Pentamethylbenzene	C6	-14.669	-30.728
8. Tert-butyl-benzene	C3 C4	-14.669	-28.274 -27.879
9. Flurobenzene	C2 C3 C4	-14.669	-26.307 -25.702 -25.564
10. Chlorobenzene	C2 C3 C4	-14.669	-27.585 -26.626 -26.385
11. Bromobenzene	C2 C3 C4	-14.669	-30.743 -28.829 -28.349
12. Methoxybenzene	C2 C4	-14.669	-27.648 -26.348
13. 1-methoxy-2-fluorobenzene	C4	-14.669	-27.493
14. 1-methoxy-3-fluorobenzene	C4	-14.669	-28.108
15. 1-methoxy-4-fluorobenzene	C2	-14.669	-28.524
16. 1-methoxy-2-chlorobenzene	C4	-14.669	-28.400
17.1-methoxy-3-chlorobenzene	C4 C6	-14.669	-29.391 -29.212
18. 1-methoxy-4-chlorobenzene	C2	-14.669	-29.449
19. 1-methoxy-2-bromobenzene	C4	-14.669	-30.311
20. 1-methoxy-3-bromobenzene	C6	-14.669	-32.549
21. 1-methoxy-4-bromobenzene	C2	-14.669	-31.651

Table 4.1.a. (continued)

Systems	Reactive Position	$V_{el}(\bar{r})$ in isolated atom (in a. u.)	$V_{el}(\bar{r})$ in molecule (in a. u.)
22.1-methoxy-2,3-dimethylbenzene	C4	-14.669	-28.968
23. 1-methoxy-2,4-dimethylbenzen	C6	-14.669	-29.763
24.1-methoxy-3,4-dimethylbenzene	C6	-14.669	-29.622
25.1-methoxy-3,5-dimethylbenzene	C4 C6	-14.669	-29.455 -29.851
26. 1,3,5-trimethyl-2-ethylbenzene	C4	-14.669	-30.530
27.1,3,5-trimethyl-2-chlorobenzene	C4	-14.669	-30.665
28.1,3,5-trimethyl-2-bromobenzene	C4	-14.669	-32.868
29. 1,4-dimethoxybenzene	C2	-14.669	-29.474
30. 1-methoxy-2-methylbenzene	C4 C6	-14.669	-27.403 -29.656
31. 1-methoxy-3-methylbenzene	C4	-14.669	-27.904
32. 1-methoxy-4-methylbenzene	C2	-14.669	-28.694
33. 4,5-indolyne	C4 C5	-14.669	-28.172 -27.605
34. 5,6-indolyne	C5 C6	-14.669	-27.652 -27.735
35. 6,7-indolyne	C6 C7	-14.669	27.843 28.594
36. C3-Br-substituted-4,5-indolyne	C4 C5	-14.669	-32.969 -31.249
37. C6-Br-substituted-4,5-indolyne	C4 C5	-14.669	-32.590 -33.592
38. Benzynocyclo-4-alkene	C1 C2	-14.669	-26.406 -26.072
39. Benzynocyclo-5-alkene	C1 C2	-14.669	-27.597 -26.929
40. Benzynocyclo-6-alkene	C1 C2	-14.669	-28.627 -27.709
41. 3-methoxybenzyne	C1 C2	-14.669	-26.534 -27.369

Table 4.1.a. (continued)

Systems	Reactive Position	$V_{el}(\bar{r})$ in isolated atom (in a. u.)	$V_{el}(\bar{r})$ in molecule (in a. u.)
42. Naphthalene	C1	-14.669	-27.528
	C2		-28.358
43. Fluoranthene	C3	-14.669	-31.805
44. Pyrene	C1	-14.669	-32.024
45. Fluorene	C2	-14.669	-29.115
46. Acenaphthene	C5	-14.669	-29.858
47. Anthracene	C9	-14.669	-32.211
48. Chrysene	C6	-14.669	-33.787

Table 4.1.b. Trend of $V_{el}(\bar{r})$ for the hetero atoms in molecules vs. isolated atoms at B3LYP/6-311+G(2d, 2p) level. Numbering of atoms (for amino acids) is given in Figure 4.1.

Systems	**Hetero Atoms**	$V_{el}(\bar{r})$ **in isolated atom (in a. u.)**	$V_{el}(\bar{r})$ **in molecule (in a. u.)**
1. Alanine	N	-18.302	-27.878
	O1	-22.232	-31.633
	O2		-31.537
2. Valine	N	-18.302	-30.426
	O1	-22.232	-33.449
	O2		-33.784
3. Leucine	N	-18.302	-30.730
	O1	-22.232	-33.999
	O2		-34.769
4. Isoleucine	N	-18.302	-31.066
	O1	-22.232	-34.398
	O2		-34.913
5. Phenylalanine	N	-18.302	-31.929
	O1	-22.232	-35.638
	O2		-36.559
6. Tryptophan	N1	-18.302	-36.301
	N2	-22.232	-34.476
	O1		-37.173
	O1		-37.451
7. Methionine	N1	-18.302	-31.193
	O1	-22.232	-34.477
	O2		-35.425
	S	-59.179	-69.464
8. Proline	N	-18.302	-31.432
	O1	-22.232	-33.421
	O2		-32.901
9. Aspartic Acid	N	-18.302	-30.579
	O1	-22.232	-33.925
	O2		-33.425
	O3		-34.433
	O4		-34.975
10. Glutamine	N1	-18.302	-30.960
	N2	-22.232	-30.133
	O1		-34.778
	O2		-34.096
	O3		-34.811
11. Glycine	N	-18.302	-26.358
	O1	-22.232	-30.503
	O2		-30.126

Table 4.1. b. (continued)

Systems	Reactive Position	$V_{el}(\bar{r})$ in isolated atom (in a. u.)	$V_{el}(\bar{r})$ in molecule (in a. u.)
12. Serine	N	-18.302	-28.901
	O1	-22.232	-32.183
	O2		-32.925
	O3		-32.576
13. Threonine	N	-18.302	-30.519
	O1	-22.232	-34.046
	O2		-33.767
	O3		-33.604
14. Cysteine	N	-18.302	-29.819
	O1	-22.232	-34.095
	O2		-33.401
	S	-59.179	-67.524
15. Tyrosine	N	-18.302	-32.357
	O1	-22.232	-36.937
	O2		-34.741
	O3		-36.652
16. Asparagine	N1	-18.302	-30.519
	N2	-22.232	-30.125
	O1		-33.944
	O2		-34.198
	O3		-34.992
17. Glutamic Acid	N1	-18.302	-30.941
	O1	-22.232	-34.750
	O2		-34.264
	O3		-33.576
	O4		-34.853
18. Lysine	N1	-18.302	-30.984
	N2	-22.232	-28.632
	O1		-34.324
	O2		-35.198
19. Arginine	N1	-18.302	-31.249
	N2	-22.232	-30.544
	N3		-33.989
	N4		-31.773
	O1		-35.771
	O2		-35.805
20. Histidine	N1	-18.302	-32.974
	N2	-22.232	-32.079
	N3		-32.927
	O1		-34.562
	O2		-34.677
21. 1-methoxy-2 methylbenzene	O	-22.232	-35.037
22. 1-methoxy-3-methylbenzene	O	-22.232	-34.386
23. 1-methoxy-4-methylbenzene	O	-22.232	-34.269
24. Methoxybenzene	O	-22.232	-33.565

Table 4.1.b. (continued)

Systems	Reactive Position	$V_{el}(\bar{r})$ in isolated atom (in a. u.)	$V_{el}(\bar{r})$ in molecule (in a. u.)
25. 1-methoxy-2-fluorobenzene	O F	-22.232 -26.519	-34.996 -37.820
26. 1-methoxy-3-fluorobenzene	O F	-22.232 -26.519	-34.449 -36.622
27. 1-methoxy-4-fluorobenzene	O F	-22.232 -26.519	-34.327 -36.297
28. 1-methoxy-2-chlorobenzene	O Cl	-22.232 -64.351	-36.080 -74.109
29. 1-methoxy-3-chlorobenzene	O Cl	-22.232 -64.351	-35.199 -73.109
30. 1-methoxy-4-chlorobenzene	O Cl	-22.232 -64.351	-34.984 -72.809
31. 1-methoxy-2-bromobenzene	O Br	-22.232 -175.794	-38.723 -185.061
32. 1-methoxy-3-bromobenzene	O Br	-22.232 -175.794	-36.953 -184.130
33. 1-methoxy-4-bromobenzene	O Br	-22.232 -175.794	-36.517 -183.841
34. 1-methoxy-2,3 dimethylbenzene	O	-22.232	-35.858
35. 1-methoxy-2,4-dimethylbenzen	O	-22.232	-35.741
36. 1-methoxy-3,4-dimethylbenzene	O	-22.232	-35.115
37. 1-methoxy-3,5-dimethylbenzene	O	-22.232	-35.231
38. 1,4-dimethoxybenzene	O1 O2	-22.232	-34.948 -34.949
39. 3-methoxybenzyne	O	-22.232	-33.565
40. Flurobenzene	F	-26.519	-34.902
41. Chlorobenzene	Cl	-64.351	-71.498
42. Bromobenzene	Br	-175.794	-182.559
43. C3-Br-substituted-4,5-indolyne	Br	-175.794	-185.158
44. C6-Br-substituted-4,5-indolyne	Br	-175.794	-184.676

Table 4.2.a. Trends of Fukui Potentials at the reactive atoms in a molecule vs isolated atom at B3LYP/6-311+G(2d, 2p) level (in atomic units). Numbering of atoms is as per standard numbering convention.

Systems	Reactive Position	$v_f^-\big\vert_{r=0}$ in isolated atom	$v_f^+\big\vert_{r=0}$ in isolated atom	$v_f^-\big\vert_{r=0}$ in molecule	$v_f^+\big\vert_{r=0}$ in molecule
1. Benzene	C1	0.512	0.467	0.258	0.141
2. Toluene	C2 C4	0.512	0.467	0.215 0.245	0.130 0.128
3. 1,2-dimethylbenzene	C3 C4	0.512	0.467	0.199 0.227	0.124 0.123
4. 1,3-dimethylbenzene	C2 C4	0.512	0.467	0.199 0.229	0.124 0.123
5. 1,4-dimethylbenzene	C2	0.512	0.467	0.211	0.119
6. 1,2,4,5-tetramethyl-benzene	C3	0.512	0.467	0.188	0.115
7. Pentamethylbenzene	C6	0.512	0.467	0.184	0.111
8. Tert-butyl-benzene	C3 C4	0.512	0.467	0.208 0.228	0.117 0.116
9. Flurobenzene	C2 C3 C4	0.512	0.467	0.229 0.225 0.259	0.168 0.172 0.164
10. Chlorobenzene	C2 C3 C4	0.512	0.467	0.213 0.207 0.228	0.136 0.141 0.141
11. Bromobenzene	C2 C3 C4	0.512	0.467	0.205 0.198 0.217	0.211 0.213 0.189
12. Methoxybenzene	C2 C4	0.512	0.467	0.211 0.227	0.127 0.122
13. 1-methoxy-2-fluorobenzene	C4	0.512	0.467	0.224	0.146
14. 1-methoxy-3-fluorobenzene	C4	0.512	0.467	0.233	0.118
15. 1-methoxy-4-fluorobenzene	C2	0.512	0.467	0.213	0.152
16. 1-methoxy-2-chlorobenzene	C4	0.512	0.467	0.209	0.184
17. 1-methoxy-3-chlorobenzene	C4 C6	0.512	0.467	0.218 0.218	0.183 0.207
18. 1-methoxy-4-chlorobenzene	C2	0.512	0.467	0.202	0.214
19. 1-methoxy-2-bromobenzene	C4	0.512	0.467	0.190	0.197
20. 1-methoxy-3-bromobenzene	C6	0.512	0.467	0.214	0.177
21. 1-methoxy-4-bromobenzene	C2	0.512	0.467	0.197	0.131
22.1-methoxy-2,3 dimethylbenzene	C4	0.512	0.467	0.214	0.114

Table 4.2.a. (continued)

Systems	Reactive Position	$v_f^-\big\vert_{r=0}$ in isolated atom	$v_f^+\big\vert_{r=0}$ in isolated atom	$v_f^-\big\vert_{r=0}$ in molecule	$v_f^+\big\vert_{r=0}$ in molecule
23. 1-methoxy-2,4-dimethylbenzen	C6	0.512	0.335	0.197	0.118
24. 1-methoxy-3,4-dimethylbenzene	C6	0.512	0.335	0.204	0.117
25. 1-methoxy-3,5-dimethylbenzene	C4 C6	0.512	0.335	0.221 0.203	0.113 0.110
26. 1,3,5-trimethyl-2-ethylbenzene	C4	0.512	0.335	0.191	0.115
27. 1,3,5-trimethyl-2-chlorobenzene	C4	0.512	0.335	0.193	0.119
28. 1,3,5-trimethyl-2-bromobenzene	C4	0.512	0.335	0.186	0.115
29. 1,4-dimethoxybenzene	C2	0.512	0.335	0.203	0.112
30. 1-methoxy-2 methylbenzene	C4 C6	0.512	0.335	0.219 0.215	0.118 0.116
31. 1-methoxy-3-methylbenzene	C4	0.512	0.335	0.224	0.117
32. 1-methoxy-4-methylbenzene	C2	0.512	0.335	0.205	0.122
33. 4,5-indolyne	C4 C5	0.512	0.335	0.199 0.194	0.235 0.237
34. 5,6-indolyne	C5 C6	0.512	0.335	0.191 0.19	0.242 0.239
35. 6,7-indolyne	C6 C7	0.512	0.335	0.197 0.206	0.242 0.234
36. C3-Br-substituted-4,5-indolyne	C4 C5	0.512	0.335	0.182 0.175	0.236 0.238
37. C6-Br-substituted-4,5-indolyne	C4 C5	0.512	0.335	0.184 0.178	0.235 0.234
38. Benzynocyclo-4-alkene	C1 C2	0.512	0.335	0.215 0.229	0.241 0.243
39. Benzynocyclo-5-alkene	C1 C2	0.512	0.335	0.209 0.218	0.238 0.239
40. Benzynocyclo-6-alkene	C1 C2	0.512	0.335	0.203 0.2174	0.233 0.234
41. 3-methoxybenzyne	C1 C2	0.512	0.335	0.202 0.216	0.121 0.120
42. Naphthalene	C1 C2	0.512	0.335	0.187 0.201	0.176 0.190
43. Fluoranthene	C3	0.512	0.335	0.166	0.165
44. Pyrene	C1	0.512	0.335	0.168	0.161
45. Fluorene	C2	0.512	0.335	0.181	0.167
46. Acenaphthene	C5	0.512	0.335	0.189	0.179
47. Anthracene	C9	0.512	0.335	0.183	0.176
48. Chrysene	C6	0.512	0.335	0.162	0.156

Table 4.2.b. Trends of Fukui Potential at hetero atoms in molecules vs isolated atoms at B3LYP/6-311+G(2d, 2p) level (in atomic units). Numbering of atoms (for amino acids) is given in Figure 4.1.

