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Do the Local Softness and Hardness Indicate the Softest and Hardest Regions of a Molecule?

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Abstract: In this work, we will show that the largest values of the local softness and hardness do not necessarily correspond to the softest and hardest regions of the molecule, respectively. Based on our results, we will argue that it is more useful to interpret the local softness and the local hardness as functions that measure the "local abundance" or "concentration" of the corresponding global properties. This new point of view helps reveal how and when these local reactivity indices are most useful.

Keywords: density functional calculations · Fukui function · local hardness · local softness

Introduction

Density functional theory (DFT) based reactivity descriptors provide a powerful framework to explain and predict the reactivity and regioselectivity of the molecular systems.[1–3] The most commonly used among these descriptors are the chemical potential,[4] the Fukui function,[5,6] the global hardness,[7] and the global softness[8] (which is merely the reciprocal of the global hardness). The overall type and intensity of a molecule's reactivity is determined by the global descriptors (chemical potential, hardness, and softness). To go beyond this and determine not just how a molecule reacts, but where it reacts, requires local reactivity indicators. The Fukui function is one such indicator. Other key local indicators are the local hardness[9,10] and local softness.[8] The local hardness and local softness provide pointwise representations of the corresponding global quantities and, naively, should allow one to identify the "hardest" and "softest" reactive sites in a molecule. One goal of this paper is to show that this expectation is incorrect: one cannot reliably identify the hardest and softest places in a molecule based on the local hardness and local softness alone. How, then, should the local hardness and local softness be interpreted? Answering that question is the second goal of this paper. Our results suggest that that the local hardness and local softness are best understood as mathematical representations for the "local abundance" or "concentration" of the corresponding global property.

The concept of chemical hardness was originally proposed by Pearson to explain certain well-known trends in inorganic chemical reactivity. He proposed classifying reagents into two categories: a) hard, for reagents that are small, highly charged, and relatively unpolarizable, b) soft, for reagents that are large and polarizable.[11–14] The hard/soft acid/base (HSAB) principle-that hard acids prefer binding to hard bases and soft acids prefer binding to soft bases-coupled with information about acid/base strengths;[13–16] then sufficed to explain many experimentally observed reactivity patterns in inorganic[11,12] and organic[17] chemistry.

The theory of chemical hardness was transformed in 1983, when Parr and Pearson formulated a quantitative hardness scale based on the realization that the hardness measured the resistance of a molecule to changes in electronic structure. This led to the definition,[7,18]

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

Here, μ is the chemical potential;[4] the chemical potential is minus one times electronegativity and measures the "intrinsic strength" of a Lewis acid or base.[16] It is related to the energy levels of the frontier Kohn-Sham orbitals.[19–21]

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The global softness, S, is simply the multiplicative inverse of the global hardness,[8]

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

With these definitions it has been possible to motivate the qualitative correlations of chemical hardness with physical properties (molecular size,[22–24] polarizability,[22,24–26] etc.) and, more importantly, to provide mathematical justifications for the HSAB principle.[16,24,27,28] The formulation of the maximum hardness principle, the idea that high hardness is ordinary associated with chemical stability, was inconceivable before Parr and Pearson established a quantitative hardness scale.[29–35]

In the original work of Pearson,[11] he also proposed a "local" HSAB principle that describes the regioselectivity of ambident electrophiles and nucleophiles. Thus hard acids tend to bind to the hardest reactive site of an ambident base, while soft acids tend to bind to the softest reactive site. Extending the mathematical description of the HSAB principle to the local level requires a reactivity indicator for the relative hardness/softness of a molecule's different possible reactive sites. This motivated Parr, Yang, Ghosh, and Berkowitz to define local versions of the hardness and the softness. The local softness is defined by recalling that the electron density, $\rho(\vec{r})$ is the distribution function for the N electrons in a molecule. The "local" counterpart of the global softness indicator [Eq. (2)], is defined as the local response of the number of electrons to a change in chemical potential,[8]

$$s(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial \mu}\right)_{v(\vec{r})} \tag{3}$$

The local softness is related to the Fukui function, $f(\vec{r})$, using the chain rule,

$$s(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial \mu}\right)_{v(\vec{r})} = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{v(\vec{r})}\left(\frac{\partial N}{\partial \mu}\right)_{v(\vec{r})} = f(\vec{r})S \tag{4}$$

The Fukui function measures the propensity of a reagent to accept (or donate) electrons from (to) another chemical system.[5,6] Because the Fukui function is normalized to one, the local softness is normalized to the global softness value,

$$S = \int s(\vec{r})d\vec{r} \tag{5}$$

Although the electron density is a probability distribution function for the number of electrons, the local softness is not a probability distribution function for the global softness. For example, the local softness can be negative (because the Fukui function can be negative).[36–40] This suggests that there may be some problem with interpreting $s(\vec{r})$ as the "local representation" of the global softness.

