PCCP

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/pccp

On the Trends of Fukui Potential and Hardness Potential Derivatives in Isolated Atoms vs Atoms in Molecules

Rituparna Bhattacharjee and Ram Kinkar Roy*

Department of Chemistry, Birla Institute of Technology and Science, Pilani-333031, Rajasthan, India.

Abstract:

In the present study, trends of 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 investigated. The generated numerical values of these three reactivity descriptors in these two electronically different situations are critically analyzed through the relevant formalism. Values of $V_{el}(\bar{r})$ (when $r \to 0$, i. e., on the nucleus) are higher for atoms in molecules than that of isolated atoms. On the contrary, higher values of $v_f^+|_{r=0}$ and $v_f^-|_{r=0}$ are observed for isolated atoms compared to these values for atoms in a molecule. However, no such regular trend is observed in the $\Delta^+h(k)$ and $\Delta^-h(k)$ values, which is attributed to the uncertainty in the Fukui function values of atoms in molecules. Sum of Fukui potential and sum of hardness potential derivatives in molecules are also critically analyzed, which shows the efficacy of orbital relaxation effects in quantifying the values of these parameters. 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 are chosen to make the investigations more insightful.

*Corresponding author. E-mail: rkroy2@rediffmail.com

1. Introduction:

'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.[1-4] The central idea in DFRT is that the response of a system to perturbations in its number of electrons, N and/or the external potential $v(\vec{r})$, determines its reactivity.[5,6] The response functions can be divided into global [chemical potential μ,[1] global hardness (η),[7] global softness(S),[8] electrophilicity index ω[9-11]], local [Fukui function $f(\vec{r})$,[12-15] local softness $s(\vec{r})$,[8] local hardness $\eta(\vec{r})$,[16-20] relative nucleophilicity and relative electrophilicity,[21,22] philicity $\omega(\vec{r})$[23] etc] and non-local [softness kernel[24] and hardness kernel[24,25]] reactivity indices.

Hardness based local reactivity indices are prescribed for intermolecular reactivity comparison because hard-hard interactions are charge controlled[26] and hence reliable to take care of long range interactions. Using the same idea, in a previous study,[27,28] 'one-into-many' model is developed and approximated form of local hardness, i. e., $\eta(\vec{r}) = \frac{-V_{el}(\vec{r})}{N}$ is used to predict the reactivity of active sites in Watson-Crick double-stranded BDNA (PDB ID: 1BNA). But in another article by the same authors,[29] it is also shown that the $\frac{1}{N}$ factor in the definition of $\eta(\vec{r})$ (N is the number of electrons) makes it unreliable to predict intermolecular reactivity trends between systems of different sizes but having common reactive centers. It is recently found by Saha et al.[30] that N-dependence problem of local hardness $\eta(\vec{r})$ can, formally, be resolved by hardness potential $h(\vec{r})$.[31]

The mathematical definition of $h(\vec{r})$ requires some detailed approximations which is discussed elsewhere.[30,32] The approximated analytical form of hardness potential [$h(\vec{r})$] is,

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

where, $V_{el}(\vec{r})$ is the electronic contribution to the molecular electrostatic potential, $\frac{10}{9} C_F \rho(\vec{r})^{2/3}$ and $\frac{4}{9} C_X \rho(\vec{r})^{1/3}$ are the kinetic energy and exchange exchange energy terms, respectively. Then it was approximated further as,

$$h(\vec{r}) = -V_{el}(\vec{r}) \quad (2)$$

The expression of $h(\vec{r})$ [i. e., Eq. (1)] contains nonlinear functions of $\rho(\vec{r})$ (the first and the third terms) and hence the condensation of $h(\vec{r})$ [as it is in Eq. (1)] is mathematically inexact.[33] So, for evaluating $V_{el}(\vec{r})$ and $\rho(\vec{r})$, 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 main advantage of taking the left and right derivative of $h(\vec{r})$ is to make a difference between the processes of gaining or loosing electron density and when this is applied to Eq. (2), they lead to the left and right derivatives of Fukui potential.[34-41] 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. For instance, several biologically active organic systems (like indolynes, substituted benzenes, polycyles) are already

studied[30,32] and a good correlation is found between experimental and our theoretically calculated reactivity trends.