Systems	Hetero Atoms	$v_f^-\big\vert_{r=0}$ in isolated atom	$v_f^+\big\vert_{r=0}$ in isolated atom	$v_f^-\big\vert_{r=0}$ in molecule	$v_f^+\big\vert_{r=0}$ in molecule
1. Alanine	N	0.616	0.382	0.335	0.149
	O1	0.661	0.486	0.215	0.159
	O2	`		0.194	0.162
2. Valine	N	0.616	0.382	0.308	0.135
	O1	0.661	0.486	0.214	0.129
	O2	`		0.192	0.138
3. Leucine	N	0.616	0.382	0.314	0.132
	O1	0.661	0.486	0.193	0.143
	O2	`		0.182	0.148
4. Isoleucine	N	0.616	0.382	0.329	0.130
	O1	0.661	0.486	0.179	0.144
	O2	`		0.170	0.147
5. Phenylalanine	N	0.616	0.382	0.119	0.129
	O1	0.661	0.486	0.138	0.121
	O2	`		0.128	0.124
6. Tryptophan	N1	0.616	0.382	0.193	0.125
	N2	0.661	0.486	0.149	0.111
	O1	`		0.120	0.115
	O1			0.114	0.126
7. Methionine	N1	0.616	0.382	0.206	0.131
	O1	0.661	0.486	0.138	0.142
	O2	`		0.135	0.146
	S			0.239	0.115
8. Proline	N	0.616	0.382	0.332	0.133
	O1	0.661	0.486	0.181	0.140
	O2	`		0.173	0.155
9. Aspartic Acid	N	0.616	0.382	0.239	0.147
	O1	0.661	0.486	0.159	0.173
	O2	`		0.285	0.127
	O3			0.205	0.133
	O4			0.158	0.178
10. Glutamine	N1	0.616	0.382	0.203	0.104
	N2	0.661	0.486	0.188	0.144
	O1	`		0.142	0.125
	O2			0.283	0.127
	O3			0.146	0.136
11. Glycine	N	0.616	0.382	0.381	0.145
	O1	0.661	0.486	0.188	0.152
	O2	`		0.182	0.163
12. Serine	N	0.616	0.382	0.297	0.148
	O1	0.661	0.486	0.166	0.153
	O2	`		0.254	0.151
	O3			0.211	0.153

Table 4.2.b. (continued)

Systems	Hetero Atoms	$v_f^-\big\vert_{r=0}$ in isolated atom	$v_f^+\big\vert_{r=0}$ in isolated atom	$v_f^-\big\vert_{r=0}$ in molecule	$v_f^+\big\vert_{r=0}$ in molecule
13. Threonine	N	0.616	0.382	0.317	0.127
	O1	0.661	0.486	0.184	0.148
	O2	`		0.200	0.126
	O3			0.184	0.133
14. Cysteine	N	0.616	0.382	0.239	0.157
	O1	0.661	0.486	0.199	0.156
	O2	`		0.171	0.162
	S			0.237	0.131
15. Tyrosine	N	0.616	0.382	0.146	0.112
	O1	0.661	0.486	0.135	0.121
	O2	`		0.204	0.124
	O3			0.129	0.127
16. Asparagine	N1	0.616	0.382	0.234	0.128
	N2	0.661	0.486	0.195	0.147
	O1	`		0.165	0.142
	O2			0.279	0.142
	O3			0.165	0.151
17. Glutamic Acid	N1	0.616	0.382	0.224	0.115
	O1	0.661	0.486	0.176	0.132
	O2	`		0.240	0.125
	O3			0.174	0.138
	O4			0.165	0.145
18. Lysine	N1	0.616	0.382	0.129	0.126
	N2	0.661	0.486	0.319	0.114
	O1	`		0.117	0.133
	O2			0.119	0.135
19. Arginine	N1	0.616	0.382	0.181	0.113
	N2	0.661	0.486	0.223	0.109
	N3	`		0.206	0.119
	N4			0.167	0.112
	O1			0.115	0.121
	O2			0.111	0.128
20. Histidine	N1	0.616	0.382	0.177	0.202
	N2	0.661	0.486	0.174	0.206
	N3			0.228	0.205
	O1			0.180	0.131
	O2			0.225	0.137
21. 1-methoxy-2 methylbenzene	O	0.661	0.486	0.229	0.122
22. 1-methoxy-3-methylbenzene	O	0.661	0.486	0.230	0.119
23. 1-methoxy-4-methylbenzene	O	0.661	0.486	0.229	0.119
24. Methoxybenzene	O	0.661	0.486	0.242	0.126
25. 1-methoxy-2-fluorobenzene	O	0.661	0.486	0.243	0.137
	F	0.764	0.532	0.200	0.130
26. 1-methoxy-3-fluorobenzene	O	0.661	0.486	0.231	0.127
	F	0.764	0.532	0.195	0.110

Table 4.2.b. (continued)

Systems	Hetero Atoms	$v_f^-\big\vert_{r=0}$ in isolated atom	$v_f^+\big\vert_{r=0}$ in isolated atom	$v_f^-\big\vert_{r=0}$ in molecule	$v_f^+\big\vert_{r=0}$ in molecule
27. 1-methoxy-4-fluorobenzene	O F	0.661 0.764	0.486 0.532	0.229 0.209	0.144 0.125
28. 1-methoxy-2-chlorobenzene	O Cl	0.661 0.487	0.486 0.371	0.235 0.189	0.157 0.161
29. 1-methoxy-3-chlorobenzene	O Cl	0.661 0.487	0.486 0.371	0.222 0.181	0.158 0.165
30. 1-methoxy-4-chlorobenzene	O Cl	0.661 0.487	0.486 0.371	0.222 0.195	0.160 0.158
31. 1-methoxy-2-bromobenzene	O Br	0.661 0.425	0.486 0.333	0.230 0.187	0.153 0.155
32. 1-methoxy-3-bromobenzene	O Br	0.661 0.425	0.486 0.333	0.214 0.181	0.153 0.158
33. 1-methoxy-4-bromobenzene	O Br	0.661 0.425	0.486 0.333	0.212 0.192	0.129 0.127
34. 1-methoxy-2,3 dimethylbenzene	O	0.661	0.486	0.228	0.119
35. 1-methoxy-2,4-dimethylbenzen	O	0.661	0.486	0.221	0.118
36. 1-methoxy-3,4-dimethylbenzene	O	0.661	0.486	0.223	0.114
37. 1-methoxy-3,5-dimethylbenzene	O	0.661	0.486	0.227	0.114
38. 1,4-dimethoxybenzene	O1 O2	0.661	0.486	0.211 0.211	0.113 0.113
39. 3-methoxybenzyne	O	0.661	0.486	0.242	0.126
40. Flurobenzene	F	0.764	0.532	0.233	0.141
41. Chlorobenzene	Cl	0.487	0.371	0.228	0.122
42. Bromobenzene	Br	0.425	0.333	0.226	0.156
43. C3-Br-substituted-4,5-indolyne	Br	0.425	0.333	0.184	0.135
44. C6-Br-substituted-4,5-indolyne	Br	0.425	0.333	0.173	0.149

Table 4.2.c. Trends of Hardness Potential Derivatives of reactive atoms in molecules vs isolated atoms at B3LYP/6-311+G(2d, 2p) level (in atomic units). Numbering of atoms is as per standard numbering convention.

Systems	Reactive Position	$\Delta^{-}h(k)$ in isolated atom	$\Delta^{+}h(k)$ in isolated atom	$\Delta^{-}h(k)$ in molecule	$\Delta^{+}h(k)$ in molecule
1. Benzene	C1	0.149	0.147	0.159	0.138
2. Toluene	C2 C4	0.149	0.147	0.196 0.188	0.132 0.099
3. 1,2-dimethylbenzene	C3 C4	0.149	0.147	0.196 0.187	0.129 0.124
4. 1,3-dimethylbenzene	C2 C4	0.149	0.147	0.199 0.181	0.135 0.130
5. 1,4-dimethylbenzene	C2	0.149	0.147	0.193	0.121
6. 1,2,4,5-tetramethyl-benzene	C3	0.149	0.147	0.189	0.117
7. Pentamethylbenzene	C6	0.149	0.147	0.183	0.112
8. Tert-butyl-benzene	C3 C4	0.149	0.147	0.187 0.175	0.121 0.119
9. Flurobenzene	C2 C3 C4	0.149	0.147	0.202 0.179 0.235	0.129 0.178 0.127
10. Chlorobenzene	C2 C3 C4	0.149	0.147	0.193 0.193 0.176	0.098 0.101 0.143
11. Bromobenzene	C2 C3 C4	0.149	0.147	0.187 0.185 0.169	0.174 0.174 0.191
12. Methoxybenzene	C2 C4	0.149	0.147	0.190 0.176	0.139 0.124
13. 1-methoxy-2-fluorobenzene	C4	0.149	0.147	0.179	0.139
14. 1-methoxy-3-fluorobenzene	C4	0.149	0.147	0.180	0.121
15. 1-methoxy-4-fluorobenzene	C2	0.149	0.147	0.186	0.136
16. 1-methoxy-2-chlorobenzene	C4	0.149	0.147	0.165	0.183
17. 1-methoxy-3-chlorobenzene	C4 C6	0.149	0.147	0.168 0.177	0.183 0.166

Table 4.2.c. (Continued)

Systems	Reactive Position	$\Delta^{-}h(k)$ in isolated atom	$\Delta^{+}h(k)$ in isolated atom	$\Delta^{-}h(k)$ in molecule	$\Delta^{+}h(k)$ in molecule
18. 1-methoxy-4-chlorobenzene	C2	0.149	0.147	0.177	0.169
19. 1-methoxy-2-bromobenzene	C4	0.149	0.147	0.177	0.165
20. 1-methoxy-3-bromobenzene	C6	0.149	0.147	0.167	0.176
21. 1-methoxy-4-bromobenzene	C2	0.149	0.147	0.175	0.132
22. 1-methoxy-2,3 dimethylbenzene	C4	0.149	0.147	0.168	0.117
23. 1-methoxy-2,4-dimethylbenzen	C6	0.149	0.147	0.181	0.124
24. 1-methoxy-3,4-dimethylbenzene	C6	0.149	0.147	0.179	0.122
25. 1-methoxy-3,5-dimethylbenzene	C4 C6	0.149	0.147	0.221 0.203	0.065 0.088
26. 1,3,5-trimethyl-2-ethylbenzene	C4	0.149	0.147	0.183	0.115
27. 1,3,5-trimethyl-2-chlorobenzene	C4	0.149	0.147	0.175	0.125
28. 1,3,5-trimethyl-2-bromobenzene	C4	0.149	0.147	0.174	0.115
29. 1,4-dimethoxybenzene	C2	0.149	0.147	0.180	0.113
30. 1-methoxy-2 methylbenzene	C4 C6	0.149	0.147	0.174 0.174	0.119 0.114
31. 1-methoxy-3-methylbenzene	C4	0.149	0.147	0.173	0.123
32. 1-methoxy-4-methylbenzene	C2	0.149	0.147	0.184	0.128
33. 4,5-indolyne	C4 C5	0.149	0.147	0.179 0.189	0.255 0.247
34. 5,6-indolyne	C5 C6	0.149	0.147	0.191 0.190	0.255 0.268
35. 6,7-indolyne	C6 C7	0.149	0.147	0.180 0.187	0.231 0.266
36. C3-Br-substituted-4,5-indolyne	C4 C5	0.149	0.147	0.168 0.164	0.266 0.246
37. C6-Br-substituted-4,5-indolyne	C4 C5	0.149	0.147	0.172 0.181	0.242 0.258
38. Benzynocyclo-4-alkene	C1 C2	0.149	0.147	0.222 0.212	0.251 0.252
39. Benzynocyclo-5-alkene	C1 C2	0.149	0.147	0.219 0.194	0.248 0.252
40. Benzynocyclo-6-alkene	C1 C2	0.149	0.147	0.213 0.193	0.241 0.249
41. 3-methoxybenzyne	C1 C2	0.149	0.147	0.195 0.187	0.126 0.123
42. Naphthalene	C1 C2	0.149	0.147	0.167 0.169	0.160 0.163
43. Fluoranthene	C3	0.149	0.147	0.141	0.141
44. Pyrene	C1	0.149	0.147	0.142	0.136
45. Fluorene	C2	0.149	0.147	0.146	0.140
46. Acenaphthene	C5	0.149	0.147	0.158	0.151
47. Anthracene	C9	0.149	0.147	0.152	0.147
48. Chrysene	C6	0.149	0.147	0.134	0.131

Table 4.2.d.: Trends of Hardness Potential Derivatives of hetero atoms in molecules vs isolated atoms at B3LYP/6-311+g(2d, 2p) level (in atomic units). Numbering of atoms (for amino acids) is given in Figure 4.1.