The local hardness, $\eta(\vec{r})$, is similarly defined. In Equation (1), replacement of the number of electrons by the electron density gives:[9,10,18]

$$\eta(\vec{r}) = \left(\frac{\delta \mu}{\delta \rho(\vec{r})}\right)_{v(\vec{r})} \tag{6}$$

In analogy to the global quantities, $\eta(\vec{r})$ and $s(\vec{r})$ are also interconnected with the following relationship:

$$\int \eta(\vec{r})s(\vec{r})d\vec{r} = 1 \tag{7}$$

Notice that this relationship between local hardness and local softness is fundamentally different from the simple inverse relationship between the global hardness and the global softness [Eq. (2)]. In particular, $\eta(\vec{r})$ is not equal to $1/s(\vec{r})$. In addition, this definition of the local hardness [Eq. (6)], does not define a unique function but, instead, defines an (very large) equivalence class of functions.[41–47] The main problem is that, according to the Hohenberg–Kohn theorem,[48] the variation in the chemical potential can be determined completely from the variation in the electron density, even without the constraint of constant external potential.[41] If, as in Equation (6), one then imposes the constraint that $v(\vec{r})$ does not change, the possible variations of the electron density become very limited, and it is impossible to determine the general response of the chemical potential to an arbitrary change in the electron density from this limited set of variations. The result is an inherent arbitrariness in the definition of the local hardness: every function which will correctly predict the change in chemical potential associated with changes in density that do not change $v(\vec{r})$, but each of these functions give different (and typically incorrect) predictions when considering changes in the electron density that do change $v(\vec{r})$.[41] One obvious way to avoid this difficulty is to remove the constraint of fixed external potential:[33]

$$\eta(\vec{r}) = \frac{\delta \mu}{\delta \rho(\vec{r})} \tag{8}$$

Unfortunately, it seems very difficult to compute this form of the local hardness.[49]

It is most practical to compute the local hardness using the relationship between the local hardness and the hardness kernel, $\eta(\vec{r},\vec{r}')$,[10,18,50]

$$\eta(\vec{r}) = \int \eta(\vec{r},\vec{r}')g(\vec{r}')d\vec{r}' = \int \frac{\delta^2 F[\rho(\vec{r})]}{\delta\rho(\vec{r})\delta\rho(\vec{r}')}g(\vec{r}')d\vec{r}' \tag{9}$$

The hardness kernel is the second functional derivative of the universal Hohenberg–Kohn functional, $F[\rho(\vec{r})]$. In Equation (9), the inherent arbitrariness in the definition of the local hardness is reflected by the fact that, according to an identity derived by Ghosh, Harbola, Chattaraj, Cedillo, and Parr, $g(\vec{r})$ can be any normalized function.[33,41,42,51] Again, most of possible choices of $g(\vec{r})$ are not chemically interesting, and most of the work on the local hardness has chosen $g(\vec{r})$ to be either the shape function,[52–54] $g(\vec{r})=\rho(\vec{r})/N$,[9,10] or the Fukui function, $f(\vec{r})$.[41,55] In a very recent article[56] it has shown that for polyatomic systems the Fukui function is the best option to obtain reliable local hardness profile and we will apply this approximation for this work. Using the relationship between the Fukui function and the local softness, [Eqs. (4) and (7)] can be rewritten as a relationship between the local hardness and the Fukui function:

$$\eta = \int \eta(\vec{r}) f(\vec{r}) d\vec{r} \tag{10}$$

Notice that in these definitions, $\eta(\vec{r})$ can be negative and so it is not a distribution function for the global hardness. In very recent works, some of the present authors have been successfully applied Equations (9) and (10) to calculate the global and local hardnesses for atomic and polyatomic systems using different approximations for the Fukui function and hardness kernel.[56–60]

The aim of the present paper is to analyze the concepts of local hardness and softness in more detail. We have already seen that the relationship between local hardness and local softness [Eq. (7)], is not enough to define the local hardness uniquely; this is fundamentally different from the simple inverse relationship between the global hardness and the global softness [Eq. (2)]. We have also seen that, unlike the electron density, the local softness and local hardness are not probability distribution functions for the corresponding global quantities. This raises questions about the utility of $s(\vec{r})$ and $\eta(\vec{r})$ in the context of the local HSAB principle.

