The Fukui Function: A Key Concept Linking Frontier Molecular Orbital Theory and the Hard-Soft-Acid-Base Principle

Yan Li and Jeremy N. S. Evans*

Contribution from the Department of Biochemistry and Biophysics, Washington State University, Pullman, Washington 99164-4660

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Abstract: This paper demonstrates that the Fukui function plays a central role in the study of chemical reactivity and selectivity. Both the Frontier Molecular Obital (FMO) Theory and the Hard-Soft-Acid-Base (HSAB) principle are intrinsically related to the Fukui function. By using an energy perturbation method within the framework of density functional theory (DFT), we have shown that the FMO theory can be understood as a part of the HSAB principle. The selectivity of a chemical reaction is determined by the nature of the reaction. Thus, for a hard reaction, the site of minimal Fukui function is preferred; for a soft reaction, the site of maximal Fukui function is preferred.

Introduction

Density functional theory (DFT) provides a very convenient framework for the discussion of chemical reactivity.[1] Many useful and important concepts in chemistry have been identified by and derived from DFT.[2-9] Among these DFT-derived concepts, the Fukui function, as derived by Parr and Yang,[4] is related to the electron density in the frontier molecular orbitals (FMO) and thus plays a vital role in chemical selectivity.[10,11] However, FMO theory fails in certain cases.[12-14] For example, the highest occupied molecular orbital (HOMO) for pyridine is not the lone pair orbital on the nitrogen but a π orbital of the whole molecule, although protonation occurs at the nitrogen lone-pair site. Fukui explained this in terms of the high energy required to change the hybridization for carbon protonation.[12] This explanation may be valid for this aromatic molecule, but for non-aromatic compounds, however, it may be not true. For the protonation of alkylamines, it was found that the site of maximal Fukui function is not the site of protonation.[13] It is important to realize that according to the HSAB principle, hard likes hard and soft likes soft and this is somehow in conflict with FMO theory, because according to the latter only the softest site, i.e. maximal Fukui function site, is favored for a chemical reaction.

In this paper, an energy perturbation method within the DFT formalism is used to discuss chemical reactivity and selectivity. The advantage of this aproach is that it is an orbital-independent method. This distinguishes the DFT method from the orbital-theory-based perturbation methods which have been used most frequently in validating both the FMO theory and the HSAB principle. Besides a proof of FMO theory and the HSAB principle, a conclusion from this study is that a site of minimal Fukui function may be favored under some circumstances. This is especially true for protonation reactions, which have also been studied in this paper by proposing a model system.

Theory

The fundamental differential equation of DFT for a virtual change of the ground state is[1]

$$dE = \mu \, dN + \int \varrho(\mathbf{r}) \, d\nu(\mathbf{r}) \, d\mathbf{r} \tag{1}$$

where E is the total electronic energy, N is the number of electrons, $\nu(\mathbf{r})$ is the external electrostatic potential an electron at $\mathbf{r}$ experiences due to the nuclei, and μ, the chemical potential, is defined as[2]

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{\nu(\mathbf{r})} \tag{2}$$

and the electron density $\varrho(\mathbf{r})$ is defined as[1]

$$\varrho(\mathbf{r}) = \left(\frac{\partial E}{\partial \nu(\mathbf{r})}\right)_N \tag{3}$$

When two molecules approach one another, as occurs in a chemical reaction, the energy of each molecule will be changed in response to the perturbation caused by the approach of the

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* Author to whom correspondence should be addressed.

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other molecule. To study this process, a Taylor series expansion can be performed up to second order. The energy change for the molecule will be, to second order in the changes ΔN and $\Delta\nu(\mathbf{r})$,