Systems	Hetero Atoms	$\Delta^{-}h(k)$ in isolated atom	$\Delta^{+}h(k)$ in isolated atom	$\Delta^{-}h(k)$ in molecule	$\Delta^{+}h(k)$ in molecule
1. Alanine	N	0.172	0.192	0.243	0.164
	O1	0.214	0.207	0.156	0.146
	O2			0.179	0.182
2. Valine	N	0.172	0.192	0.263	0.154
	O1	0.214	0.207	0.139	0.122
	O2			0.185	0.171
3. Leucine	N	0.172	0.192	0.232	0.143
	O1	0.214	0.207	0.149	0.133
	O2			0.179	0.163
4. Isoleucine	N	0.172	0.192	0.241	0.144
	O1	0.214	0.207	0.145	0.134
	O2			0.166	0.159
5. Phenylalanine	N	0.172	0.192	0.069	0.146
	O1	0.214	0.207	0.106	0.109
	O2			0.123	0.141
6. Tryptophan	N1	0.172	0.192	0.151	0.142
	N2			0.141	0.116
	O1	0.214	0.207	0.102	0.107
	O1			0.113	0.155
7. Methionine	N1	0.172	0.192	0.185	0.139
	O1	0.214	0.207	0.113	0.131
	O2			0.148	0.163
	S	0.187	0.189	0.120	0.108
8. Proline	N	0.172	0.192	0.223	0.133
	O1	0.214	0.207	0.145	0.122
	O2			0.140	0.171
9. Aspartic Acid	N	0.172	0.192	0.188	0.159
	O1	0.214	0.207	0.129	0.158
	O2			0.181	0.113
	O3			0.179	0.135
	O4			0.166	0.203
10. Glutamine	N1	0.172	0.192	0.131	0.104
	N2			0.202	0.187
	O1	0.214	0.207	0.122	0.119
	O2			0.198	0.115
	O3			0.154	0.159
11. Glycine	N	0.172	0.192	0.169	0.162
	O1	0.214	0.207	0.156	0.155
	O2			0.176	0.190
12. Serine	N	0.172	0.192	0.236	0.176
	O1	0.214	0.207	0.165	0.169
	O2			0.167	0.132
	O3			0.189	0.160

Table 4.2.d. (continued)

Systems	Hetero Atoms	$\Delta^{-}h(k)$ in isolated atom	$\Delta^{+}h(k)$ in isolated atom	$\Delta^{-}h(k)$ in molecule	$\Delta^{+}h(k)$ in molecule
13. Threonine	N	0.172	0.192	0.236	0.131
	O1	0.214	0.207	0.180	0.159
	O2			0.153	0.118
	O3			0.174	0.152
14. Cysteine	N	0.172	0.192	0.225	0.199
	O1	0.214	0.207	0.164	0.153
	O2			0.162	0.186
	S	0.197	0.189	0.126	0.115
15. Tyrosine	N	0.172	0.192	0.138	0.122
	O1	0.214	0.207	0.115	0.121
	O2			0.145	0.130
	O3			0.131	0.139
16. Asparagine	N1	0.172	0.192	0.177	0.144
	N2			0.209	0.189
	O1	0.214	0.207	0.128	0.128
	O2			0.190	0.125
	O3			0.171	0.174
17. Glutamic Acid	N1	0.172	0.192	0.179	0.114
	O1	0.214	0.207	0.131	0.129
	O2			0.171	0.108
	O3			0.155	0.148
	O4			0.164	0.174
18. Lysine	N1	0.172	0.192	0.071	0.134
	N2			0.296	0.126
	O1	0.214	0.207	0.094	0.121
	O2			0.124	0.146
19. Arginine	N1	0.172	0.192	0.168	0.134
	N2	0.214	0.207	0.144	0.102
	N3			0.162	0.125
	N4			0.133	0.114
	O1			0.100	0.142
	O2			0.115	0.122
20. Histidine	N1	0.172	0.192	0.152	0.171
	N2			0.166	0.204
	N3			0.186	0.195
	O1	0.214	0.207	0.159	0.139
	O2			0.152	0.114
21. 1-methoxy-2 methylbenzene	O	0.214	0.207	0.155	0.117
22. 1-methoxy-3-methylbenzene	O	0.214	0.207	0.154	0.113
23. 1-methoxy-4-methylbenzene	O	0.214	0.207	0.152	0.113
24. Methoxybenzene	O	0.214	0.207	0.157	0.120
25. 1-methoxy-2-fluorobenzene	O	0.214	0.207	0.163	0.133
	F	0.234	0.250	0.155	0.123
26. 1-methoxy-3-fluorobenzene	O	0.214	0.207	0.149	0.124
	F	0.234	0.250	0.155	0.102

Table 4.2.d. (continued)

Systems	Hetero Atoms	$\Delta^{-}h(k)$ in isolated atom	$\Delta^{+}h(k)$ in isolated atom	$\Delta^{-}h(k)$ in molecule	$\Delta^{+}h(k)$ in molecule
27. 1-methoxy-4-fluorobenzene	O F	0.214 0.234	0.207 0.250	0.142 0.154	0.137 0.109
28. 1-methoxy-2-chlorobenzene	O Cl	0.214 0.216	0.207 0.218	0.150 0.147	0.151 0.138
29. 1-methoxy-3-chlorobenzene	O Cl	0.214 0.216	0.207 0.218	0.150 0.133	0.149 0.139
30. 1-methoxy-4-chlorobenzene	O Cl	0.214 0.216	0.207 0.218	0.148 0.135	0.153 0.135
31. 1-methoxy-2-bromobenzene	O Br	0.214 0.226	0.207 0.212	0.149 0.140	0.146 0.134
32. 1-methoxy-3-bromobenzene	O Br	0.214 0.226	0.207 0.212	0.148 0.134	0.145 0.135
33. 1-methoxy-4-bromobenzene	O Br	0.214 0.226	0.207 0.212	0.142 0.136	0.122 0.123
34. 1-methoxy-2,3 dimethylbenzene	O	0.214	0.207	0.151	0.115
35. 1-methoxy-2,4-dimethylbenzen	O	0.214	0.207	0.150	0.113
36. 1-methoxy-3,4-dimethylbenzene	O	0.214	0.207	0.149	0.109
37. 1-methoxy-3,5-dimethylbenzene	O	0.214	0.207	0.227	0.033
38. 1,4-dimethoxybenzene	O1 O2	0.214	0.207	0.144 0.144	0.108 0.108
39. 3-methoxybenzyne	O	0.214	0.207	0.157	0.120
40. Flurobenzene	F	0.234	0.250	0.158	0.116
41. Chlorobenzene	Cl	0.216	0.218	0.152	0.098
42. Bromobenzene	Br	0.226	0.212	0.155	0.134
43. C3-Br-substituted-4,5-indolyne	Br	0.226	0.212	0.132	0.122
44. C6-Br-substituted-4,5-indolyne	Br	0.226	0.212	0.128	0.136

Table 4.3.a. Electron Density values at the nucleus (i. e., $r \to 0$, see text) at B3LYP/6-31G(d,p) level for isolated atoms (in atomic units)

Isolated Atom	Neutral	Cation	Anion
C	119.268	119.775	118.903
O	291.190	291.911	290.678
N	192.405	193.059	192.047
F	419.257	420.127	418.830
Cl	3021.419	3023.132	3020.237
Br	28288.661	28292.370	28286.012
S	2504.004	2505.342	2502.889

Table 4.3.b. Electron Density values at the nucleus (i. e., $r \to 0$, see text) at B3LYP/6-311G(2d,2p) (in atomic units).

Isolated Atom	Neutral	Cation	Anion
C	121.243	122.156	120.547
O	296.867	298.419	295.579
N	196.023	197.339	195.135
F	427.307	429.379	425.782
Cl	3122.533	3124.403	3121.392
Br	28733.053	28735.977	28731.024
S	2589.053	2590.527	2588.019

Table 4.3.c. Electron Density values at the nucleus (i. e., $r \to 0$, see text) at B3LYP/6-311+G(2d,2p) level for isolated atoms (in atomic units).

Isolated Atom	Neutral	Cation	Anion
C	121.283	122.138	120.843
O	296.944	298.358	296.064
N	196.080	197.306	195.557
F	427.397	429.288	426.393
Cl	3122.516	3124.381	3121.460
Br	28733.074	28735.948	28731.328
S	2589.043	2590.505	2588.066

Table 4.4.a. Trend of the sum of Fukui Potentials at B3LYP/6-311+G(2d, 2p) level (in atomic units).

Systems	$\sum_K v_f^-(\bar{r})\mid_{r=0}$	$\sum_K v_f^+(\bar{r})\mid_{r=0}$
1. Benzene	2.725	1.681
2. Toluene	3.144	1.922
3. 1,2-dimethylbenzene	3.547	2.239
4. 1,3-dimethylbenzene	3.523	2.202
5. 1,4-dimethylbenzene	3.541	2.196
6. 1,2,4,5-tetramethyl-benzene	4.261	2.764
7. Pentamethylbenzene	4.619	3.0565
8. Tert-butyl-benzene	4.195	2.809
9. Flurobenzene	2.726	1.958
10. Chlorobenzene	2.523	1.644
11. Bromobenzene	2.425	2.345
12. Methoxybenzene	3.977	2.014
13. 1-methoxy-2-fluorobenzene	3.226	2.234
14. 1-methoxy-3-fluorobenzene	3.215	1.992
15. 1-methoxy-4-fluorobenzene	3.223	2.347
16. 1-methoxy-2-chlorobenzene	3.092	2.779
17.1-methoxy-3-chlorobenzene	3.071	2.801
18. 1-methoxy-4-chlorobenzene	3.041	2.854
19. 1-methoxy-2-bromobenzene	3.026	2.693
20. 1-methoxy-3-bromobenzene	2.996	2.699
21. 1-methoxy-4-bromobenzene	2.952	2.216

Table 4.4.a. (Continued)

Systems	$\sum_K v_f^-(\bar{r})\mid_{r=0}$	$\sum_K v_f^+(\bar{r})\mid_{r=0}$
22.1-methoxy-2,3 dimethylbenzene	3.965	2.533
23. 1-methoxy-2,4-dimethylbenzen	3.961	2.517
24.1-methoxy-3,4-dimethylbenzene	3.953	2.516
25.1-methoxy-3,5-dimethylbenzene	3.931	2.506
26. 1,3,5-trimethyl-2-ethylbenzene	4.579	3.145
27.1,3,5-trimethyl-2-chlorobenzene	3.691	2.453
28.1,3,5-trimethyl-2-bromobenzene	3.602	2.412
29. 1,4-dimethoxybenzene	3.669	2.307
30. 1-methoxy-2-methylbenzene	3.610	2.272
31. 1-methoxy-3-methylbenzene	3.589	2.273
32. 1-methoxy-4-methylbenzene	3.598	2.254
33. 4,5-indolyne	3.216	2.821
34. 5,6-indolyne	3.232	2.851
35. 6,7-indolyne	3.214	2.879
36. C3-Br-substituted-4,5-indolyne	2.993	2.782
37. C6-Br-substituted-4,5-indolyne	2.992	2.748
38. Benzynocyclo-4-alkene	2.929	2.541
39. Benzynocyclo-5-alkene	3.358	2.884
40. Benzynocyclo-6-alkene	3.702	3.198
41. 3-methoxybenzyne	3.228	2.014

Table 4.4.a. (Continued)

Systems	$\sum_K v_f^-(\bar{r})\mid_{r=0}$	$\sum_K v_f^+(\bar{r})\mid_{r=0}$
42. Naphthalene	3.363	3.182
43. Fluoranthene	4.045	3.929
44. Pyrene	4.097	3.979
45. Fluorene	3.845	3.629
46. Acenaphthene	3.858	3.624
47. Anthracene	3.873	3.751
48. Chrysene	4.383	4.273
49. Alanine	3.059	2.009
50. Valine	3.824	2.550
51. Leucine	4.105	2.895
52. Isoleucine	4.162	2.910
53. Phenylalanine	3.915	2.869
54. Tryptophan	4.339	3.051
55. Methionine	3.502	2.592
56. Proline	3.649	2.434
57. Aspartic Acid	3.271	2.422
58. Glutamine	3.673	2.528
59. Glycine	2.645	1.534
60. Serine	3.127	2.105
61. Threonine	3.566	2.345
62. Cysteine	2.871	2.082
63. Tyrosine	4.049	2.787

Table 4.4.a. (Continued)

Systems	$\sum_K v_f^-(\bar{r})\mid_{r=0}$	$\sum_K v_f^+(\bar{r})\mid_{r=0}$
64. Asparagine	3.416	2.381
65. Glutamic Acid	3.569	2.501
66. Lysine	4.018	2.979
67. Arginine	4.099	3.126
68. Histidine	3.783	3.698

