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Chemical Reactivity and Selectivity: Local HSAB Principle versus Frontier Orbital Theory

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It has been argued that the maximum Fukui function site is the best for the frontier-controlled soft−soft reactions whereas for the charge-controlled hard−hard interactions the preferred site is associated with the maximum net charge and not necessarily the minimum Fukui function.

Several recent publications[1−5] have recommended the application of a local hard−soft acid−base (HSAB) principle in analyzing the site selectivity in a molecule. Therein it has been shown that the soft−soft interactions are preferred in the site of the maximum Fukui function whereas the minimum Fukui function site is the best for the hard−hard interactions. The Li−Evans[2] minimum Fukui function criterion correctly describes the protonation process in systems presenting a unique protonation site embedded in different chemical environments, yet it markedly fails in polyfunctional systems presenting more than one site for protonation. In the present article it is highlighted that the Fukui function is not the proper descriptor of the hard−hard interactions since they are not frontier-controlled. Possible descriptors for these interactions are mentioned.

Global reactivity parameters like electronegativity[6,7] (χ) and hardness[8−10] (η) for an N-electron system with total energy E are respectively defined, within density functional theory[11] (DFT), as follows:

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

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{\nu(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{\nu(\vec{r})} \tag{2}$$

where μ and $\nu(\vec{r})$ are chemical and external potentials, respectively. Softness[11,12] is the inverse of hardness

$$S = \frac{1}{2\eta} \tag{3}$$

Maximum hardness principle (MHP) states that[9,13,14] "there seems to be a rule of nature that molecules arrange themselves so as to be as hard as possible" while the statement of the minimum polarizability principle[15] (MPP) is "the natural direction of evolution of any system is toward a state of minimum polarizability". Thus, hardness measures the stability and softness (polarizability) measures the reactivity. According to the HSAB principle,[9,11,16−18] "among potential partners of a given electronegativity, hard likes hard and soft likes soft". The restriction of constant chemical potential difference may akin to comparable strengths of acids and bases, a condition necessary for HSAB principle to be operative.[9] While the global properties may explain the reactivity, for understanding selectivity one resorts to the local quantities. The most important local quantity is the density $\rho(\vec{r})$ itself, the basic variable of DFT,[11] given as

$$\rho(\vec{r}) = \left(\frac{\delta E[\rho]}{\delta \upsilon(\vec{r})}\right)_N \tag{4}$$

Other quantity is the Fukui function,[19] defined as

$$f(\vec{r}) = \left(\frac{\delta \mu}{\delta \upsilon(\vec{r})}\right)_N = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{\nu(\vec{r})} \tag{5}$$

Due to the discontinuity in the $\rho(\vec{r})$ vs N curve, one can define[19] three different types of Fukui functions, viz.

$$f^+(r) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)^+_{\nu(\vec{r})} = [\rho_{N+1}(\vec{r}) - \rho_N(\vec{r})] \approx \rho_{\mathrm{LUMO}}(\vec{r}),\quad \text{governing nucleophilic attack} \tag{6a}$$

$$f^-(r) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)^-_{\nu(\vec{r})} = [\rho_N(\vec{r}) - \rho_{N-1}(\vec{r})] \approx \rho_{\mathrm{HOMO}}(\vec{r}),\quad \text{governing electrophilic attack} \tag{6b}$$

$$f^0(\vec{r}) = \frac{1}{2}[f^+(\vec{r}) + f^-(\vec{r})] \approx \frac{1}{2}[\rho_{\mathrm{LUMO}}(\vec{r}) + \rho_{\mathrm{HOMO}}(\vec{r})],\quad \text{governing radical attack} \tag{6c}$$

Chemical reactions are mainly adjustment of valence electrons among the reactant orbitals. Fukui proposed his frontier orbital theory[20] (FOT) which allows a chemical reaction to be understood in terms of HOMO and LUMO only. Fukui functions capture this concept of classical FOT. Condensed Fukui functions at each atomic site in a molecule can also be defined in terms of the associated electron populations.[11] The largest value of $f(\vec{r})$ at the reaction site will be preferable[19] since that will imply a large dμ value. Since the hard species are generally of small size and high charge and the soft species are large in size with a low charge, it is expected that in the hard−hard reactions ionic bonding would predominate[21,22] and in the soft−soft reactions covalent bonding would predominate. For the soft species the nuclear charge is adequately screened by the core electrons and the two soft species will mainly interact via frontier orbitals but the core orbitals are not just "spectators" for the hard−hard reactions, implying that soft−soft interactions are frontier-controlled (follow "through bond" interactions) while hard−hard interactions are charge-controlled (follow "through space" interactions).[21] One should not expect FOT to work in the case of hard−hard interactions. While soft−soft interactions are controlled by $f(\vec{r})$, for hard−hard interactions the charges