$$\Delta E = \left(\frac{\partial E}{\partial N}\right)_{\nu(\mathbf{r})}\Delta N + \int\left(\frac{\partial E}{\partial\nu(\mathbf{r})}\right)_N \Delta\nu(\mathbf{r})\,\mathrm{d}\mathbf{r} + \int\left(\frac{\partial^2 E}{\partial N\,\partial\nu(\mathbf{r})}\right)\Delta N\Delta\nu(\mathbf{r})\,\mathrm{d}\mathbf{r} + \frac{1}{2}\left(\frac{\partial^2 E}{\partial^2 N}\right)_{\nu(\mathbf{r})}\Delta N^2 + \frac{1}{2}\int\left(\frac{\partial^2 E}{\partial\nu(\mathbf{r})\,\partial\nu(\mathbf{r}')}\right)_N \Delta\nu(\mathbf{r})\Delta\nu(\mathbf{r}')\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' = \mu\Delta N + \eta\Delta N^2 + \int\varrho(\mathbf{r})\Delta\nu(\mathbf{r})\,\mathrm{d}\mathbf{r} + \Delta N\int f(\mathbf{r})\Delta\nu(\mathbf{r})\,\mathrm{d}\mathbf{r} + \frac{1}{2}\int\left(\frac{\partial\varrho(\mathbf{r})}{\partial\nu(\mathbf{r}')}\right)_N \Delta\nu(\mathbf{r})\Delta\nu(\mathbf{r}')\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' \quad (4)$$

where $\mathbf{r}$ and $\mathbf{r}'$ are independent variables of position and η is the global hardness, which is defined as[3]

$$\eta = \frac{1}{2}\left(\frac{\partial\mu}{\partial N}\right)_{\nu(\mathbf{r})} \quad (5)$$

and $f(\mathbf{r})$, the Fukui function, is defined as[4]

$$f(\mathbf{r}) = \left(\frac{\partial\varrho(\mathbf{r})}{\partial N}\right)_{\nu(\mathbf{r})} \quad (6)$$

Berkowitz and Parr[15] have derived the expression for $(\partial\varrho(\mathbf{r})/\partial\nu(\mathbf{r}'))_N$:

$$\left(\frac{\partial\varrho(\mathbf{r})}{\partial\nu(\mathbf{r}')}\right)_N = -s(\mathbf{r},\mathbf{r}') + \frac{s(\mathbf{r})s(\mathbf{r}')}{S} \quad (7)$$

where $S = 1/\eta$ is the global softness, and $s(\mathbf{r},\mathbf{r}')$ is the softness kernel, related to the local softness $s(\mathbf{r})$ by[15]

$$s(\mathbf{r}) = \int s(\mathbf{r},\mathbf{r}')\,\mathrm{d}\mathbf{r}' \quad (8)$$

The local softness is related to the Fukui function through[5]

$$s(\mathbf{r}) = f(\mathbf{r})S \quad (9)$$

To express the softness kernel in terms of local softness, one must consider both local and nonlocal natures of the kernel. We assume that the kernel can be approximated as a linear combination of two parts—a local one and a nonlocal one:

$$s(\mathbf{r},\mathbf{r}') = as(\mathbf{r}')\delta(\mathbf{r}-\mathbf{r}') + b\frac{s(\mathbf{r})s(\mathbf{r}')}{S} \quad (10)$$

with

$$a + b = 1 \quad (11)$$

where a and b are constants. For a local model, $a = 1$ and $b = 0$; for a nonlocal model, $a = 0$ and $b = 1$. Since the quantity $(\partial\varrho(\mathbf{r})/\partial\nu(\mathbf{r}'))_N$ is nonlocal in nature, when eq 10 is substituted into eq 7, it follows that b must not equal one, or, a must not equal zero. In other words, the softness kernel must have a local character. Equation 10 with the condition of eq 11 satisfies the constraint imposed by eq 8. Note that when $a = 1$, eq 10 reduces to the approximation of the softness kernel by Vela and Gazquez.[16] Substituting eq 10 in eq 7, one gets

$$\left(\frac{\delta\varrho(\mathbf{r})}{\delta\nu(\mathbf{r}')}\right)_N = -as(\mathbf{r}')\delta(\mathbf{r}-\mathbf{r}') + (1-b)\frac{s(\mathbf{r})s(\mathbf{r}')}{S} \quad (12)$$

Substituting eq 12 into eq 4, and using the following relations

$$\int s(\mathbf{r})s(\mathbf{r}')\,\mathrm{d}\nu(\mathbf{r})\,\mathrm{d}\nu(\mathbf{r}')\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' = \left[\int s(\mathbf{r})\,\mathrm{d}\nu(\mathbf{r})\,\mathrm{d}\mathbf{r}\right]^2 \quad (13)$$

$$\int s(\mathbf{r}')\delta(\mathbf{r}-\mathbf{r}')\,\mathrm{d}\nu(\mathbf{r})\,\mathrm{d}\nu(\mathbf{r}')\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' = \int s(\mathbf{r})\,\mathrm{d}\nu(\mathbf{r})^2\,\mathrm{d}\mathbf{r} \quad (14)$$