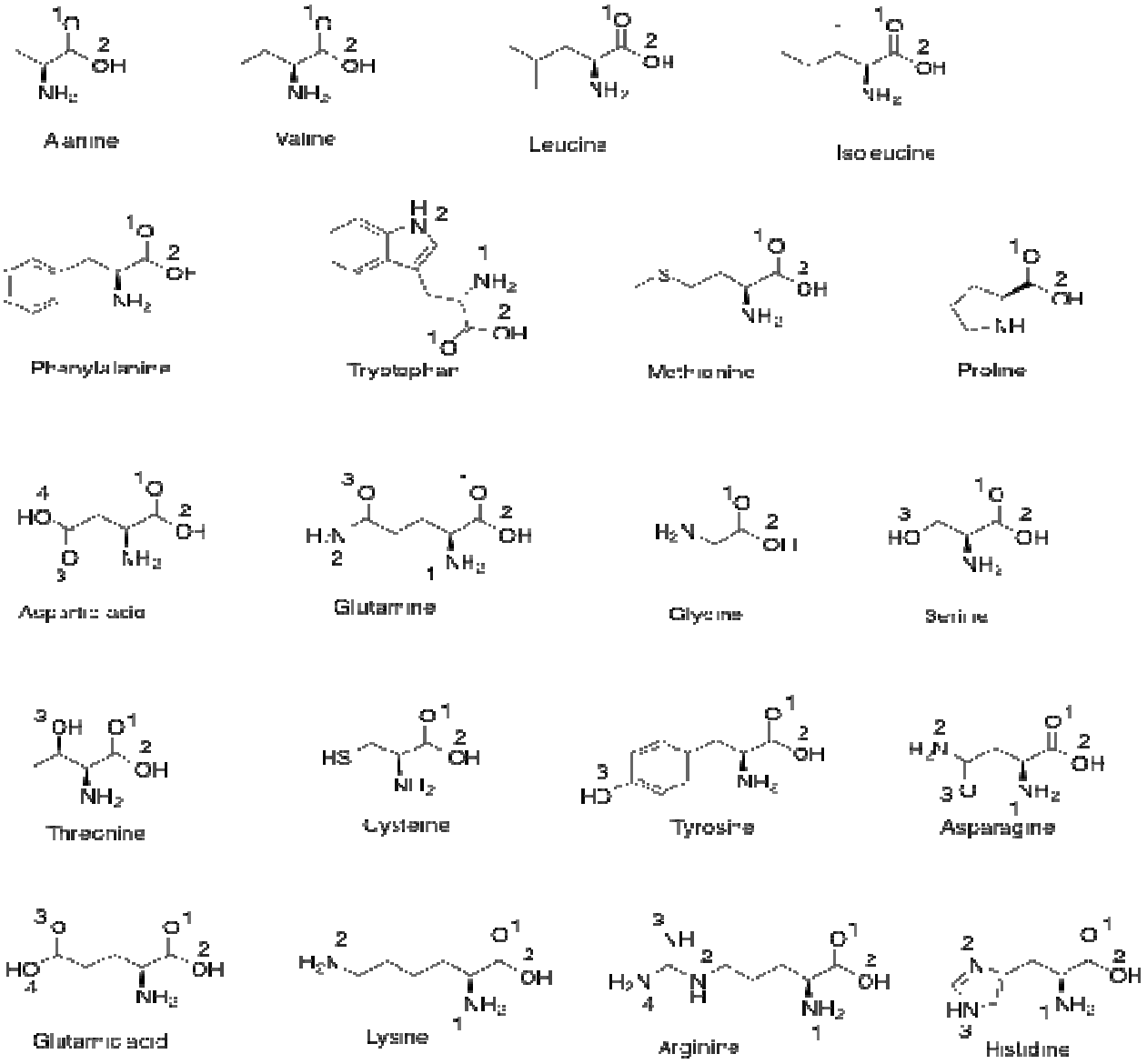
Table 4.4.b. : Trends of the sum of Hardness Potential Derivatives at B3LYP/6-311+G(2d,2p) level (in atomic units).

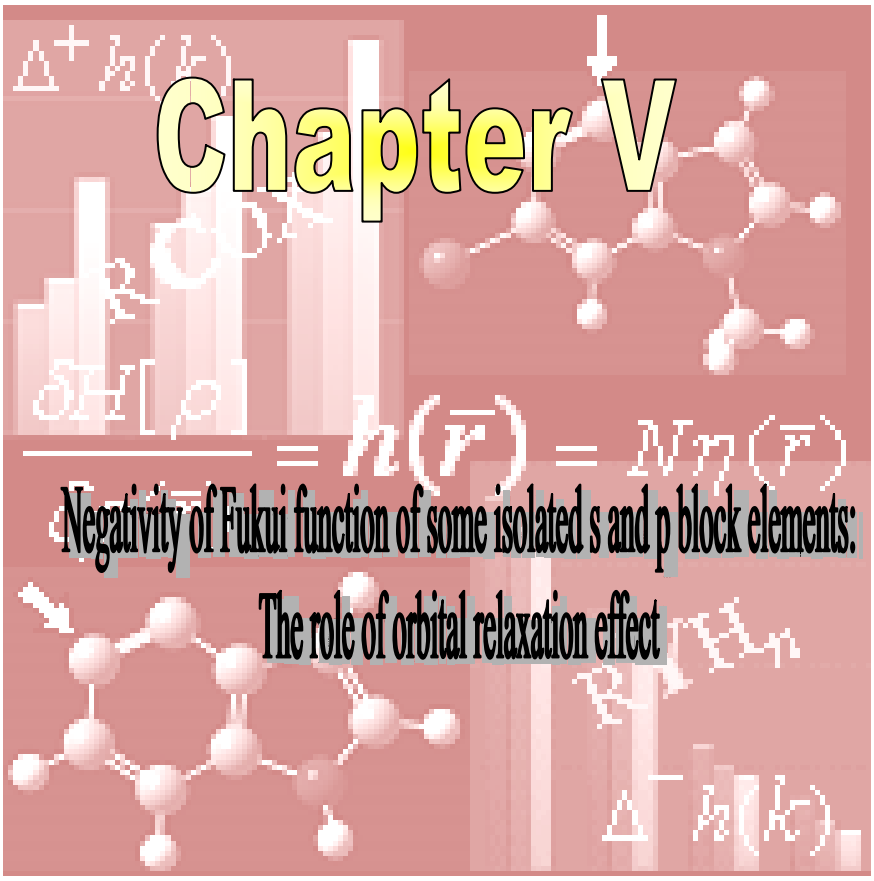
Systems	$\sum_K \Delta^- h(K)$	$\sum_K \Delta^+ h(K)$
1. Benzene	2.448	1.834
2. Toluene	3.163	1.885
3. 1,2-dimethylbenzene	3.597	2.259
4. 1,3-dimethylbenzene	3.575	2.224
5. 1,4-dimethylbenzene	3.609	2.222
6. 1,2,4,5-tetramethylbenzene	4.415	2.772
7. Pentamethylbenzene	4.746	3.113
8. Tert-butyl-benzene	4.207	2.843
9. Flurobenzene	2.593	1.842
10. Chlorobenzene	2.398	1.528
11. Bromobenzene	2.312	2.229
12. Methoxybenzene	3.163	2.036
13. 1-methoxy-2-fluorobenzene	3.105	2.230
14. 1-methoxy-3-fluorobenzene	3.094	2.012
15. 1-methoxy-4-fluorobenzene	3.081	2.309
16. 1-methoxy-2-chlorobenzene	4.326	2.969
17. 1-methoxy-3-chlorobenzene	2.951	2.677
18. 1-methoxy-4-chlorobenzene	2.908	2.736
19. 1-methoxy-2-bromobenzene	2.908	2.586
20. 1-methoxy-3-bromobenzene	2.880	2.582
21. 1-methoxy-4-bromobenzene	2.827	2.154
22. 1-methoxy-2,3-dimethylbenzene	3.945	2.556
23. 1-methoxy-2,4-dimethylbenzen	3.970	2.546
24. 1-methoxy-3,4-dimethylbenzene	3.954	2.542
25. 1-methoxy-3,5-dimethylbenzene	3.931	2.517
26. 1,3,5-trimethyl-2-ethylbenzene	4.716	3.145
27. 1,3,5-trimethyl-2-chlorobenzene	3.668	3.057
28. 1,3,5-trimethyl-2-bromobenzene	3.579	2.492
29. 1,4-dimethoxybenzene	3.583	2.334
30. 1-methoxy-2-methylbenzene	3.581	2.294
31. 1-methoxy-3-methylbenzene	3.557	2.297
32. 1-methoxy-4-methylbenzene	3.582	2.275

Table 4.4.b. (continued)

Systems	$\sum_K \Delta^- h(K)$	$\sum_K \Delta^+ h(K)$
33. Alanine	3.168	2.027
34. Valine	3.874	2.618
35. Leucine	4.256	2.916
36. Isoleucine	4.295	2.914
37. Phenylalanine	3.916	2.877
38. Tryptophan	4.302	3.066
39. Methionine	3.569	2.595
40. Proline	3.772	2.420
41. Aspartic Acid	3.248	2.408
42. Glutamine	3.692	2.560
43. Glycine	2.676	1.581
44. Serine	3.140	2.113
45. Threonine	3.644	2.364
46. Cysteine	2.857	2.116
47. Tyrosine	4.024	2.793
48. Asparagine	3.445	2.431
49. Glutamic Acid	3.564	2.491
50. Lysine	4.207	2.977
51. Arginine	4.109	3.141
52. Histidine	3.701	3.662
53. 4,5-indolyne	3.144	2.972
54. 5,6-indolyne	3.163	3.016
55. 6,7-indolyne	3.139	3.005
56. C3-Br-substituted-4,5-indolyne	2.919	2.864
57. C6-Br-substituted-4,5-indolyne	2.869	2.857
58. Benzynocyclo-4-alkene	2.919	2.674
59. Benzynocyclo-5-alkene	3.413	3.027
60. Benzynocyclo-6-alkene	3.748	3.346
61. 3-methoxybenzyne	3.163	2.036
62. Naphthalene	3.307	3.101
63. Fluoranthene	3.973	3.849
64. Pyrene	4.063	3.896
65. Fluorene	3.792	3.563
66. Acenaphthene	3.882	3.561
67. Anthracene	3.805	3.675
68. Chrysene	4.319	4.195

Figure 4.1: Numbering of Atoms in amino acids




Chapter V
Negativity of Fukui function of some isolated s and p block elements:
The role of orbital relaxation effect

5.1. Introduction:

In the last chapter, trends of three reactivity descriptors i. e., electronic contribution to molecular electrostatic potential [$V_{el}(\bar{r})_{r=0}$], Fukui potential [$v_f^+|_{r=0}$ and $v_f^-|_{r=0}$] and hardness potential derivatives [$\Delta^+h(k)$ and $\Delta^-h(k)$] for isolated atoms as well as atoms in molecules are critically investigated through the relevant formalism. Here, in this chapter, the negativity of Fukui function using orbital relaxation effects for some s and p block elements will be inspected.

5.2. Theoretical Background:

Fukui function measures[1-4] the propensity of a region in a molecule to accept or donate electrons in a chemical reaction in chemical reactivity theory.[5-8] In molecular orbital (MO) framework, electrons are taken away from the highest occupied molecular orbital (HOMO) and added to the lowest unoccupied molecular orbital (LUMO). Fukui function inherits the essence of frontier molecular orbital (FMO) theory but with corrections for orbital relaxation[9-12] and electron correlation. It is defined as:

$$f(\bar{r}) = \left(\frac{\delta\mu}{\delta v(\bar{r})}\right)_N = \left(\frac{\partial\rho(\bar{r})}{\partial N}\right)_{v(\bar{r})} \tag{5.1}$$

where μ is the chemical potential[5], $v(\bar{r})$ is the external potential (which acts on an electron at position $\bar{r}$ due to the nuclear attraction along with other external forces which may be present in the system) and N is the total number of electrons of the system. In a finite difference approximation, it can be written as:

$$f^+(r) = \rho_{N+1}(r) - \rho_N(r) \quad \text{: for nucleophilic attack} \tag{5.2a}$$

$$f^-(r) = \rho_N(r) - \rho_{N-1}(r) \quad \text{: for electrophilic attack} \tag{5.2b}$$

$$f^0(r) = \frac{\rho_{N+1}(r) - \rho_{N-1}(r)}{2} \quad \text{: for radical attack} \tag{5.2c}$$

where, $\rho_N(r)$, $\rho_{N-1}(r)$ and $\rho_{N+1}(r)$ are the electron densities for neutral and the corresponding cation and anion respectively.

Fukui function may be elucidated in terms of Kohn-Sham spin-orbitals and the expressions are given as,[2, 11]

$$f_N^+(r) = |\phi_{N+1}(r)|^2 + \sum_{i=1}^{N} \left(\frac{\partial |\phi_i(r)|^2}{\partial N}\right)^+_{v(r)} \quad (5.3)$$

$$f_N^-(r) = |\phi_N(r)|^2 + \sum_{i=1}^{N} \left(\frac{\partial |\phi_i(r)|^2}{\partial N}\right)^-_{v(r)} \quad (5.4)$$

where, $\phi_i(r)$ represents all occupied molecular orbitals, $\phi_N(r)$ is the HOMO and $\phi_{N+1}(r)$ is the LUMO. Fukui function delivers information about frontier molecular orbitals and also orbital relaxation effects [i. e., the change in the shape of an orbital, when an electron is added (Eq. (5.3)) or removed (Eq. (5.4)] as evident from the second term in Eqs. (5.3) and (5.4). The second term may be neglected if it is reasonably lower compared to the first one in Eqs. (5.3) and (5.4).[12]

In literature,[13-16] the importance of orbital relaxation in determining chemical reactivity is fruitfully discussed by several researchers. Molecules where substantial negative Fukui functions are observed usually undergo redox induced electron transfer (RIET).[13,16] For a molecule, the Fukui function in a region is negative when removal (or addition) of an electron increases (or decreases) the electron density in that region. It is known that negative values of the condensed Fukui function is well correlated with the orbital relaxation effect and nodal surfaces of the frontier orbitals.[12, 13, 16] Recently, Bhattacharjee and Roy[17] elaborated that the values of $\sum_K v_f^-(\bar{r})|_{r=0} - \sum_K v_f^+(\bar{r})|_{r=0}$ (difference between sum of variants of Fukui potential) as well as $\sum_K \Delta^- h(K) - \sum_K \Delta^+ h(K)$ (difference between sum of variants of hardness potential derivatives) for a polyatomic molecule are significantly informative about the orbital relaxation effects. These values are large when evaluated at the positions of the atomic nuclei where orbital relaxation effects are more. They also observed that cations have higher electron densities compared to those of anions for some isolated atoms (belonging to p block) which can be qualitatively explained on the basis of 'higher electronic repulsion and lower effective nuclear charge' (for anions) and vice versa (for cations). Trends of hardness potential derivatives [$\Delta^+h(k)$ and $\Delta^-h(k)$] for isolated atoms are also justified on the basis of negative Fukui function. This study deals with only s and p block elements. For other elements of higher periods, many more complex factors, such as relativistic effects are to be considered to evaluate Fukui function values.