Finding an appropriate quantitative representation of the local HSAB principle has been, and continues to be, one of the largest areas of research in the DFT-based approach of chemical reactivity. Much of our current understanding of the issue can be attributed to Klopman, who was the first to note that soft–soft interactions tend to be covalent in nature and thus dictated by the shapes of the frontier orbitals.[61] The Fukui function is the DFT analogue of the frontier orbitals,[62] and so the preferred site for chemical reactions between soft compounds is hypothesized to be the site with the maximum Fukui function or, equivalently, the site with maximum local softness, $s(\vec{r})=Sf(\vec{r})$.[63–66] Gázquez and Méndez were the first to suggest a "local softness matching condition" (similar to the global HSAB rule), which would indicate that a molecule's most reactive site is the one that resembles most closely the local softness of the attacking reagent.[64] So the idea that the local softness should be largest in the "softest" places in a molecule is considered to be generally reliable, even though there are other factors associated with the softness of a reactive site (e.g., the size and polarizability of the electron cloud at the site) that are at best imperfectly captured by the value of the local softness.[24]

The question of how to identify the hard reactive sites is much less clear.[61,63–68] Li and Evans suggested that hard reactions tend to occur at the site with the smallest Fukui function.[65] This "minimum Fukui function rule" has been broadly applied,[69–71] but also criticized as overly simplistic.[67,72] Klopman asserts that hard–hard interactions are predominately ionic in nature, and so electrostatic effects dominate and frontier-orbital effects are relatively unimportant. The minimum Fukui function principle captures the irrelevance of the frontier orbitals but misses the fact that electrostatic interactions normally dominate hard–hard interactions.[67,68,72] In contrast to the well studied local softness, few studies of the local hardness are reported in the literature, mainly by our group using the local hardness as an indicator for charge concentration in studies on zeolite-catalyzed reactions,[73–75] noncovalent intermolecular interactions,[76–80] and local HSAB.[81] Then, one of the goals of this work is to see if the local hardness is able to locate the hardest reactive sites in a molecule.

To obtain complete and quantitative description of the local HSAB principle, one needs to combine a reactivity indicator appropriate for soft reactive sites (associated with frontier-orbital control) with a reactivity indicator appropriate for hard reactive sites (associated with electrostatic control), as suggested earlier by two of the present authors.[44] With an appropriate choice of and weight for the reactivity indicators, then one can describe the whole gamut of chemical reactivity, ranging from strong frontier-orbital control (for reactions between very soft reagents) to strong electrostatic control (for reactions between very hard reagents). One of the authors recently formulated a "general purpose reactivity indicator" of this type.[68,82,83] That study showed that for reactions that are in the strong electrostatic control regime, small values of the Fukui function are favourable; for reactions in the weak electrostatic control regime, large values of the Fukui function are favourable. In both cases, however, the reactivity preferences are ordinarily governed by electrostatic effects.

The purpose of mathematical definitions of a local hardness and local softness is to provide a quantitative representation of qualititative concepts. If the mathematical definitions are good ones, then they will agree with clear qualitative trends based on "chemical intuition." So our approach is to compute the local hardness and local softness for several families of molecules in which "trends" in the local hardness and local softness are well-known. The quantitative results can then be compared against the qualitative trends, and the quality of the proposed definitions can be assessed.

The next section of the paper will summarize our computational methods; we present and interpret our results in the Results settion. The Discussion section summarizes our findings and our perspective on the local hardness and local softness concepts.

Computational Details

All calculations were carried with 6-31+G(d) and 6-311++G(2d,2p) basis sets[84,85] at the B3LYP[86,87] level using the Gaussian03 package.[88] The calculations have been done within the restricted formalism except for open-shell systems, where the unrestricted approach has been used.

There are many different approaches to computing the global hardness. First of all, the Parr–Pearson formula[7] in terms of the vertical ionization potential and the vertical electron affinity,

$$\eta \cong I - A \tag{11}$$

which can be approximated using Koopmans' theorem,[89]

$$\eta \cong \varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}} \tag{12}$$

Here, $\varepsilon_{\mathrm{HOMO}}$ and $\varepsilon_{\mathrm{LUMO}}$ are the orbital energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), respectively. The global softness can be computed from the Equation (2).