one can derive the expression for ΔE as follows:

$$\Delta E = \mu\Delta N + \eta\Delta N^2 + \int\varrho(\mathbf{r})\Delta\nu(\mathbf{r})\,\mathrm{d}\mathbf{r} + \Delta N\int f(\mathbf{r})\Delta\nu(\mathbf{r})\,\mathrm{d}\mathbf{r} + a\frac{\eta}{2}\left(\int s(\mathbf{r})\Delta\nu(\mathbf{r})\,\mathrm{d}\mathbf{r}\right)^2 - \frac{a}{2}\int s(\mathbf{r})(\Delta\nu(\mathbf{r}))^2\,\mathrm{d}\mathbf{r} \quad (15)$$

The cross term $\Delta\nu(\mathbf{r})\Delta\nu(\mathbf{r}')$ in eq 4 is absent in eq 15 after integration. This equation is our basic working equation, which is based on the assumption of eq 10, and we assume that it correctly embodies the main physical effects.

Chemical Reactivity and Selectivity

A. Reactivity—Global Nature. Consider two molecules i and j approaching one another, then the energy perturbations at the beginning of the reaction are ΔE_i and ΔE_j, respectively. The total electronic energy change of the system is $\Delta E_i + \Delta E_j$, and the second-order perturbation is

$$\Delta E_{\mathrm{total}} = \Delta E_i + \Delta E_j = \underbrace{(\mu_i - \mu_j)\Delta N}_{(16.1)} + \underbrace{(\eta_i + \eta_j)\Delta N^2}_{(16.2)} + \underbrace{\int[\varrho_i(\mathbf{r})\Delta\nu_i(\mathbf{r}) + \varrho_j(\mathbf{r})\Delta\nu_j(\mathbf{r})]\,\mathrm{d}\mathbf{r}}_{(16.3)} + \underbrace{\Delta N\int[f_i(\mathbf{r})\Delta\nu_i(\mathbf{r}) - f_j(\mathbf{r})\Delta\nu_j(\mathbf{r})]\,\mathrm{d}\mathbf{r}}_{(16.4)} + \underbrace{\frac{\eta_i a}{2}\left(\int s_i(\mathbf{r})\Delta\nu_i(\mathbf{r})\,\mathrm{d}\mathbf{r}\right)^2}_{(16.5)} + \underbrace{\frac{\eta_j a}{2}\left(\int s_j(\mathbf{r})\Delta\nu_j(\mathbf{r})\,\mathrm{d}\mathbf{r}\right)^2}_{(16.6)} - \underbrace{\frac{a}{2}\int[s_i(\mathbf{r})(\Delta\nu_i(\mathbf{r}))^2 + s_j(\mathbf{r})(\Delta\nu_j(\mathbf{r}))^2]\,\mathrm{d}\mathbf{r}}_{(16.7)} \quad (16)$$

with

$$\Delta N = \Delta N_i = -\Delta N_j \geq 0 \quad (17)$$

where $\Delta\nu_i(\mathbf{r})$ is the external field that molecule i experiences due to molecule j (we ignore the $\Delta\nu_i(\mathbf{r})$ caused by the change in geometry of molecule i). Similarly, $\Delta\nu_j(\mathbf{r})$ is the external field that molecule j experiences due to molecule i. In eq 16, η_i is the global hardness of molecule i and η_j is the global

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hardness of molecule j. When the nuclear–nuclear repulsion interaction is included, the energy change is

$$\Delta E_{\mathrm{total}} = \Delta E_i + \Delta E_j + \Delta E_{\mathrm{nucl}} \tag{18}$$

In the following discussion, we will only consider the electronic portion of the energy expression since this is where all the new concepts come from within the DFT formalism. However, we should always keep in mind the nuclear–nuclear repulsive interaction, and in a given case it is not difficult to estimate its contribution to the reaction energy.