Although, inclusion of relativistic effects are known to improve the reliability of FF values,[18] the calculations are computationally intensive and the analysis is not straightforward. A comparatively economic and affordable approach, within a non-relativistic framework, which includes relativistic effects, is by replacement of the inner atomic shells by effective core potential (ECP).[19,20] However, some disadvantages of using ECP concerning relativistic effects on electron densities in the atomic core region are already reported.[21, 22, 23] As the focus of the present study is on the negativity of FF on the atomic nucleus only, ECP may not be a very suitable choice here.

In earlier studies, the effect of orbital relaxation on Fukui function is investigated but primarily for molecular systems. Most of the organic (as well as inorganic) molecules consist of s and p block elements upto fourth period (especially hydrogen, carbon and other p block atoms). So, this study tries to investigate whether Fukui function emerges out to be negative for simple isolated atoms and that is also at the atomic nuclei where orbital relaxation is large. There may be several factors which make condensed-to-atom Fukui function value in a molecule or Fukui function at any position ($\bar{r}$) in a molecule negative.[24] It may also incidentally enhance the understanding of three useful descriptors (which are closely related to Fukui function) to study intra and intermolecular reactivities: $V_{el}(\bar{r})$ (electronic contribution to molecular electrostatic potential which is related to electronic distribution in a molecule), Fukui potential (i. e., electrostatic potential due to a distribution of charge equal to the Fukui function) and hardness potential derivatives (which have dominant contribution from Fukui potential and moderate dependence on electron density, evaluated at the atomic nuclei).

Computational Details:

Calculations for some s block (H, He, Li, Be, Na, Mg) and p block (B-Ne, Al-Ar, Ga-Kr) neutral atoms and their corresponding cations and anions are performed at CCSD/aug-cc-PVQZ and UCCSD/aug-cc-PVQZ levels (depending on the type of atoms and their corresponding ions, as some of them have closed-shell framework and some belong to open-shell type). For carbon anion, calculation could not be simply converged. For fourth row s block elements, i. e., K and Ca, the chosen basis sets are not available in Gaussian03.[25] Electron densities are evaluated at

atomic nuclei (i. e, $r \to 0$). All calculations are performed in gas phase. For calculating $f^+(\bar{r})$ and $f^-(\bar{r})$, Eqs. (5.3) and (5.4) are used respectively.

Results and Discussions:

In the frozen orbital approximation, removal of an electron does not lead to any change in the electron density at the nucleus. So, some other factor should be important for the change in electron density at the nucleus. It is already established that Fukui function is negative valued in regions where the highest occupied molecular orbital (HOMO) (for $f^-(\bar{r})$) or the lowest unoccupied molecular orbital (LUMO)) (for $f^+(\bar{r})$) have nodal surfaces and some atomic and molecular examples are discussed in literature.[9,13,26-34] Usually, the most negative values are located at the site where electron-nuclear attraction potential is highest.[9] The negative values of Fukui function may be attributed to the failure of simple FMO theory.[9,13] It is observed that orbital relaxation seems to be at the root of the failure.[9,13] The scenario is 'quantitatively similar' for both correlated calculations (Configuration Interaction, Kohn-Sham) and the independent electron model (Hartree-Fock).[9] The electron density on the nodal surfaces of the HOMO orbital does not alter directly when an electron is removed from the highest-occupied molecular orbital (HOMO). But if orbital relaxation is considered in the cation, there may be a reduced screening of the electrons near the nodal surfaces of the HOMO resulting in a net increase in the electron density. In other words, the shielding of the core electrons is reduced upon removal of an electron from HOMO. The remaining electrons tend to move towards the most positively charged site of the atom (i. e., the nucleus) and hence the electron density increases in the nodal planes of the HOMO. Hence $f^-(\bar{r})$ is negative.[13]

On the other hand, if the lowest unoccupied molecular orbital (LUMO) has a nodal surface at an atomic nucleus, the electron density at that nucleus is not enhanced by adding an electron to the LUMO. But due to the presence of some electron density in LUMO near the atomic nucleus, core electrons will be shielded by the additional electron in the vicinity of the nodal region of LUMO. This lowers the effective nuclear charge felt by these contributing orbitals (towards electron density) and thus decreases the electron density at the nucleus, making $f^+(\bar{r})$ is negative.

The effect of electron-electron repulsion on cationic and anionic electron densities at the nucleus can be used as an alternative tool to explain the negativity of Fukui function. In a similar line of argument with our recent work,[17] for anions [i. e., for $f^+(\bar{r})$], the extra added electron will increase the electron-electron repulsion and effective nuclear charge will decrease. The protons in the nucleus cannot effectively drag electrons towards itself as these used to do in the neutral atom. So, anions exhibit lowest electron density at the nucleus. For cations [i. e., for $f^-(\bar{r})$], when the removal of an electron occurs, electron–electron repulsion decreases and the effective nuclear charge increases. Consequently, the protons in the nucleus can efficiently pull the remaining electrons towards itself. As a result, the cations have highest electron density at the nucleus. Now, with all these facts in mind, we proceed to discuss our results for some s and p block elements below:

A) s-Block Elements:

If we look at Table 5.1.a. and Figures 5.1-5.6, $f^-(\bar{r})$ values are positive for all the chosen s-block atoms (i. e., H, He, Li, Be, Na, Mg) and $f^+(\bar{r})$ values are negative for all except H and He. For these atoms, HOMO does not have any node at the origin. Hence the explanation of the observed trends for them will be somewhat straightforward and different from what is discussed in the earlier paragraph. Hydrogen does not have any electron density in its cationic form and hence its neutral electron density is equal to the value of $f^-(\bar{r})$. Removing electrons from these atoms will decrease the electron density at the nuclei (as there is no node of HOMO at the nuclei). Also, orbital relaxation effect may not be strong enough to reduce the screening of the remaining electrons in the near-nucleus regions and hence effective nuclear charge cannot efficiently pull more electron density towards the nucleus in the cationic form. So, positive values of $f^-(\bar{r})$ are acceptable Eq. (5.2.b.). It is worthy of noting that the higher value of $f^-(\bar{r})$ for Na than Li (Table 5.1.a.) can also be explained on the basis of atomic size. As we go down in the Group I, the size of the atoms increases (addition of an extra electronic shell). So when an electron is removed from Li, due to its smaller size (compared to Na), the electronic repulsion is reduced more. So the Li^+ nucleus can more ably pull the electrons (compared to Na, which is larger in size) towards itself and the trend of the value of electron density at the nucleus is $Li^+ > Na^+$. So the value of the difference in electron densities between neutral and cationic

systems [i. e., $\rho_N(r)-\rho_{N-1}(r)$ or $f^-(\bar{r})$] is higher for Na as compared to Li (Table 5.1.a., Figure 5.1). Again, when we compare the values of $f^-(\bar{r})$ at the nucleus for Na and Mg atoms, the trend is $f_{Na}^-(\bar{r}) <. f_{Mg}^-(\bar{r})$ (Table 5.1.a., Figure 5.2). The removal of an electron causes greater release in electron-electron repulsion for Mg (as compared to Na which has $3s^1$) because it has a $3s^2$ configuration and the electron will be lost from the same orbital where the remaining outermost electron resides. But for Na^+, the size will be decreased more [due to the loss of the electron from the outer (i. e., 3rd) shell] as compared to Mg^+ and effective nuclear charge will be higher. So the cationic electron density will be higher in Na^+ nucleus than Mg^+ nucleus. Hence, the value of the difference in electron densities between neutral and cationic systems [i. e., $\rho_N(r)-\rho_{N-1}(r)$ or $f^-(\bar{r})$] is lower for Na as compared to Mg [i. e., $f_{Na}^-(\bar{r}) <. f_{Mg}^-(\bar{r})$, when $r \to 0$]

On the other hand, addition of an electron to the LUMO, enhances the electron density at the nucleus if it has no nodes at the nuclear position, thus expecting $f^+(\bar{r})$ to be positive Eq. (5.2a). However, it also enhances the shielding of orbitals in the near-nuclear region due to relaxation effect. Earlier study by Bartolotti and Ayers[12] argued that orbital relaxation effects are much larger for small ionization potential which is the case for anion. The net effect is the lowering of effective nuclear charge which leads to lower electron density at the nucleus compared to the neutral atoms. It makes values of $f^+(\bar{r})$ negative. The argument, as is given here, may be exploited to explain the negativity of FF indices of Li, Be, Na and Mg. When it comes to the increasing trend of negativity from Li to Na or (Be to Mg), decreasing effective nuclear charge as we go down the group (because the extra electron is added to a higher shell) becomes handy for the explanation. However, as one moves along a period (e.g. $Li \to Be$ or $Na \to Mg$) negativity of FF also increases. It seems that effective nuclear charge is not the determining factor here as it increases along a period. Instead the presence of nodes of the LUMO (i. e., p-orbitals) on the nuclear position, in case of Be and Mg, may be the reason of higher negative FF values as we move from $Li \to Be$ or $Na \to Mg$ (Table 5.1.a., Figures 5.4 and 5.5). As there are only two/three elements per group for s block elements, these data are not plotted.

For H and He, when an extra electron is added to LUMO, orbital relaxation may not be dominant and screening of contributing orbitals (towards electron density at the nucleus) is

not effective as well. Hence contraction of electron density towards nucleus is slightly higher for anions. As a result, $f^+(\bar{r})$ is positive for H and He. Also, the contraction of electron density towards nucleus may be higher for He^- anion compared to that of H^- anion and hence the difference i. e., $\rho_{N+1}(r) - \rho_N(r)$ [or $f^+(r)$] is higher for He than H, i. e., $f_{He}{}^+(r) > f_H{}^+(r)$.

B) p-Block Elements:

As evident from Table 5.1.b. and Figures 5.1-6, $f^-(\bar{r})$ and $f^+(\bar{r})$ values for all of the chosen p-block elements are negative (except Ne, Ar and Kr, which shows positive $f^+(\bar{r})$ values). For these atoms both the HOMO and LUMO have nodes at atomic nuclei. Hence, after removing an electron, the initial decrease in electron density near nodal surfaces of HOMO can be overcompensated by the increment due to orbital relaxation. So, cationic electron density at the nuclear position is higher compared to that of the neutral atom and $f^-(\bar{r})$ is negative. If we follow the increase in negativity of $f^-(\bar{r})$ along the period, for p-block elements (Table 5.1.b., Figure 5.1, 5.2 and 5.3), it also indicates the gradual increase in cationic electron densities at the nuclear position for these atoms along the same direction. The regression coefficients are 0.98385, 0.90928 and 0.98764 for Figures 5.1, 5.2 and 5.3 respectively. It further justifies the reliability of our calculated values. Incidentally, it suggests that orbital relaxation effect also enhances along the period, making cationic density higher at the nucleus. But without investigating further, it is better not to make any strong comment here.

Now, the trend in negativity of $f^-(\bar{r})$ down the group may be analyzed briefly. Usually, if atomic size increases, effective nuclear charge decreases down the group. But orbital relaxation may play a crucial role to increase the cationic density at the nucleus which enhances the negativity of $f^-(\bar{r})$ down the group (i. e., $B \rightarrow Al \rightarrow Ga$, $C \rightarrow Si \rightarrow Ge$, $P \rightarrow As$, $S \rightarrow Se$, $Cl \rightarrow$Br, $Ar \rightarrow Kr$) (Table 5.1.b.). But for some elements (i. e., $N \rightarrow P$, $O \rightarrow S$, $F \rightarrow Cl$ or $Ne \rightarrow Ar$) (Table 5.1.b.), the trend is exactly opposite. The reason may be computational artifacts. But it is difficult to provide any strong justification at this point of time.

Similarly, for anions, when an electron is added to LUMO, it screens the contributing (towards electron density in the near-nucleus regions) orbitals. This diminishes effective nuclear charge which is felt by those orbitals and so electron density is reduced at the nucleus. As a result, anions have lower electron density and $f^+(\bar{r})$ is negative. The increase in negativity for the values of $f^+(\bar{r})$ along the period, for p-block elements, may be explained qualitatively on the

basis of lowering in effective nuclear charge. As the no. of electrons increase along the period, the addition of extra electron will cause more electron-electron repulsion and it reduces the effective nuclear charge. Hence anionic density at the nucleus falls down and the negativity of $f^+(\bar{r})$ increases along the period (Table 5.1.b., Figures 5.4, 5.5 and 5.6). Similar kind of logic may be applied to the enhancement in negativity for the values of $f^+(\bar{r})$ down the group (i. e. from one period to the next), for p-block elements. As the size of the atom increases, effective nuclear charge is expected to decrease down the group. Hence anionic density will be lower at the nucleus, resulting in more negative $f^+(\bar{r})$ values down the group (Table 5.1.b.). For Ne, Ar and Kr, when an electron is added to LUMO, it goes to the next higher s orbital. Due to absence of nodal surface for LUMO at atomic nuclei, orbital relaxation is not prominent. So, addition of electron leads to more contribution of electron density at the nuclear position. Hence anionic density is higher compared to that of the neutral atom and $f^+(\bar{r})$ is positive. The regression coefficients are 0.90295, 0.99727 and 0.97554 for Figures 5.4, 5.5 and 5.6 respectively. It also shows the credibility of the generated data. Inert atoms [i. e., Ne, Ar and Kr] are not included while plotting the data along the period for $f^+(\bar{r})$. The reason is that they have positive $f^+(\bar{r})$ values and the explanation is different compared to that of the rest of the atoms.