In a recent study by the present authors,[32] the relative contribution of the sum of kinetic $[\frac{10}{9}C_F\rho(\bar{r})^{2/3}]$ and exchange $[\frac{4}{9}C_X\rho(\bar{r})^{1/3}]$ energy terms to that of the electronic part of the molecular electrostatic potential $[V_{el}(\bar{r})]$ is investigated to assess the proposed definition of hardness potential derivatives as, $\Delta^{+}h(\bar{r}) \approx -[V_{el}^{N+1}(\bar{r}) - V_{el}^{N}(\bar{r})]$ and $\Delta^{-}h(\bar{r}) \approx -[V_{el}^{N}(\bar{r}) - V_{el}^{N-1}(\bar{r})]$ (at the nucleus, i.e., $r \to 0$). It was also concluded that reactivity trends generated by Fukui potential [containing only $V_{el}(\bar{r})$ term] and hardness potential derivatives [containing $V_{el}(\bar{r})$, $\frac{10}{9}C_F\rho(\bar{r})^{2/3}$ and $\frac{4}{9}C_X\rho(\bar{r})^{1/3}$ terms] are in good agreement with experimental ones.[32] Numerical demonstration also reveals the fact 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 $V_{el}(\bar{r})$. Hence it is safer to use the differences of all the three terms in the definition of hardness potential derivatives (Eq. (6) and (7), see Section 2), rather than only the differences of $V_{el}(k)$ term (as shown above). 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 $[V_{el}(\bar{r})]$ exists in the definition of hardness potential.

In this article, a critical study is performed to obtain some systematic and qualitative trends of hardness potential derivatives and Fukui potentials in isolated atoms vs atoms within a

molecule. Several types of molecules containing reactive carbon centres (where reactivities are known experimentally)[42-52] and hetero atoms are chosen to make our study elaborative (i. e., not confined within a specific type of systems). Based on electron density, $\rho(\bar{r})$, and the electronic part of the molecular electrostatic potential, $V_{el}(\bar{r})$, an interpretative investigation will be conducted on how two electronically different situations, i.e., isolated atoms and atoms within a molecule, affect hardness potential derivatives and Fukui potentials.

2. Theoretical Background:

I. Working Equations of Fukui Potential:

Fukui Potentials are defined as,[30, 35, 37,41]

$$v_f^+ |_{r=0} = \int \frac{f^+(\bar{r})}{|r-r'|} dr' = -[V_{el}^{N+1}(\bar{r}) - V_{el}^{N}(\bar{r})] \quad (3)$$

$$v_f^- |_{r=0} = \int \frac{f^-(\bar{r})}{|r-r'|} dr' = -[V_{el}^{N}(\bar{r}) - V_{el}^{N-1}(\bar{r})] \quad (4)$$

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 r^{-1} [i. e., $\langle\phi|\hat{r}^{-1}|\phi\rangle$, where ϕ stands for the unperturbed molecular wave function].

The expression for MEP (Φ) is as follows :

$$\Phi = V_{Nu}(\dot{r}) + V_{el}(\dot{r}) = \sum_A \frac{Z_A}{|\bar{r} - \bar{r}'|} - \sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(\bar{r})\chi_\nu(\bar{r})}{|\bar{r} - \bar{r}'|} d\bar{r}' \qquad (5)$$

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. (3) and (4) we get two new expressions,

$$v_f^+\big|_{r=0} = -\left[\left(\sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(r)\chi_\nu(r)}{|r - r'|} dr'\right)_{N+1} - \left(\sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(r)\chi_\nu(r)}{|r - r'|} dr'\right)_N\right] \qquad (3a)$$

$$v_f^-\big|_{r=0} = -\left[\left(\sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(r)\chi_\nu(r)}{|r - r'|} dr'\right)_N - \left(\sum_\mu \sum_\nu P_{\mu\nu} \int \frac{\chi_\mu(r)\chi_\nu(r)}{|r - r'|} dr'\right)_{N-1}\right] \qquad (4a)$$