In addition the global hardness can be also evaluated from Equations (10) and (9), but approximations for the universal Hohenberg–Kohn functional and the Fukui function are required to calculate the global and local hardness. As we have done in our previous article,[60] the hardness kernel is approximated by the second functional derivative of the Coulombic–Thomas–Fermi-$^1/_9$th Weizsäcker–Dirac–Wigner density functional. Since we are considering electrophilic attack on organic nucleophiles, the Fukui function appropriate for nucleophiles is the "Fukui function from below,"

$$\mathrm{f}(\vec{r}) \cong \mathrm{f}^-(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \cong \rho_{\mathrm{HOMO}}(\vec{r}) \; = \; |\phi_{\mathrm{HOMO}}(\vec{r})|^2 \tag{13}$$

For simplicity, we have chosen to approximate the Fukui function with the orbital density of the highest-occupied Kohn–Sham orbital (HOMO). This approximation is accurate whenever orbital relaxation effects can be ignored, and it seems that orbital relaxation is negligible almost all of the time.[62,90–93] (This approximation certainly seems to be very reliable for small organic molecules like the ones of interest in this paper.) One advantage of this approximation to the Fukui function is that it leads to simpler figures, without the qualitatively insignificant, but visually confusing, near-nuclear nodes associated with orbital relaxation.[39,40]

Then the local hardness is evaluated by integrating the product of $\rho_{\mathrm{HOMO}}(\vec{r})$ and the hardness kernel, as in Equation (9) and the global hardness is evaluated by integrating the product of $\rho_{\mathrm{HOMO}}(\vec{r})$ and the local hardness, as in Equation (10). As in our previous works,[58,60] the integrals of Equations (9) and (10) have been evaluated numerically using Becke's multicenter integration scheme,[94] as implemented in a program developed in our laboratory. In addition, the condensed atomic hardness can be obtained by integrating Equation (10) atomic domains,

$$\eta_{\mathrm{i}} = \int_{\Omega_{\mathrm{i}}} \eta(\vec{r})\mathrm{f}(\vec{r})\mathrm{d}\vec{r} \tag{14}$$

For instance, using the "fuzzy Voronoi polyhedra", which is the basis of our integration method, one obtains

$$\eta_{\mathrm{i}} = \int_{\Omega_{\mathrm{i}}} \mathrm{w}_{\mathrm{i}}(\vec{r})\eta(\vec{r})\mathrm{f}(\vec{r})\mathrm{d}\vec{r} \tag{15}$$

where $w_{\mathrm{i}}(\vec{r})$ is the "weight function" for the atomic integration; this function is one in the interior of the atomic Voronoi polyhedron and falls off smoothly to zero outside the atom. In a very similar way, one can obtain the condensed local softness using the formula proposed by Gilardoni et al.,[95]

$$s_{\mathrm{i}} = \int_{\Omega_{\mathrm{i}}} w_{\mathrm{i}}(\vec{r})s(\vec{r})\mathrm{d}\vec{r} \; = \; S\int_{\Omega_{\mathrm{i}}} w_i(\vec{r})\mathrm{f}(\vec{r})\mathrm{d}\vec{r} \tag{16}$$

Then, applying the frontier orbital approximation to the global softness and the Fukui function,

$$s_{\mathrm{i}} \cong \frac{1}{\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}} \int_{\Omega_{\mathrm{i}}} w_{\mathrm{i}}(\vec{r})\rho_{\mathrm{HOMO}}(\vec{r})\mathrm{d}\vec{r} \tag{17}$$

In addition, the global softness and condensed local softness can be evaluated using the finite difference approximation[96] and integrating over regions with different population analysis techniques.

$$s_{\mathrm{i}} \cong \frac{1}{I-A}(q_{i,N} - q_{i,N-1}) \tag{18}$$

where $q_{i,N}$ and $q_{i,N-1}$ are the charges on atom i with N and $N-1$ electrons, respectively. In this work we will present results for Mulliken,[97] Merz–Kollman (MK),[98] and natural population analysis (NPA).[99] The Mulliken scheme is known to be generally unreliable for large, diffuse, basis sets like the one used here. The Merz–Kollmann scheme is rather different from the other two methods because it is based on choosing charges to fit the electrostatic potential, not orbital analysis. Notice that the Equations (15) and (16) are examples of what Bultinck et al.[100] refer to as the "fragment of molecular response" approach to condensed reactivity indicators,[39] while the Equation (17) is an example of the "response of molecular fragment" approach.[96]