Conclusion:

Negativity of Fukui function remains an open-ended question since its inception.[30,31, 33] The contributions of orbital relaxation (which is qualitatively important in chemistry) in Fukui function is already well known [Eq. (5.3) and (5.4)].[2,11] Orbital relaxation is important for 'orbital-controlled' reactions.[16] We have chosen some s and p block elements to explain negativity of Fukui function using orbital relaxation effects.

It is found from Table 5.1.a., that $f^-(\bar{r})$ values are positive for all the chosen s-block atoms (i. e., H, He, Li, Be, Na, Mg) and $f^+(\bar{r})$ values are negative for all except He. Table 5.1.b. suggests that $f^-(\bar{r})$ for B-Ne, Al-Ar, Ga-Kr and $f^+(\bar{r})$ values for these atoms (except Ne, Ar and Kr) are also negative. Nodal surfaces for HOMO and LUMO at the atomic nuclei are the most probable regions for negative Fukui functions. Negative values of Fukui function arise if orbital relaxation is found to be dominant.[9,12,13,16,28] This study may help in gathering important information about three useful descriptors to study intra and intermolecular reactivities: $V_{el}(\bar{r})$

[i.e., electronic contribution to molecular electrostatic potential), Fukui potential and hardness potential derivatives, all of which have subtle or direct dependence on Fukui function, evaluated at the atomic nuclei. So if the value of Fukui function is guided by orbital relaxation, the value of these descriptors should also be so. In a similar line of work, Bhattcharjee and Roy[17] have already shown that the orbital relaxation effect plays a pivotal role while analyzing the sum of Fukui potential and sum of hardness potential derivatives in molecules. As organic molecules are mostly made up of carbon, hydrogen and some p block elements, it will be interesting to explore how the calculated values of the three above mentioned reactivity descriptors for molecules get affected by the influence of orbital relaxation on their constituting atoms (though it may be the subject of another detailed study).

References and Notes

1. R. G. Parr, W. Yang, J. Am. Chem. Soc. 106 (1984) 4049.
2. W. Yang, R. G. Parr, R. Pucci, J. Chem. Phys. 81 (1984) 2862.
3. W. Yang, W. Mortier, J. Am. Chem. Soc. 108 (1986) 5708.
4. P. W. Ayers, M. Levy, Theor. Chem. Acc. 103 (2000) 353.
5. R. G. Parr, R. A. Donnelly, M. Levy, W. E. Palke, J. Chem. Phys. 68 (1978) 3801.
6. R. G. Parr, W. Yang, Density–Functional Theory of Atoms and Molecules, Oxford University Press: New York (1989).
7. P. Geerlings, F. De Proft, W. Langenaeker, Chem. Rev. 103 (2003) 1793.
8. P. A. Johnson, L. J. Bartolotti, P. W. Ayers, T. Fievez, P. Geerlings, Gatti, C., Macchi, P., Eds. Springer: New York, (2012), pp 715.
9. J. Melin, P. W. Ayers, J. V. Ortiz, J. Phys. Chem. Lett. 111 (2007) 10017.
10. W. Langenaeker, K. Demel, P. Geerlings, J. Mol. Struct. (THEOCHEM) 80 (1991) 329.
11. M. H.Cohen, M.V. Ganduglia-Pirovano, J. Chem. Phys. 101 (1994) 8988.
12. L. J. Bartolotti, P. W. Ayers, J. Phys. Chem. A. 109 (2005) 1146.
13. P. W. Ayers, Phys Chem Chem. Phys. 8 (2006) 3387.
14. K. Flurchick, L. Bartolotti, J. Mol. Graphics. 13 (1995) 10.
15. W. Langenaeker, K. Demel, P. Geerlings, THEOCHEM. 80 (1991) 329.
16. E. Echegaray, C. Cárdenas, S. Rabi, N. Rabi, S. Lee, F, H. Zadeh, A. Toro-Labbe, J. S. M. Anderson, P. W. Ayers, J. Mol. Model. 19 (2013) 2779.
17. R. Bhattacharjee, R. K. Roy, Phys. Chem. Chem. Phys. 16 (2014) 22237.
18. N. Sablon, R. Mastalerz, F. De Proft, P. Geerlings, M. Reiher, Theor Chem Acc. 127, (2010) 195.
19. M. Dolg M (2000) In: Grotendorst J (ed) Modern methods and algorithms of quantum chemistry. John von Neumann Institute for Computing, Jülich.
20. M. Dolg (2002) In: Schwerdtfeger P (ed) Relativistic quantum chemistry—part 1 fundamentals. Elsevier, Amsterdam.
21. M. Kohout, A. Savin, H. Preuss, J Chem Phys 95 (1991) 1928.
22. N. Hebben, H. J. Himmel, G. Eickerling, C. Herrmann, M. Reiher, V. Herz, M. Presnitz, W. Scherer, Chem Eur J 13 (2007) 10078.

23. G. Eickerling, M Reiher, J Chem Theory Comput 4 (2008) 286.
24. P. Bultinck, R. Carbó-Dorca, W. Langenaeker, J. Chem. Phys. 118 (2003) 4349.
25. M. J. Frisch, et al. Gaussian 03, Revision E.01; Gaussian, Inc. Wallingford, CT (2004).
26. C. Cárdenas, W. Tiznado, P. W. Ayers, P. Fuentealba, J. Phys. Chem. A. 115 (2011) 2325.
27. P. W. Ayers, R. C. Morrison, R. K. Roy. J. Chem. Phys. 116 (2002) 8731.
28. E. Echegaray, S. Rabi, C. Cárdenas, F, H. Zadeh, N. Rabi, S. Lee, J. S. M. Anderson, , A. Toro-Labbe, P. W. Ayers, J. Mol. Model. 20 (2014) 2162. Also see references therein.
29. R. Bhattacharjee, R. K. Roy, J. Phys. Chem. A. 117 (2013) 11528.
30. R. K. Roy, S. Pal, K. Hirao, J. Chem. Phys. 110 (1999) 8236.
31. R. K. Roy, K. Hirao, S. Pal, J. Chem. Phys. 113 (2000) 1372.
32. S. Saha, R. Bhattacharjee, R. K. Roy, J. Comp. Chem. 34 (2013) 662.
33. R. K. Roy, K. Hirao, S. Krishnamurty, S. Pal, J. Chem. Phys. 115 (2001) 2901.
34. C. Cárdenas, Chem. Phys. Lett. 513 (2011) 127.

Table 5.1.a.: Fukui function values at the nucleus (i. e., $r \to 0$, see text) at CCSD/aug-cc-pVQZ (in atomic units) for s-block elements.

Atoms	$\boldsymbol{f^{-}(\bar{r})}$	$\boldsymbol{f^{+}(\bar{r})}$
1. H	0.299	0.009
2. He	0.988	0.036
3. Li	0.138	-0.005
4. Be	0.253	-0.076
5. Na	0.526	-0.02
6. Mg	0.630	-0.153

Table 5.1.b.: Fukui function values at the nucleus (i. e., $r \to 0$, see text) at CCSD/aug-cc-pVQZ (in atomic units) for s-block elements.

Atoms	$f^{-}(\bar{r})$	$f^{+}(\bar{r})$
1. B	-0.619	-0.153
2. C*	-0.806	--
3. N	-1.200	-0.536
4. O	-1.459	-0.860
5. F	-1.909	-1.033
6. Ne	-2.204	1.009
7. Al	-0.816	-0.262
8. Si	-0.894	-0.492
9. P	-1.228	-0.626
10. S	-1.096	-0.604
11. Cl	-1.408	-0.933
12. Ar	-1.599	1.184
13. Ga	-1.900	-0.633
14. Ge	-1.920	-1.129
15. As	-2.416	-1.308
16. Se	-2.293	-1.526
17. Br	-2.427	-1.722
18. Kr	-2.631	1.658