III. Working Equations of Hardness Potential Derivatives:

Hardness Potential Derivatives are expressed as (evaluated at the nucleus of the atom 'k', i. e., when, $r \to 0$),

$$\Delta^{+}h(k) = \frac{10}{9}C_F\left[\rho_{N+1}(k)^{2/3} - \rho_N(k)^{2/3}\right] - \left[V_{el}{}^{N+1}(k) - V_{el}{}^{N}(k)\right] - \frac{4}{9}C_X\left[\rho_{N+1}(k)^{1/3} - \rho_N(k)^{1/3}\right] \quad (6)$$

$$\Delta^{-}h(k) = \frac{10}{9}C_F\left[\rho_{N}(k)^{2/3} - \rho_{N-1}(k)^{2/3}\right] - \left[V_{el}{}^{N}(k) - V_{el}{}^{N-1}(k)\right] - \frac{4}{9}C_X\left[\rho_{N}(k)^{1/3} - \rho_{N-1}(k)^{1/3}\right] \quad (7)$$

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. (6) and (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]

$$f_N^+(r) = |\phi_{N+1}(r)|^2 + \sum_{i=1}^{N}\left(\frac{\partial|\phi_i(r)|^2}{\partial N}\right)^+_{v(r)} \quad (8)$$

$$f_N^-(r) = |\phi_N(r)|^2 + \sum_{i=1}^{N}\left(\frac{\partial|\phi_i(r)|^2}{\partial N}\right)^-_{v(r)} \quad (9)$$

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. (8) and (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. (8)) or removed (Eq. (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 (Eqns. (3) and (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.

3. Computational Details:

To obtain some qualitative trends of $V_{el}(\bar{r})$, hardness potential derivatives (Eqns. (6) and (7)) and Fukui potential (Eqns. (3) and (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. 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 1.

I. Trends of $V_{el}(\bar{r})$ in isolated atoms vs atoms in molecules:

As evident from Table 1.a. and 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. (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. (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 2.a. and 2.b., it is observed that the values of $v_f^+|_{r=0}$ and $v_f^-|_{r=0}$ 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 Eqn 3 (or 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 Eqn. 3 (or 3.a.) will be much lower. This explains why $v_f^+|_{r=0}$ 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 Eqn 4 (or 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 $v_f^-|_{r=0}$ 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 2.c.) are higher for carbon atoms in molecules than when it is isolated. However, trends of $\Delta^{+}h(k)$ values (in Table 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 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 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., $v_f^{+}|_{r=0}$ and $v_f^{-}|_{r=0}$) 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 2.a., 2.b., 2.c. and 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 3.a.), 6-311G(2d,2p) (Table 3.b.) and 6-311G+(2d,2p) (Table 3.c.) and all using the B3LYP method for isolated atoms, it is found that the order of electron densities is as follows (Table 3.a., 3.b. and 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 eqns 6 and 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 Section 4.II and Eqns (3) and (4) it is obvious that Fukui potential values [i.e., the net values within the second square bracket of Eqns (6) and (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 Eqns (6) and (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 $v_f^+|_{r=0}$ and $v_f^-|_{r=0}$ (in Table 2.a., 2.b., 2.c. and 2.d.) of constituent atoms of a molecule (or isolated atoms), it is revealed that the value of $v_f^-|_{r=0}$ is always substantially higher than that of $v_f^+|_{r=0}$ (this is true for either carbon atom or any other hetero atoms). Although, the values of $v_f^+|_{r=0}$ and $v_f^-|_{r=0}$ 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 (details on orbital relaxation effects are discussed in section 2.II.). As a result, the overall sum of $v_f^-|_{r=0}$ is higher compared to that of $v_f^+|_{r=0}$ for all the chosen molecules [which are mostly comprised of atoms of second period (C, N, F, O)] as evident from Table 4.a.

Now, if we look at the sum of hardness potential derivatives, we also observe the same trend (Table 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. (6) and (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 $v_f^{-}|_{r=0}$ values are higher compared to those of $v_f^{+}|_{r=0}$ (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 2.c. and 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.b.).