The term (16.1) in eq 16 shows that in order for a reaction to proceed via a low-energy path, an electron should be transferred from a molecule with higher chemical potential to a molecule with lower chemical potential. *The larger the difference in chemical potential between the two molecules, the easier the reaction will be.* The second term (16.2) shows that the global hardness acts against electron transfer. To minimize the initial activation energy of the reaction, the global hardness of both molecules needs to be minimized. Therefore, *the softer a molecule is, the more reactive it will be.*

B. Selectivity–Local Nature. It is hard to separate selectivity from reactivity. It may be understood here that selectivity relates to the local properties of molecules. The third term (16.3) is local in nature, and therefore the Coulombic interaction (as, of course, is ΔE_{nucl}) can be a good selectivity index, as in the electronic theory of chemical reactions. However, we are more concerned with the other terms of eq 16, which are particularly important in the proof of FMO theory and the HSAB principle.

First, consider the situation where electron transfer during the reaction is small, so that the contribution from the term (16.4) to the energy change can be ignored. Since the terms (16.5) and (16.6) always contribute positively to the energy change, the local softness of the reactive site of both molecules i and j should be minimized in order to minimize the reaction energy, provided that the value of the term (16.7) is smaller than that of the terms (16.5) and (16.6). This will be the case when the η_i and/or η_j is large. Reaction between two molecules that both have a large global hardness may be defined as a hard reaction. Thus for a hard reaction, the Fukui function and therefore the local softness of the reactive site of both molecules i and j should be minimized. This is the first part of the HSAB principle: *hard likes hard* (both globally and locally).

On the other hand, when the global hardnesses of η_i and η_j are small and thus the reaction is determined by the last term (16.7), then the site of maximal local softness would be favored at the reaction center. Since local softness is related to the Fukui function through eq 9, this leads to Parr and Yang's theory that a site of maximal Fukui function is preferred during a reaction, and thus Fukui's theory is correct in this context. Reaction between two molecules that both have a small global hardness (i.e. a large global softness) may be defined as a soft reaction. Thus, for a soft reaction, both local softnesses at molecules i and j should be maximized. This is the second part of the HSAB principle: *soft likes soft* (both globally and locally).

However, when the transfer of electrons cannot be ignored and the contribution from term (16.4) to the reaction energy is dominant, then this contribution needs to be analyzed. Following the approach of Berkowitz,[10] the change of the external field acting on molecule i can be divided into two parts: the nuclear part $\Delta v_i^{(\mathrm{n})}(\mathbf{r})$ and the electronic part $\Delta v_i^{(\mathrm{e})}(\mathbf{r})$, i.e.

$$\Delta v_i(\mathbf{r}) = \Delta v_i^{(\mathrm{n})}(\mathbf{r}) + \Delta v_i^{(\mathrm{e})}(\mathbf{r}) \tag{19}$$

To a first approximation, one can assume a point-charge model for each individual atom (k) in molecule j in order to discuss the effect of the external field of molecule j on the molecule i easily. Thus, for the nuclear part, one has

$$\begin{aligned}\Delta v_i^{(\mathrm{n})}(\mathbf{r}) &= \sum_{k\in j}\left(-\frac{q_{jk}}{R_{jk}(\mathbf{r})} + \frac{q_{jk}}{R_{jk}^0(\mathbf{r})}\right)\\ &= \sum_{k\in j}\left(-\frac{q_{jk}}{R_{jk}^0(\mathbf{r})\left(1+\dfrac{\Delta R_{jk}(\mathbf{r})}{R_{jk}^0(\mathbf{r})}\right)} + \frac{q_{jk}}{R_{jk}^0(\mathbf{r})}\right)\\ &\approx \sum_{k\in j}\frac{q_{jk}\Delta R_{jk}(\mathbf{r})}{(R_{jk}^0(\mathbf{r}))^2}\end{aligned} \tag{20}$$

where q_{jk} is the net charge at atom k within molecule j, $\Delta R_{jk}(\mathbf{r})$ is the change of the distance between the atom k of molecule j and the position $\mathbf{r}$ of molecule i, and $R_{jk}^0(\mathbf{r})$ is the distance between the atom k of molecule j and the position $\mathbf{r}$ of molecule i before the change. When two molecules approach one another, $\Delta R_{jk}(\mathbf{r})$ is always smaller than zero, so that a positively charged atom of molecule j causes a favorable change of the field at molecule i. For the electronic part, which is due to electron transfer between molecule i and molecule j, one has

$$\Delta v_i^{(\mathrm{e})}(\mathbf{r}) = \sum_{k\in j}\frac{\Delta N_{jk}}{R_{jk}(\mathbf{r})} \tag{21}$$