*For carbon anion, calculation could not be simply converged

Figure 5.1: Trend of $f^{-}(r)$ along 2nd period

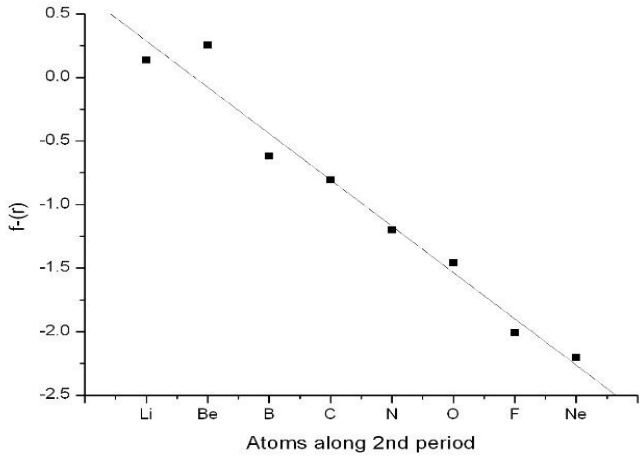


Figure 5.2: Trend of $f^{-}(r)$ along 3rd period

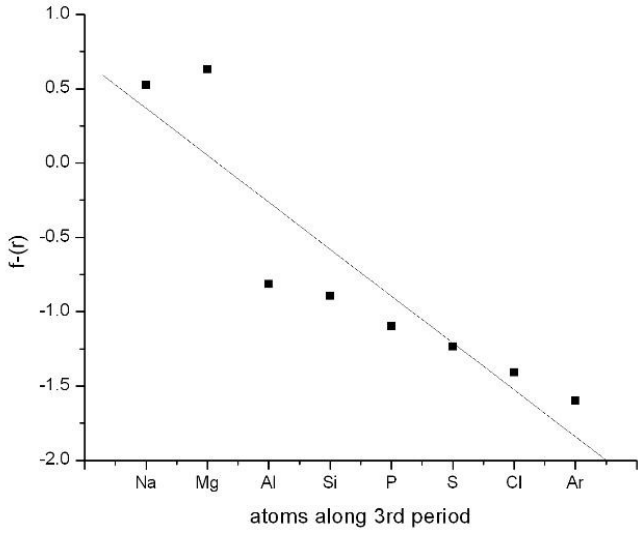


Figure 5.3: Trend of $f^{-}(r)$ along 4th period

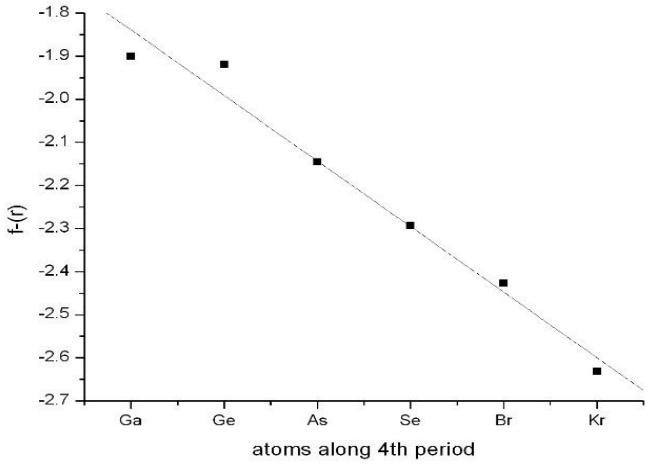


Figure 5.4: Trend of $f^{+}(r)$ along 2nd period

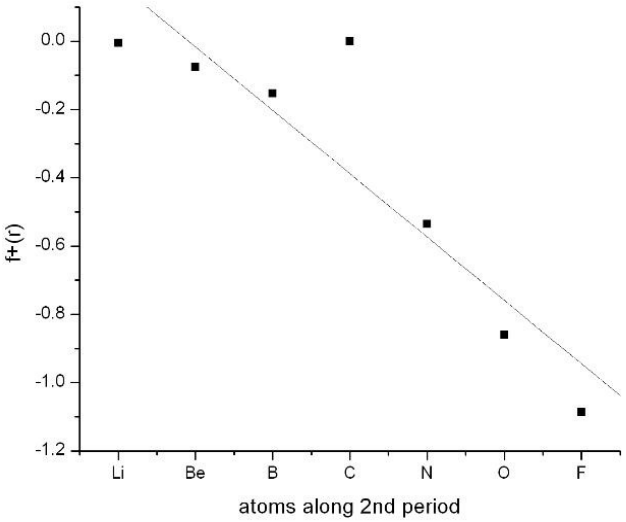


Figure 5.5: Trend of $f^+(r)$ along 3rd period

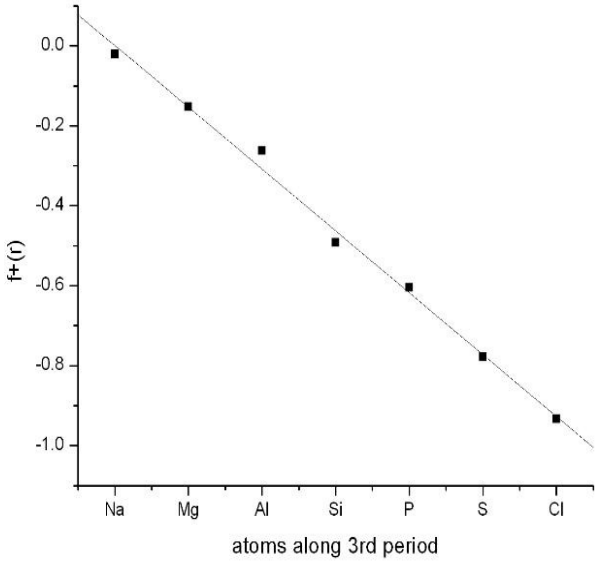
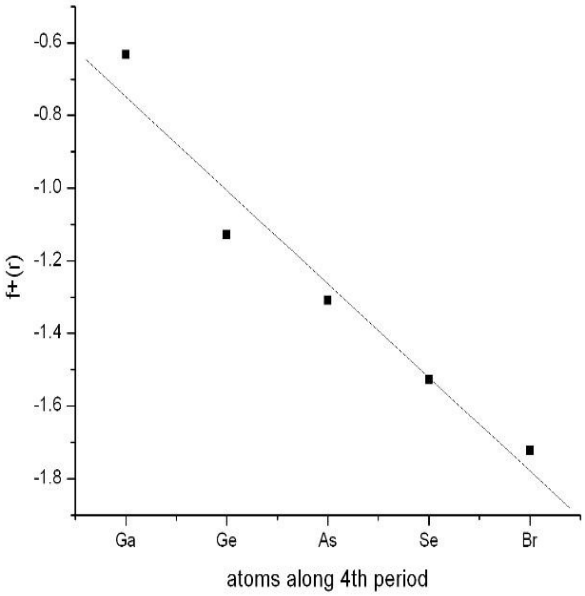
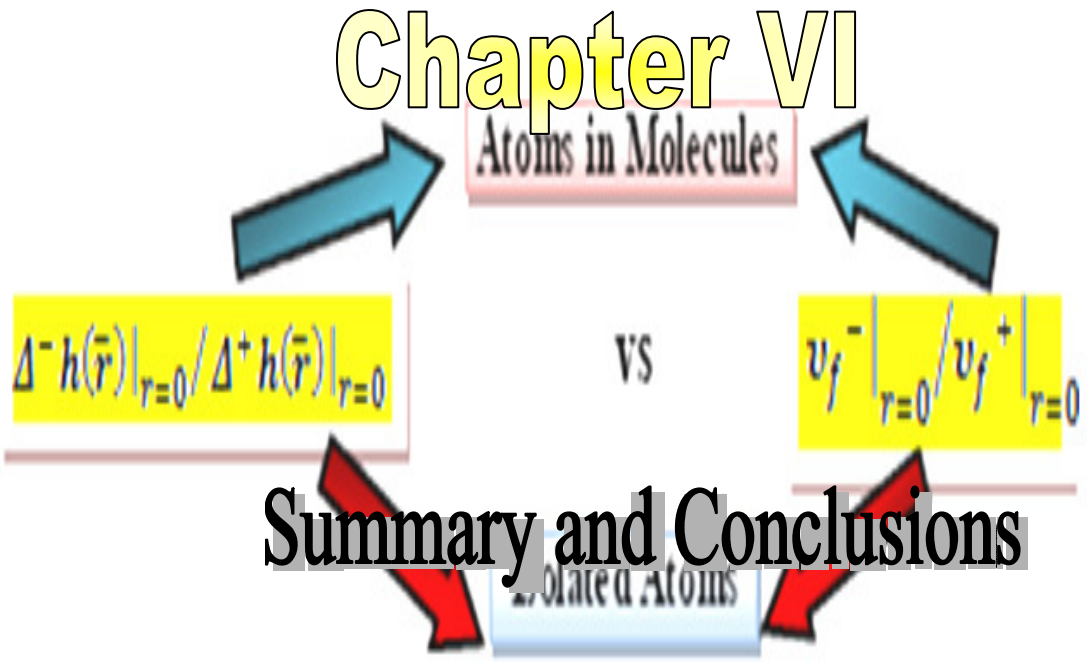


Figure 5.6: Trend of $f^+(r)$ along 4thperiod




Chapter VI
Atoms in Molecules
$\Delta^- h(\bar{r})|_{r=0} / \Delta^+ h(\bar{r})|_{r=0}$
vs
$v_f^-|_{r=0} / v_f^+|_{r=0}$
Summary and Conclusions
Isolated Atoms

6.1. General Conclusions

The prime focus of this work is to develop parameters based on 'Chemical Reactivity Theory' and apply them to study important chemical phenomena. Computational chemists always strive to find out cost effective methods to investigate large chemical and biological systems. A detailed study on the intra and intermolecular reactivity trends of systems with multiple reactive sites is also a challenging task. In order to take care of these issues, theoretical investigation on electrophilic $[\Delta^{+}h(\bar{r})]$ and nucleophilic $[\Delta^{-}h(\bar{r})]$ variants of hardness potential[1,2] $[h(\bar{r})]$ and their applications in intra and intermolecular reactivity studies for relevant chemical and biological systems is carried out. This new approach is suitable for charge-controlled chemical reactions, e.g., interaction of drugs with biomolecules (amino acids, peptides etc).

It is revealed that these descriptors are more sensitive to the electronic environment of an atom in a molecule and hence, they can, potentially, be implemented in the 'One-into-Many' model[3,4] to locate the most reactive site in large chemical and biological systems.

The inner connectivity of electrophilic $[\Delta^{+}h(\bar{r})]$ and nucleophilic $[\Delta^{-}h(\bar{r})]$ variants of hardness potential $[h(\bar{r})]$, Fukui indices[5,6] and Fukui potential [7-13] is also highlighted. It is critically analyzed how these parameters are affected by two electronically different environments, i. e., isolated atoms vs atoms in a molecule.

Orbital relaxation is important for 'Fukui-function-controlled reactions'.[23] The values of $\sum_{K} v_f^{-}(\bar{r})|_{r=0}$ - $\sum_{K} v_f^{+}(\bar{r})|_{r=0}$ as well as $\sum_{K}\Delta^{-}h(K)$ - $\sum_{K}\Delta^{+}h(K)$ for a polyatomic molecule provide more prominent information about the relaxation effects. The correlation between orbital relaxation effect and nature of atomic Fukui functions is also emphasized for some s and p block elements.

This thesis work demonstrates that the differences of the values of Fukui potentials as well as hardness potential derivatives in isolated atom and the same atom in a molecule provide information about the extent of electron delocalization in the molecule.

Broadly, it may be stated that this work provides an alternative pathway towards the study of chemical reactivity apart from the conventional energetics based approach, which is computationally expensive**.**

6.2. Specific Conclusions

The study of large organic and biomolecules using high level electronic structure theory accelerates the interest of computational chemists for decades. Conceptual Density Functional Theory'(CDFT) or 'Chemical Reactivity Theory' (CRT) or 'Density Functional Reactivity Theory (DFRT) exploits the electron density and its various response functions to understand and predict chemical reactivity.[14-22] The central idea in DFRT is that the response of a system to perturbations in its number of electrons, and/or the external potential, determines its reactivity. The density-functional language is advantageous as it closely relates to the language of structural chemistry.

To account for the the N-dependence problem of local hardness, formal development of hardness potential is discussed. Hardness potential, $h(k)$, in its original working definition, is unable to explain the reactivity sequence when the systems belong to different homologous series i.e., when the reactive centres in the chemical systems vary from each other. The superiority of the hardness potential derivatives, i. e., $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ over $h(k)$ stems from the fact that they can take care of the response (i.e., the changing electron density scenario) of the reactive centres toward a nucleophilic (Nu^{-}) or an electrophilic (El^{+}) attack on them. It is interesting to observe that both of these two new descriptors, when evaluated at the nuclei, correlate very well with the expected intramolecular reactivity trends of bioactive indolynes and unsymmetric arynes along with some homologous series of chemical systems containing common functional groups, *viz*, $-COOH$, $-COF$, $-CONH_2$, $-OH$, $-SH$, $-NH_2$, $-PH_2$. It is also worth mentioning here that the electronegativity differences of the reactive atoms are also well taken care by these new descriptors and its electrophilic [$\Delta^{+}h(k)$] and nucleophilic [$\Delta^{-}h(k)$] variants. Interestingly, these two variants of the hardness potential lead to the right and left derivatives of Fukui potential. It is important to mention here that these two variants of hardness potential are originated (with some approximation) from hardness functional, $H[\rho]$,[1,2] which in turn belongs to grand canonical ensemble.(i.e., $-H[\rho] = E - \mu N = \Omega$). As local descriptors from this ensemble has the ability to take care of both intramolecular (i.e. site selectivity) as well as intermolecular reactivity (e.g., local softness), $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ can, in principle, serve both the purpose. Also, the operational definitions of these two reactivity descriptors, involve the difference of 'electronic part of the electrostatic potential'. Because, electrostatic potential can

take care of long range effect, these two may act as more suitable descriptors than local softness, [$s(\bar{r})$] for intermolecular comparison. [2]

The relative contribution of the sum of kinetic [$\frac{10}{9}C_F\rho(\bar{r})^{2/3}$] and exchange energy [$\frac{4}{9}C_X\rho(\bar{r})^{1/3}$] terms to that of the electronic part of the molecular electrostatic potential [$V_{el}(\bar{r})$] in the variants of hardness potential is investigated to assess the proposed definition of $\Delta^{+}h(k) = -[V_{el}^{N+1}(k) - V_{el}^{N}(k)]$ and $\Delta^{-}h(k) = -[V_{el}^{N}(k) - V_{el}^{N-1}(k)]$. Some substituted benzenes and polycyclic aromatic hydrocarbons (PAHs) (undergoing electrophilic aromatic substitution), carboxylic acids and their derivatives are chosen to carry out the theoretical investigation as stated above. The reason behind considering only the electronic part of molecular electrostatic potential, unlike many other approaches where total electrostatic potential i.e., both electronic and nuclear components are used, is also addressed. The net contribution of the sum of kinetic [$\frac{10}{9}C_F\rho(\bar{r})^{2/3}$] and exchange energy [$\frac{4}{9}C_X\rho(\bar{r})^{1/3}$] terms is found to be negligible when compared to that of electronic contribution to the molecular electrostatic potential [$V_{el}(\bar{r})$] for systems like substituted benzenes and polycyclic aromatic hydrocarbons. However, this is not the case for systems like carboxylic acids and their derivatives. So, it may be broadly concluded that depending on the type of systems, the net contribution of the sum of the kinetic and exchange energy terms may or may not be negligible when compared to that of $V_{el}(\bar{r})$. $\Delta^{-}h(k)$ is able to reproduce experimental trends for site-selectivity for almost all alkylbenzenes, halobenzenes and polycyclic aromatic hydrocarbons in electrophilic aromatic substitution. It is observed that intramolecular reactivity trends for toluene, 1,2-dimethylbenzene and 1,3 dimethylbenzene (where ortho steric effects should be dominant) were also satisfactorily predicted by $\Delta^{-}h(k)$. This latter observation is particularly encouraging because earlier study using total electrostatic potential at the nucleus (EPN) could not produce experimental trends. The success of $\Delta^{-}h(k)$ in generating expected reactivity trends is attributed to the fact that it can take care of the changing electron density scenario when the electrophile approaches towards the nucleophilic system of interest. Although electrophilic aromatic substitutions are multistep processes, the first step itself is the rate-determining one. Hence, $\Delta^{-}h(k)$ can predict expected

reaction rates. Moreover, on the basis of 'the most reactive site' model of the individual species, $\Delta^{-}h(k)$ and $\Delta^{+}h(k)$ can generate satisfactory intermolecular reactivity trends for most of the chosen systems having multiple sites of comparable (but not equal) reactivity. The probable reason of this success is that these descriptors are based primarily on electrostatic potential, which can take care of large distance effects and so the intermolecular reactivity.[24]

The next aim is to gain an insight into the trends of electronic contribution to molecular electrostatic potential [$V_{el}(\bar{r})$], Fukui potential and hardness potential derivatives in isolated atoms and atoms in molecules. It is observed that values of $V_{el}(\bar{r})$ are higher for atoms in molecules than those of isolated atoms. The observation was justified on the basis of differences in the scenario of charge density for isolated atoms and atoms in a molecule. As Fukui potential and hardness potential derivatives are significantly dependent on the differences of electronic contribution to molecular electrostatic potential $V_{el}(\bar{r})$, it is expected that the effect of electronic environment on $V_{el}(\bar{r})$ should also be kept in mind while evaluating those descriptors. As electron delocalization plays a major role in chemical reactivity (when an electrophile or nucleophile approaches towards a substrate, there is change in electron density within a molecule) the above findings may be useful in intra and intermolecular reactivity studies by these two descriptors [25]

Systematic trends of higher values of $v_f^{-}(\bar{r})|_{r=0}$ and $v_f^{+}(\bar{r})|_{r=0}$ for isolated atoms, compared to those of atoms in molecules, are observed. It is explained by difference in electron density distribution (while addition or removal of an electron takes place) in isolated atom and atom in a molecule. Interpretation of the trends of hardness potential derivatives [$\Delta^{+}h(k)$ and $\Delta^{-}h(k)$] are not straightforward, as such, for isolated atoms and atoms in molecules. Plausible explanations are found on the basis of negative Fukui function for isolated atoms (not for molecules, due to their electronic complexity).[25]

It is also concluded that the values of $\sum_K v_f^{-}(\bar{r})|_{r=0}$ - $\sum_K v_f^{+}(\bar{r})|_{r=0}$ as well as $\sum_K \Delta^{-}h(K)$ - $\sum_K \Delta^{+}h(K)$ for a polyatomic molecule provide more prominent information about the relaxation effects. This is because, by definition, these values are evaluated at the positions

of the atomic nuclei where orbital relaxation effects are more causing large differences between the values of $\sum_K v_f^-(\bar{r})|_{r=0}$ and $\sum_K v_f^+(\bar{r})|_{r=0}$ as well as between $\sum_K \Delta^- h(K)$ and $\sum_K \Delta^+ h(K)$.