Results and Discussion

In Figures 1 and 2, we plot the local hardness, local softness, and Fukui function for a soft molecule (benzocyclobutadiene, $\eta_{\mathrm{exp}}(\mathrm{C_8H_6}) = 7.55$ eV[101,102]) and a hard molecule (water, $\eta_{\mathrm{exp}}(\mathrm{H_2O}) = 19$ eV[103]). Benzocyclobutadiene can be seen as fusion of an aromatic benzene ring and an antiaromatic cyclobutadiene ring. Using the well-known relationship between aromaticity and hardness, the six-membered ring should be harder than the four-membered ring.[104,105] However, Figure 1 shows that the largest values of the local hardness are located on the four-membered ring. Even more surprisingly, the largest values of the local softness are also attained on the four-membered ring. The hardest and softest rings are the same!

Lest the reader suppose that benzocyclobutadiene is exceptional, we provide analogous plots for a very hard molecule (water) in Figure 2. In this case, the local hardness successfully locates the hard reactive site (the oxygen atom).

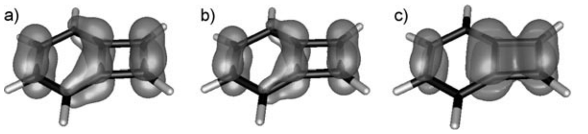

Figure 1. Three-dimensional contour plots of a) $\mathrm{f}(\vec{r}) \cong \rho_{\mathrm{HOMO}}(\vec{r})$ (0.003 a.u.), b) $s(\vec{r}) = \rho_{\mathrm{HOMO}}(\vec{r})/\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}$ (0.003 a.u.), and c) $\eta(\vec{r})[\rho_{\mathrm{HOMO}}(\vec{r}')]$ (0.3 a.u.) for the benzocyclobutadiene molecule evaluated at B3LYP/6-31+G(d,p). $\eta(\vec{r})[\rho_{\mathrm{HOMO}}(\vec{r}')]$ has been evaluated with Eq. (9), where $g(\vec{r})$ and $\eta(\vec{r},\vec{r}')$ have been approximated using the density of the HOMO and the second order derivative of the Coulombic–Thomas–Fermi–$^1/_9$th Weizsäcker–Dirac–Wigner functional with respect to the density, respectively.

However, the local hardness and local softness functions are almost entirely located on the oxygen atom. Again, the hardest reactive site and the softest reactive site are the same.

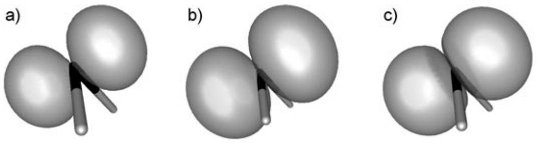

Figure 2. Three-dimensional contour plots of a) $f(\vec{r})$ (0.05 a.u.), b) $s(\vec{r})$ (0.05 a.u.), and c) $\eta(\vec{r})[\rho_{\mathrm{HOMO}}(\vec{r}')]$ (0.8 a.u.) for the water molecule evaluated at B3LYP/6-311++G(2d,2p) level. $\eta(\vec{r})[\rho_{\mathrm{HOMO}}(\vec{r}')]$ has been evaluated with Eq. (9), where $g(\vec{r})$ and $\eta(\vec{r},\vec{r}')$ have been approximated using the density of the HOMO and the second order derivative of the Coulombic–Thomas–Fermi–$^1/_9$th Weizsäcker–Dirac–Wigner functional with respect to the density, respectively.

How can the local hardness and local softness be large in the same places? First, recall that the Fukui function and the local softness are strictly proportional to one another, so they contain the same information about relative site reactivity. For the Coulombic–Thomas–Fermi–$^1/_9$th Weizsäcker–Dirac–Wigner hardness kernel used here, previous studies have shown that the Coulomb term is usually dominant,[59,106–109] although the contribution from the kinetic energy term is occasionally comparable.[57,58] If one considers only the dominant term, the Coulomb energy, then it follows from Equations (9) and (10) that the local hardness is equal to the Fukui potential,

$$\eta(\vec{r}) \cong \int \frac{f(\vec{r}')}{|\vec{r}-\vec{r}'|} d\vec{r}' = v_f(\vec{r}) \tag{19}$$

and the global hardness is equal to the Fukui electrostatic repulsion,

$$\eta \cong \int\int \frac{f(\vec{r})f(\vec{r}')}{|\vec{r}-\vec{r}'|} d\vec{r} d\vec{r}' = J_f \tag{20}$$