where ΔN_{jk} is the change in the number of electrons of atom k in molecule j. In the same way, one can derive an expression for $\Delta v_j(\mathbf{r})$. Using these expressions for $\Delta v_i(\mathbf{r})$ and $\Delta v_j(\mathbf{r})$, one can rewrite term (16.4) in eq 16 as

$$\begin{aligned}&\int f_i(\mathbf{r})\Delta N_i \Delta v_i(\mathbf{r})\,\mathrm{d}\mathbf{r} + \int f_j(\mathbf{r})\Delta N_j \Delta v_j(\mathbf{r})\,\mathrm{d}\mathbf{r} = \\ &\int f_i(\mathbf{r})\left(\sum_{k\in j}\left(\underbrace{\frac{q_{jk}\Delta R_{jk}(\mathbf{r})\Delta N_i}{(R_{jk}^0(\mathbf{r}))^2}}_{(22.1)}\right) + \underbrace{\frac{\Delta N_{jk}\Delta N_i}{R_{jk}(\mathbf{r})}}_{(22.2)}\right)\mathrm{d}\mathbf{r} + \\ &\int f_j(\mathbf{r})\left(\sum_{l\in i}\left(\underbrace{\frac{q_{il}\Delta R_{il}(\mathbf{r})\Delta N_j}{(R_{il}^0(\mathbf{r}))^2}}_{(22.3)}\right) + \underbrace{\frac{\Delta N_{il}\Delta N_j}{R_{il}(\mathbf{r})}}_{(22.4)}\right)\mathrm{d}\mathbf{r}\end{aligned} \tag{22}$$

where l defines atoms belonging to molecule i. For a reaction between two oppositely charged molecules, if the following conditions hold

$$q_{jk} > 0; \quad \Delta N_i < 0 \tag{23}$$

and

$$q_{il} < 0; \quad \Delta N_j > 0 \tag{24}$$

then, when two molecules approach one another, the terms (22.1) and (22.3) in eq 22 are always positive. This is especially true for a typical acid–base reaction where the acid is a proton and therefore there is no disproportionation reaction, i.e. an acid will always accept an electron rather than donate an electron during a reaction. Thus, if the values of (22.1) and (22.3) are larger than that of (22.2) and (22.4) (which requires that the charges of the molecules are relatively large), such that the overall contribution from eq 22 to the perturbation energy of the reaction is positive, then the Fukui function needs to be minimized in order for the reaction to proceed smoothly. However, when the charges of two interacting molecules are small or may be even zero, for example in a reaction between two neutral molecules, and the contributions from terms (22.2) and (22.4) to the reaction energy are dominant, because terms (22.2) and (22.4) always contribute negatively to the reaction energy ($\Delta N_i = -\Delta N_j$), then the maximal Fukui function site is preferred for the reaction. This leads again to Parr and Yang's theory and therefore to Fukui's theory.

Thus, by analyzing the various different terms of eq 16 under different conditions, we have demonstrated that the Fukui function can be used to characterize chemical selectivity and reactivity. Either a maximal or a minimal Fukui function may be preferred at the reaction site, depending on the nature of the reaction. Thus, the HSAB principle is a more general principle of chemical reactivity: hard likes hard (minimal Fukui function site is preferred), and soft likes soft (maximal Fukui function site is preferred). Our primitive semiempirical quantum calculations of the proton affinity of alkylamines confirmed that the minimal Fukui sites are the favored sites of reaction for protonations (data not shown).

Recently, while this paper was under review, two papers appeared[17,18] which discuss the HSAB principle using DFT methods and also concluded that the site of maximal Fukui function is not necessarily the most reactive site. However, they did not provide a detailed theoretical analysis, and did not recognize that the site of minimal Fukui function can be the most reactive site under specific conditions.

Conclusion

DFT has been shown to be a very convenient and powerful tool in the study of chemical reactivity and selectivity. Within DFT formalism, a perturbation method has been used to study chemical reactivity and selectivity. The results, based on the proposed model for the softness kernel, support the ideas that global hardness determines the chemical reactivity of a molecule as a whole, whereas the Fukui function determines chemical selectivity. It has been shown that the role of the Fukui function during a chemical reaction is defined by the nature of the reaction. Thus, the HSAB principle is a general chemical principle useful in the study of reactivity and selectivity, and FMO theory can be viewed as a part of the HSAB principle.

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