Conclusion:

The main objective of the present article 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 eqn. (5)) for isolated atoms and atoms in a molecule. As Fukui potential and hardness potential derivatives are significantly dependent on the differences of $V_{el}(\bar{r})$ (eqns. 3, 4, 6 and 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 $v_f^{+}|_{r=0}$ and $v_f^{-}|_{r=0}$ 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. Bartolotti and Ayers[78] 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 (involving molecules chosen in the present study), where frontier-molecular-orbital-control or charge-control cannot play a decisive role.

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). But it is an open-ended question and it requires an in-depth investigation, both analytically and conceptually. Further studies are in progress.

Acknowledgments:

R. B is thankful to Birla Institute of Technology and Science (BITS Pilani), Pilani Campus, Rajasthan, India for financial support in the form of Institute Research Fellowship. R.K.R. acknowledges the DST (Project Ref. No. SB/S1/PC-067/2013), Government of India, New Delhi and Departmental Research Support under Special Assistance Program (DRS-SAP) of UGC (Project Ref. No. F. 540/5/DRS/2013 (SAP-I)], Government of India, New Delhi, for financial support of this research. Computational facilities extended by the Department of Chemistry, BITS PILANI, Pilani campus, is also thankfully acknowledged. Enriching discussions with Prof. Paul W. Ayers, Department of Chemistry & Chemical Biology, McMaster University, Hamilton, Ontario, Canada and Prof. Carlos Cárdenas, Departamento de Física, Facultad de Ciencias, Universidad de Chile, Santiago, Chile are also gratefully acknowledged. Helpful discussion with Prof. Dmitri Fedorov, Research Institute for Computational Sciences (RICS), National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Japan is thankfully acknowledged. Finally, the Authors would like to thank the Reviewers for their valuable suggestions, taking care of which has helped in raising the standard of the manuscript.

References:

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. E. Scrocco and J. Tomasi, *Top. Curr. Chem*., 1973, **42,** 95.

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. Pérez, and R. Contreras, *J. Chem. Phys*., 2000, **113**, 2544.

93. P. Bultinck, R. Carbó-Dorca, and W. Langenaeker, *J. Chem. Phys.,* 2003, **118**, 4349.

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

95. S. M. Krishnamurti, R. K. Roy, R. Vetrivel, S. Iwata, and S. Pal, *J. Phys.Chem.*, 1997, **101**, 7253.

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

Table 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 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 1.a. (continued)

Systems	Reactive Position	$V_{el}(\vec{r})$ in isolated atom (in a. u.)	$V_{el}(\vec{r})$ in molecule (in a. u.)
42. Naphthalene	C1 C2	-14.669	-27.528 -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 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 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 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 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 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 2. a. (continued)

Systems	Reactive Position	$v_f^-\|_{r=0}$ in isolated atom	$v_f^+\|_{r=0}$ in isolated atom	$v_f^-\|_{r=0}$ in molecule	$v_f^+\|_{r=0}$ 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 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 1.

Systems	Hetero Atoms	$v_f^-\|_{r=0}$ in isolated atom	$v_f^+\|_{r=0}$ in isolated atom	$v_f^-\|_{r=0}$ in molecule	$v_f^+\|_{r=0}$ 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 2. b. (continued)

Systems	Hetero Atoms	$v_f^-\|_{r=0}$ in isolated atom	$v_f^+\|_{r=0}$ in isolated atom	$v_f^-\|_{r=0}$ in molecule	$v_f^+\|_{r=0}$ 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 2. b. (continued)

Systems	Hetero Atoms	$v_f^-\|_{r=o}$ in isolated atom	$v_f^+\|_{r=o}$ in isolated atom	$v_f^-\|_{r=o}$ in molecule	$v_f^+\|_{r=o}$ 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 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 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 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 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 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 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 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 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 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. 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. a. (Continued)

Systems	$\sum_K v_f^-(\bar{r})\|_{r=0}$	$\sum_K v_f^+(\bar{r})\|_{r=0}$
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. a. (Continued)

Systems	$\sum_K v_f^-(\bar{r})\|_{r=0}$	$\sum_K v_f^+(\bar{r})\|_{r=0}$
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. a. (Continued)

Systems	$\sum_K v_f^-(\bar{r})\|_{r=0}$	$\sum_K v_f^+(\bar{r})\|_{r=0}$
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. 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. 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 1: Numbering of Atoms in amino acids