As first established by Berkowitz,[63] these expressions play a key role in the density-functional theory of frontier-orbital controlled reactions. It is unsurprising, then, that the Coulombic contribution to the local hardness is closely related to the Fukui function and, through Equation (4), the local softness. We expect, then, that the profiles of $s(\vec{r})$ and $\eta(\vec{r})$ will be "similar." In addition, a more severe approximation to the hardness kernel can be applied using the Dirac delta function, $\eta(\vec{r},\vec{r}') \cong \delta(\vec{r}-\vec{r}')$, giving a direct link between the Fukui function and local and global hardnesses

$$\eta(\vec{r}) = f(\vec{r}) \tag{21}$$

$$\eta = \int f^2(\vec{r}) d\vec{r} \tag{22}$$

It is worth noting that that the crude approximation of Equation (22) has been successfully applied to a large set of acid and base Lewis systems.[109,110] Once again, the local hardness and local softness are predicted to be similar. Therefore the similarity between the local softness, Fukui function, and the local hardness that revealed by Figures 1 and 2 is not surprising.

In Table 1 and 2, the global hardness, local hardness, and local softness values are computed for four families of molecules: OR_2, SR_2, NR_3, and PR_3, with R denoting hydrogen atoms and/or methyl groups. The trends in these molecules are well known:[96,111,112] the central atom becomes softer when hydrogen atoms are replaced by methyl groups; for example, the oxygen atom in water is harder than the oxygen atom in methanol. Similarly, replacing oxygen with sulfur or nitrogen with phosphorous results in a softer nucleophilic reactive site; for example, the oxygen atom in methanol is harder than the sulfur atom in methyl mercaptan.

In Table 1 we see that all of three definitions recover the correct trends for the global hardness: the global hardness decreases as hydrogen atoms are replaced by methyl groups and the global hardness decreases when the oxygen atom is replaced with sulfur. Although the different computational approaches all give the same trends, the values they give for the global hardness are rather different, with the local-hardness-based formula, Equation (10), giving the largest values and the frontier-orbital formula, Equation (12), giving the smallest values.

Table 1. Global softness, S, global hardness, η, condensed local softness, s_X, and condensed atomic hardness, η_X, of oxygen and sulfur atoms for six selected molecules evaluated at B3LYP/6-311++G(2d,2p) level. All units are eV.

	S[a]	S[b]	η[a]	η[b]	$\eta[\rho_{\mathrm{HOMO}}(\vec{r})]$[c]	s_O or s_N[d]			s_O or s_S[e]	η_0 or η_N[f]
						Mulliken	MK	NPA		
H_2O	0.122	0.074	8.187	13.492	28.525	0.055	0.056	0.065	0.111	27.265
CH_3OH	0.135	0.086	7.390	11.568	21.743	0.043	0.052	0.053	0.095	18.650
CH_3OCH_3	0.143	0.094	6.994	10.621	19.661	0.036	0.041	0.052	0.090	16.355
H_2S	0.148	0.091	6.751	11.006	15.228	0.067	0.078	0.084	0.140	14.724
CH_3SH	0.164	0.100	6.090	9.976	14.329	0.065	0.078	0.080	0.144	13.415
CH_3SCH_3	0.422	0.145	2.370	6.889	12.144	0.080	0.089	0.084	0.280	8.817

[a] Calculated with the frontier orbital approximation, Eq. (11). [b] Calculated with the Parr–Pearson approximation, Eq. (12). [c] Global hardness obtained from Eq. (10). For more details see ref. [60]. [d] Condensed local softness evaluated from Eq. (18). [e] Condensed local softness obtained from Eq. (17). [f] Condensed atomic hardness obtained from the numerical integration of the Eq. (16). For more details see ref. [60].

Table 2. Global softness, S, global hardness, η, condensed local softness, s_X, and condensed atomic hardness, η_X, of nitrogen and phosphorus atoms for eight selected molecules evaluated at B3LYP/6–311++G(2d,2p) level. All units are eV.