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on each atom will decide the actual reaction site.[9] It has also been shown[21] that for the interaction between a hard and a soft species the reactivity is generally very low and it cannot be identified as a charge-/frontier-controlled reaction, vindicating the HSAB principle.[9,11,16−18] When two reactants A and B approach each other, the energy change (upto second order) may be written as[11]

$$\Delta E = \Delta E_{\mathrm{covalent}} + \Delta E_{\mathrm{electrostatic}} + \Delta E_{\mathrm{polarization}} \tag{7a}$$

where

$$\Delta E_{\mathrm{covalent}} = -\frac{[\mu_{\mathrm{B}}^{0} - \mu_{\mathrm{A}}^{0} + \int f_{\mathrm{B}}(\vec{r})\Delta v_{\mathrm{B}}(\vec{r})\,\mathrm{d}\vec{r} - \int f_{\mathrm{A}}(\vec{r})\Delta v_{\mathrm{A}}(\vec{r})\,\mathrm{d}\vec{r}]^{2}}{4(\eta_{\mathrm{A}} + \eta_{\mathrm{B}})} \tag{7b}$$

$$\Delta E_{\mathrm{electrostatic}} = \int \rho_{\mathrm{A}}(\vec{r})\Delta v_{\mathrm{A}}(\vec{r})\,\mathrm{d}\vec{r} + \int \rho_{\mathrm{B}}(\vec{r})\Delta v_{\mathrm{B}}(\vec{r})\,\mathrm{d}\vec{r} + \Delta V_{\mathrm{nn}} \tag{7c}$$

$$\Delta E_{\mathrm{polarization}} = \int\int \chi_{\mathrm{A}}(\vec{r},\vec{r}\,')\Delta v_{\mathrm{A}}(\vec{r})\Delta v_{\mathrm{A}}(\vec{r}\,')\,\mathrm{d}\vec{r}\,\mathrm{d}\vec{r}\,' + \int\int \chi_{\mathrm{B}}(\vec{r},\vec{r}\,')\Delta v_{\mathrm{B}}(\vec{r})\Delta v_{\mathrm{B}}(\vec{r}\,')\,\mathrm{d}\vec{r}\,\mathrm{d}\vec{r}\,' \tag{7d}$$

In eq 7c ΔV_{nn} is the nuclear−nuclear repulsion term and the linear response function $\chi_{\mathrm{A}}(\vec{r},\vec{r}\,')$ in eq 7d is given by

$$\chi_{\mathrm{A}}(\vec{r},\vec{r}\,') = \left[\frac{\delta\rho_{\mathrm{A}}(\vec{r})}{\delta v_{\mathrm{A}}(\vec{r}\,')}\right]_{N_{\mathrm{A}}} = -s_{\mathrm{A}}(\vec{r},\vec{r}\,') + \frac{s_{\mathrm{A}}(\vec{r})s_{\mathrm{A}}(\vec{r}\,')}{S} \tag{8a}$$

$$= -\,s_{\mathrm{A}}(\vec{r},\vec{r}\,') + f_{\mathrm{A}}(\vec{r})s_{\mathrm{A}}(\vec{r}\,') \tag{8b}$$

where $s(\vec{r},\vec{r}\,')$ is the softness kernel and the local softness $s(\vec{r})$ is given by

$$s(\vec{r}) = f(\vec{r})S \tag{8c}$$

Note that three different local softnesses (cf. eqs 6) and their condensed-to-atom variants can also be defined. Definition of a corresponding local hardness is, however, ambiguous.[23]