There are a class of reactions where not only frontier molecular-orbital and orbital-relaxation control are important, but collaborative effects between the suitable frontier orbitals and orbital relaxation can ably determine chemical reactivity as well.[23] As conventional evaluation of condensed Fukui indices are based on condensed atomic population, information about relaxation effect is missing. Analysis of the trends of the sum of Fukui potential and hardness potential derivatives are also touched upon, which demonstrates the importance of orbital relaxation effects in near-nucleus region. Moreover, one interesting observation, i. e., cations have higher electron densities compared to those of anions (for isolated atoms) is qualitatively explained on the basis of 'higher electronic repulsion and lower effective nuclear charge' (for anions) and vice versa (for cations).

Another study with some s and p block elements is carried out to explain negativity of Fukui function using orbital relaxation. It is useful in gathering valuable information about three useful descriptors to study intra and intermolecular reactivities: $V_{el}(\bar{r})$ [i.e., electronic contribution to molecular electrostatic potential), Fukui potential and hardness potential derivatives, all of which have subtle or direct dependence on Fukui function, evaluated at the atomic nuclei. [26]

Finally, it may be specifically concluded that elaborate exploitation along with further theoretical investigation of these DFRT based parameters may lead to their fruitful applications in studying several important chemical and biological phenomena in a computationally cost-effective way.

6.3. Limitations and Future Scope of Work:

In this thesis, computationally economic and simple approaches are adopted to develop and apply DFRT based reactivity descriptors to predict the intra as well as intermolecular reactivities of large chemical and biological systems (especially for charge-controlled reactions).

Situations where steric factor plays a significant role or electronic factors operate through space (arising out of the artifact of different condensation schemes of electric potential or

electronic density) the generated $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ values may not reproduce the expected trends. It is particularly true for intermolecular reactivity trends where wide structural variation causes large difference in the 'through space' effects of electronic and steric factors around the sites (i.e., atoms) of interest. This may be investigated further analytically and computationally.

Recently, the effect of degenerate (or quasi-degenerate) ground states on the reactivity descriptors of DFT is thoroughly investigated by Cárdenas et. al[27] and Bultinck et. al[28]. They have shown that average density approximation of the degenerate (or quasi-degenerate) states always underestimates the reactivity. They have specifically shown that this average density approximation is 'qualitatively incorrect' and unable to predict that a positive point-charge perturbation and a negative point-charge perturbation split the degeneracy in qualitatively different ways. So, different electrostatic potentials are required to describe reactivity with positively charged and negatively charged reagents. As the variants of hardness potential are evaluated as the differences of electronic contribution to the electrostatic potential, the degeneracy (or quasi-degeneracy) of states (if any) will have some effect on the values of these two descriptors, when evaluated using 'average density approximation'. The study by Bultinck et al.[28] suggests that for different perturbations different mixing of degenerate states (which is induced by a perturbation in the external potential) is possible, thus generating different Fukui matrices and so different Fukui functions (as Fukui functions are the diagonal elements of the Fukui matrix in position space). It is obvious that both $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$ will be affected when degeneracy appear in the electronic states of the system.

It is worth mentioning here that complete mathematical definition of $h(\bar{r})$ requires some pretty strong approximations. The Hohenberg–Kohn functional $F[\rho]$[22,29] is approximated on the basis of Thomas–Fermi–Dirac (TFD)[30-32] approach plus the Weizsäcker[33] term, to DFT. So, basically, the universal functional of Hohenberg and Kohn is approximated by Thomas-Fermi-Dirac-Weizsäcker approach while obtaining mathematical definition of $h(\bar{r})$. One can systematically improve TFD functional by considering $\frac{1}{9}$ of the Weizsäcker functional (for gradient expansion).[33] Thus, formally, the presence of the Weizsäcker term in the kinetic energy description compensates for several of the deficiencies of the Thomas–Fermi–Dirac functional. Thomas-Fermi like theories supports the existence of the electrostatic potential component of the hardness kernel. But from the first derivative of Kohn-Sham kinetic energy with respect to the

electron density (which emerges out to be the difference between chemical potential and effective Kohn-Sham potential), it can be demonstrated that the electrostatic term as well as exchange correlation term cancel out. Liu and Ayers[34] discussed it while showing that the functional derivative of the non-interacting kinetic energy density functional can unambiguously be represented as the negative of the Kohn–Sham effective potential, arbitrary only to an additive orbital-independent constant. However, while discussing second functional derivative of Kohn-Sham kinetic energy, Ayers has shown[35] that the derivative of the Kohn–Sham potential with respect to the electron density contains a contribution from a coulomb term. Here, the explicit coulomb contribution vanishes, but an implicit dependence (which is embedded in the Kohn–Sham potential derivative) exists. Without going into the ambiguity of adopting any particular approach to DFT (i.e., either TFD or Kohn-Sham) the two variants [i.e., $\Delta^{+}h(k)$ and $\Delta^{-}h(k)$] of hardness potential emerge out to be two useful reactivity descriptors in their own merit, but a detailed study on this aspect may be interesting.

Bartolotti and Ayers[23] proved the importance of orbital relaxation effects in case of the electrophilic attack on $M_2(hpp)_4$ complexes, (which is neither frontier-molecular-orbital-controlled nor charge-controlled). It seems to be fascinating to explore this aspect further by studying some important reactions, where neither frontier-molecular-orbital-control nor charge-control play a decisive role in determining reactivity, using hardness potential derivatives and Fukui potential.

Also, the explanation for the negativity of Fukui function using orbital relaxation, for s and p block elements, may be extended to all other members of the periodic table, especially for transition elements, only after a thorough investigation and analytical support.

The striking observation, i. e., cations have higher electron densities compared to those of anions (for isolated atoms) is qualitatively explained on the basis of 'higher electronic repulsion and lower effective nuclear charge' (for anions) and vice versa (for cations). But it is an open-ended question and it requires an in-depth investigation, both analytically and conceptually.

It is also predicted that as hardness potential derivatives and Fukui potential are more sensitive to the electronic environment of an atom in a molecule they can, efficiently, be implemented in the 'One-into-Many' model[3,4] to locate the most reactive site in large chemical and biological systems.

It is also encouraging to note that the Coulomb term is identical for both the ground and excited states in Hardness Kernel expression. This may help in probable extension of Hardness Potential Derivatives to excited states.

The overall findings of this work can be extended to study the total interaction energy of the stacked systems, (i.e., the structure of the energetically most favourable stacked DNA base-pairs). Since electrostatics plays an important role in protein-ligand interactions, Hardness Potential Derivatives (where electronic contribution to the molecular electrostatic potential is involved) will also be useful in studying such type of interactions. Thus the in-depth theoretical study of these descriptors and their application towards different chemical phenomena may be interesting for computer-aided drug discovery.

References and Notes

1. R. G. Parr and J. L. Gázquez, *J. Phys. Chem.*, 1993, **97,** 3939.
2. S. Saha, R. Bhattacharjee and R. K. Roy, *J. Comp. Chem.,* **2013,** *34***,** 662.
3. S. Saha and R. K. Roy, *J. Phys. Chem. B.,* 2007, **111**, 9664.
4. S. Saha and R. K. Roy, *J. Phys. Chem. B*., 2008, **112,** 1884.
5. R. G. Parr, W. Yang, *J. Am. Chem. Soc*., **1984,** *106*, 4049;
6. W. Yang, W. Mortier, *J. Am. Chem. Soc.,* **1986**, *108*, 5708.
7. M. Torrent-Sucarrat, F. De Proft, P. Geerlings, P. W. Ayers, *Phys. Chem. Chem. Phys.,* **2010**, *12*, 1072.
8. M. Berkowitz, *J. Am. Chem. Soc*., **1987,** *109*, 4823.
9. M. Torrent-Sucarrat, F. De Proft, P. Geerlings and P. W. Ayers, *Chem. - Eur. J*., **2008,** *14*, 8652.
10. C. Cárdenas, W. Tiznado, P. W. Ayers and P. Fuentealba, *J. Phys. Chem. A.,* **2011,** *115*, 2325.
11. C. Cárdenas, *Chem. Phys. Lett*., **2011,** *513*, 127.
12. P. Senet, *J. Chem. Phys.,* **1997**, *107*, 2516.
13. P. Senet, *Chem. Phys. Lett.,* **1997,** *275*, 527
14. R. G. Parr and J. L. Gázquez, *J. Phys. Chem*., **1993,** *97*, 3939.
15. M. Berkowitz, S. K. Ghosh and R. G. Parr, *J. Am. Chem. Soc*., **1985,** *107*, 6811.
16. S. K. Ghosh and M. Berkowitz, *J. Chem. Phys*., **1985,** *83*, 2976.
17. P. K. Chattaraj, D. R. Roy, P. Geerlings and M. Torrent-Sucarrat, *Theor. Chem. Acc*., **2007,** *118*, 923.
18. P. W. Ayers and R. G. Parr, *J. Chem.Phys*., **2008**, *128*, 184108.
19. S. Saha, R. Bhattacharjee and R. K. Roy, *J. Comp. Chem.,* **2013,** *34***,** 662.
20. R. G. Parr, R. A. Donnelly, M. Levy and W. E. Palke, *J. Chem. Phys*., **1978,** *68,* 3801.
21. R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc*., **1983**, *105*, 7512.
22. P. Hohenberg and W. Kohn, *Phys. Rev. B, **1964**, 136,* 864.
23. L. J. Bartolotti and P. W. Ayers, J. Phys. Chem. A., **2005,** *109*, 1146.
24. R. Bhattacharjee and R. K. Roy, Phys. Chem. Chem. Phys., **2014,** *16*, 22237.
25. R. Bhattacharjee and R. K. Roy, J. Phys. Chem. A*.,* **2013,** *117,* 11528.
26. R. Bhattacharjeee and R. K. Roy (Communicated)

27. C. Cárdenas, P. W. Ayers, A. Cedillo, *J. Chem. Phys*., **2011**, *134*, 174103

28. P. Bultinck, D. V. Neck, G. Acke, P. W. Ayers, *Phys. Chem. Chem. Phys*., **2012,** *14*, 2408

29. W. Kohn and L. Sham, *Phys. Rev. A,* **1965,** *140,* 1133.

30. L. H. Thomas, *Proc. Cambridge Philos. Soc*., **1927**, *23*, 542.

31. E. Z. Fermi, Z. *Phys*., **1928**, *48*, 73.

32. P. A. M. Dirac, *Proc Cambridge Philos*. Soc., **1930**, *26*, 376.

33. C. F. von Weizsäcker, *Z. Physik,* **1935**, *96*, 431. In German

34. S. Liu and P. W. Ayers, *Phys Rev. A.,* **2004,** *70*, 022501.

35. P. W. Ayers, *Theor. Chem. Acc.,* **2001,** *106*, 271

LIST OF PUBLICATIONS

➢ From thesis work

1. Hardness Potential Derivatives and Their Relation to Fukui Indices, Soumen Saha, Rituparna Bhattacharjee, and Ram Kinkar Roy, *Journal of Computational Chemistry*, **2013,** *34***,** 662.
2. On the Relative Contribution of Combined Kinetic and Exchange energy terms vs Electronic Component of Molecular Electrostatic Potential in Hardness Potential Derivatives, Rituparna Bhattacharjee and Ram Kinkar Roy *The Journal of Physical Chemistry A,* **2013,** *117*, 11528.
3. On the Trends of Fukui Potential and Hardness Potential Derivatives in Isolated Atoms vs Atoms in Molecules, Rituparna Bhattacharjee and Ram Kinkar Roy, *Physical Chemistry Chemical Physics*., **2014**, *16*, 22237.
4. Negativity of Fukui function of some s and p block elements: The role of orbital relaxation effect, Rituparna Bhattacharjee and Ram Kinkar Roy **(communicated).**

➢ Other Publications

1. Estimation of ground and excited state dipole moments of quinidine and quinidine dication: Experimental and Theoretical studies, Sunita Joshi, Rituparna Bhattacharjee, Tej Varma Y., Debi D Pant, *Journal of Molecular Liquids,* **2013**, *179*, 88.
2. Synthesis and estimation of ground and excited state dipole moments of coumarin derivative [*N*-(2-oxo-2*H*-chromen-4-yl)imino] triphenyl phosphorane, Sunita Joshi, Santosh kumari, Rituparna Bhattacharjee, Rajeev Sakhuja, Debi D Pant, *Journal of Molecular Liquids,* **2014,** *200, Part B*, 115.
3. Solvent effect on absorption and fluorescence spectra of cinchonine and cinchonidine dications: Estimation of ground and excited state dipole moments by experimental and numerical studies, Ritika Sharma, Sunita Joshi, Rituparna Bhattacharjee, Debi D. Pant *Journal of Molecular Liquids* **(in press)**.
4. Estimation of ground and excited state dipole moments of newly synthesized coumarin-triazole derivatives and application as turn off fluorescence sensor: high sensitivity for iron (III) ions, S. Joshi, S. Kumari, A. Sarmah, R. Bhattacharjee, R. Sakhuja and D. D. Pant **(communicated)**
5. Estimation of ground and excited-state dipole moments of synthesized coumarin derivative, (S)-(1-((7-hydroxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl 2-(((9H-fluoren-9-yl)methoxy)cabonylamino)-3-phenylpropanoate from a solvatochromic shift and theoretical methods, S. Joshi, S. Kumari, R. Bhattacharjee, R. Sakhuja and D. D. Pant (**manuscript under preparartion**).

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