	$S^{[a]}$	$S^{[b]}$	$\eta^{[a]}$	$\eta^{[b]}$	$\eta[\rho_{HOMO}(\vec{r})]^{[c]}$	s_S or s_P[d]			s_N or s_p[e]	η_S or η_P[f]
						Mulliken	MK	NPA		
NH_3	0.143	0.086	7.016	11.666	22.737	0.056	0.087	0.071	0.120	20.966
NH_2CH_3	0.158	0.097	6.341	10.300	19.500	0.044	0.095	0.062	0.113	16.795
$NH(CH_3)_2$	0.168	0.105	5.944	9.487	17.997	0.032	0.090	0.060	0.110	15.019
$N(CH_3)_3$	0.176	0.112	5.695	8.951	16.983	0.020	0.068	0.061	0.107	13.870
PH_3	0.137	0.089	7.311	11.227	13.634	0.049	0.085	0.065	0.111	12.063
PH_2CH_3	0.153	0.098	6.533	10.231	12.938	0.046	0.100	0.063	0.118	11.122
$PH(CH_3)_2$	0.162	0.102	6.173	9.813	12.530	0.035	0.099	0.061	0.120	10.626
$P(CH_3)_3$	0.169	0.107	5.926	9.372	12.234	0.005	0.103	0.064	0.122	10.291

[a] Calculated with the frontier orbital approximation, Eq. (11). [b] Calculated with the Parr–Pearson approximation, Eq. (12). [c] Global hardness obtained from Eq. (10). For more details see ref. [60]. [d] Condensed local softness evaluated from Eq. (18). [e] Condensed local softness obtained from Eq. (17). [f] Condensed atomic hardness obtained from the numerical integration of the Eq. (16). For more details see ref. [60].

The results in Table 2 are less clear-cut. Within the families, NR_3 and PR_3, the correct trends are obtained: replacing H with CH_3 reduces the global hardness. Between the families, the results are less favourable. All three methods for computing the hardness correctly predict that PH_3 is softer than NH_3. However, the frontier molecular orbital formula incorrectly predicts that PH_2CH_3 is harder than NH_2CH_3, and both the frontier-molecular orbitals formulae and the Parr–Pearson approximation incorrectly predict that $PH(CH_3)_2$ and P $(CH_3)_3$ are harder than their nitrogen analogues. Only the local-hardness-based formula, Equation (10), gives the correct result in all cases.

Tables 1 and 2 also contain the values of the condensed local softness, Equations (17) and (18), and the condensed atomic hardness, Equation (15), on the nucleophilic atoms (O, S, N, and P). Condensed reactivity indicators are used to provide a numerical—as opposed to a pictorial—representation for local reactivity indicators.[39,96,113,114] Then, we can examine whether these definitions of local hardness and local softness are likely to suffice for the purposes of the local HSAB principle. The condensed atomic hardness, Equation (15), seems to perform very well. It successfully predicts that the hardness of the nucleophilic site in OR_2, SR_2, NR_3, and PR_3 families decreases when a methyl group replaces a hydrogen atom. It also correctly predicts that replacing a first-row heteroatom (N,O) with its second-row analogue (P,S) decreases the hardness of the nucleophilic site.

Like the condensed atomic hardness, the condensed local softness almost always reproduces our intuition about heteroatom substitution. The only exceptions are a) every method for computing the condensed local softness erroneously predicts that the nitrogen atom in ammonia is softer than the phosphorous atom in phosphine and b) the Mulliken population analysis predicts that the nitrogen atom in trimethylamine is softer than the phosphorous atom in trimethylphosphine.

Within families of molecules, the condensed local softness does not recover the expected chemical trends nearly as well. The effect on the condensed local softness of replacing hydrogen with methyl groups is generally, but not always, monotonic. For example, using the Merz–Kollman method, the softness of the nitrogen atom in ammonia increases when one performs the first methyl replacement (to form NH_2CH_3), but decreases when a second methyl group is added. The condensed local softness approach of Equation (17) produces monotonic results. The overall trends of all four methods of computing the condensed local softness are broadly similar. The sulfur and phosphorous series give results in agreement with chemical intuition: replacing H with CH_3 increases the softness of the nucleophilic site. The oxygen and nitrogen series give results that are exactly opposed to chemical intuition: replacing H with CH_3 decreases the softness of the nucleophilic site. This suggests that the local softness may not be a very reliable reactivity indicator for hard molecules (like those in the OR_2 and NR_3 families), though it seems to be generally satisfactory for softer molecules.

The local hardness values agree with chemical intuition even for the hard molecules, which leads to another paradox: in the oxygen and nitrogen series, replacing H with CH_3 decreases the softness of the nucleophilic site and decreases the hardness of the nucleophilic site. This counterintuitive observation reinforces the fact that the local softness and local hardness are not “inverse quantities” in the same sense that the global softness and the global hardness are.