For the soft−soft interactions, $\Delta E_{\mathrm{covalent}}$ dominates in ΔE and the nature of frontier control is transparent. Since hard−hard interactions are charge-controlled, the predominant term in ΔE is the Hellmann−Feynman type interaction term $\Delta E_{\mathrm{electrostatic}}$. The corresponding Hellmann−Feynman force on a particular nucleus or the associated nuclear Fukui function (and the related local hardness in an appropriate ensemble)[24] may be a reliable local descriptor of selectivity. Minimization of $\Delta E_{\mathrm{covalent}}$ leads to the HSAB principle.[10,17,18] A local version of the HSAB principle has also been derived[1] using this approach at the local level. As in its global counterpart, a difference in chemical potential (first-order response in energy for change in N) will drive an electron transfer even between two species (sites) of very different hardness (second-order response in energy for change in N) values. Therefore, only potential sites are to be selected for applying the local HSAB principle, if there is any. Another elegant proof of the local HSAB principle has been provided by Li and Evans[2] by modelling the softness kernel comprising a local and a nonlocal part. Following an earlier work of Berkowitz,[25] they have shown[2] that for hard−hard interactions the minimum Fukui function site is preferred and for soft−soft interactions the maximum Fukui function site is preferred. It may be noted that Berkowitz[25] showed that for the soft−soft interactions, which are covalent in nature and hence frontier-controlled, the amount of electronic charge transferred between the reactants during the small displacement along the reaction coordinate is large for small η, maximum overlap of the Fukui functions and larger value of the frontier quantity ($f_{\mathrm{A}} - f_{\mathrm{B}}$). He also mentioned[25] that for hard−hard interactions this amount is small and the reaction is controlled by Coulomb interactions between the reactants. Larger difference in Fukui functions (or equivalently local softness) is counter to the local HSAB principle. Similar aspect has also been noticed[26] in the context of application of maximum complimentarity rule in locating low-energy transition states of 1,3-dipolar cycloadditions where the local HSAB principle is violated. The importance of electrostatic interactions in understanding this type of reactions has been shown through ab initio calculations.[27] An appropriate local descriptor for analyzing hard−hard interactions could have been the local hardness which, however, cannot be defined in an unambiguous way.[23] Even if it is considered that a minimum Fukui function[2] (or equivalently local softness) site corresponds to maximum local hardness the highest reactivity/selectivity of this is counter to MHP[9,13,14] and MPP.[15] For systems like allyl carbocation (carbanion) where the terminal carbon atoms carry positive (negative) charges, preference of attack to those sites will be definitely governed by electrostatics. Addition (removal) of an electron to (from) an allyl carbocation (carbanion) will prefer the site with the maximum value of the Fukui function. The fact is in general true for any molecule where there are centers with positive/negative charges. So a local version of Coulomb law may be more appropriate in analyzing the hard−hard interactions, viz.

$$F_{ij}^{\mathrm{AB}} \propto \frac{q_i^{\mathrm{A}}\, q_j^{\mathrm{B}}}{r^2} \tag{9}$$

where q_i^{A} (q_j^{B}) is the net charge on the i(j)th atom in molecule A (B) obtained by condensing $\rho(\vec{r})$, an important local reactivity index (eq 4), to an atom, including sign of the charge and augmented by nuclear charge. In eq 9 r refers to the distance between the sites of charges q_i^{A} and q_j^{B}. Unfortunately, the various population analysis schemes[9] have their inherent deficiencies associated with the arbitrariness in density partitioning in defining an atom in a molecule.[9,11,18] Of course, the original Klopman terms[21] describing the charge-controlled reactions can also be used which in addition take care of the effect of the environment through the dielectric constant. Another possible candidate for a local descriptor of charge-controlled reactions is the molecular electrostatic potential (MEP)[28] (or the MEP-derived charges) which comprises potentials due to all the nuclei and electrons in a molecule, calculated at every points in space or a condensed-to-atom version of it. There are several systems such as HCHO, NCS^-, and malonaldehyde anion for which it has been shown[9] through ab initio calculations that a soft electrophile prefers the site with the maximum Fukui function while a hard electrophile prefers a site with maximum net charge. Reactivity and selectivity in the Diels−Alder reaction has been studied[29] recently through the net change in global hardness, calculated as the electrostatic potential due to the Fukui function at the point where MEP equals molecular electronegativity,[30] followed by the use of MHP.[9,13,14] Some recent calculations[3−5] have shown that a minimum Fukui function site is preferred for hard−hard interactions. For the protonation reactions[2,5] it may be possible because H^+ is a special hard acid[9,31] devoid of filled inner shells and it forms[9] strong bond with soft H^- to give H_2. Since hard–hard interactions can be understood even at the Hartree–Fock level and inclusion of correlations is important for interactions of soft species which are generally large in size and having a highly polarizable core,[31] many more soft–soft interactions (both at the local and global levels) are to be studied for greater understanding of the HSAB principle including its local variant. Minimum Fukui function condition for the hard–hard reactions may complement the maximum net charge condition in certain situations where the approximations involved in the Li–Evans proof[2] are valid and may be rationalized through the equality of softness and charge capacity of a group.[32] The connection, however, is not obvious.

In conclusion, the global HSAB principle and the frontier orbital theory properly augmented by Klopman's ideas are adequate in explaining both reactivity and selectivity. Soft–soft interactions are frontier-controlled and predominantly covalent in nature, and the site with the maximum value of the Fukui function would be preferred in these reactions whereas hard–hard interactions are charge-controlled and predominantly ionic in nature and for these reactions the preferred site is that which contains maximum net charge that may coincide in certain cases with the site associated with the minimum value of the Fukui function.

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