The basic strategy of this paper is in accord what Parr and his research group have called the “noumenistic” nature of chemical concepts.[115] Chemical concepts like the “hardness” and the “electronegativity” are, by their nature, impossible to define precisely and uniquely. Instead, one must take what a mathematician would call an “axiomatic” approach: one defines what properties one wants a concept to have, and then seeks to design a mathematical object that reproduces those properties.[115] Such a mathematical representation represents one (of many) possible reifications of that abstract chemical concept.[24]

In this paper we have examined different nucleophiles where chemical intuition provides very clear expectations for what the hard and soft reactive sites of a molecule should be. We then computed the local hardness and local softness as they are commonly defined, and examined whether the usual definitions agreed with our chemical requirements. Sometimes they did; often they did not. This leads to the inescapable conclusion that the “mathematical” local softness and local hardness [cf. Eqs. (3) and (9)] are not adequate reifications for the "chemical" concepts of local hardness and local softness.

How should we then interpret the "mathematical" definitions for the local softness and the local hardness? We would argue for a minimalist interpretation wherein the local softness and the local hardness represent pointwise measures of the "local abundance" of the corresponding global quantity. In this interpretation, the fact that the local softness value at the oxygen atom in water is large does not mean that the oxygen atom in water is soft in a "chemical" sense; it just means that the oxygen atom in water makes a large contribution to the global softness of the molecule. Similarly, the results in Table 1 ($s_0(H_2O) = 0.111$ eV and $s_0(CH_3OH) = 0.095$ eV) do not imply that the oxygen atom in water is actually softer than the oxygen atom in methanol in a chemical sense. Rather, one merely states that the oxygen atom in water contributes 91% ($=0.111/0.122 \times 100\%$) to the global softness of the molecule while the oxygen atom in methanol contributes just 70% ($=0.095/0.135 \times 100\%$) to the global softness of the molecule.

The corresponding "local abundance function" for the local hardness is not the local hardness itself, but the hardness density, $f(\vec{r})\eta(\vec{r})$[44] [see Eq. (10)]. But because the local hardness typically resembles the Fukui function, similar statements about the local hardness are justifiable. So we can say—with only a little imprecision—that the fact that the largest values of the local hardness in benzocyclobutadiene occur on the four-membered ring does not mean that the four-membered ring is harder in a chemical sense; it only means that the contribution of the four-membered ring to the global hardness is larger than the contribution of the six-membered ring.

It is disappointing, of course, that the popular "mathematical" representations of local softness and local hardness often do not correspond to the tried-and-true chemical analogues. This is even more disappointing if one considers that the same considerations almost certainly apply to the local representations of other global reactivity indicators like, for example, the local electrophilicity.[116–118]

Then, we can conclude that $s(\vec{r})$ and $\eta(\vec{r})$ contain the same potential "information" and they can be used to compare site reactivity when the molecules have similar values of the global property (global hardness or softness). In the traditional context $s(\vec{r})$ and $\eta(\vec{r})$ can be only applied to soft and hard systems, respectively, where the "local abundance" interpretation of the local softness and hardness is similar to the "chemical" interpretation. However in this new framework, these indices become more general, because they can be applied both to hard and soft systems. In a soft system $s(\vec{r})$ and $\eta(\vec{r})$ *both* describe the soft site of the molecule, while in a hard system $s(\vec{r})$ and $\eta(\vec{r})$ *both* describe the hard site of the molecule. The difference is that the integration of the former will result in the global softness, while the integration of $f(\vec{r})\eta(\vec{r})$ will result in the global hardness.

Conclusion

In summary, it seems that the only universally acceptable interpretation for the local softness and the local hardness is that these functions are pointwise measures of the "local abundance" of the corresponding global quantities. This "mathematical" interpretation sometimes, but not always, gives results that agree with "chemical" intuition about the relative softness and hardness of reactive sites. Further work is certainly warranted. In particular, the conditions under which the "mathematical" and the "chemical" formulations of the local softness and local hardness coincide need to be precisely delineated. The extent to which the arguments in this paper extend to other local reactivity indicators, like the local electrophilicity, needs to be explored.[116–118] Finally, and most ambitiously, the community of density-functional theorists should examine whether there may be alternative mathematical definitions for the local softness and the local hardness that more faithfully model the eponymous chemical concepts.

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