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$$\eta_{\substack{\text{information}\\ \text{theory}}}\left(\mathbf{r}\right)=\left(\frac{1}{f\left(\mathbf{r}\right)}\right)\left(\arg\underbrace{\min}_{\left\{p(\mathbf{r})\middle|\eta=\int p(\mathbf{r})d\mathbf{r}\right\}}\int p\left(\mathbf{r}\right)\ln\left(\frac{p\left(\mathbf{r}\right)}{p_0\left(\mathbf{r}\right)}\right)d\mathbf{r}\right)$$

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An Information-Theoretic Resolution of the Ambiguity in the Local Hardness

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The ambiguity of the local hardness is resolved by using information theory to select definitions of the local hardness that are as close as possible to a well-defined approximate formula for the local hardness. A condensed local hardness is derived by using the atomic hardnesses as a reference distribution; a pointwise local hardness is derived by using the uniform electron gas as a reference distribution. This information-theoretic condensed local hardness is tested by examining electrophilic attack on some substituted pyridines.

I. Introduction

While there is an abundance of experimental evidence for and theoretical insight into the global hard/soft acid/base (HSAB) principle,[1-10] the local HSAB principle is on much shakier ground, both experimentally and theoretically.[9, 11-25] On the one hand, the reactivity of nucleophiles and electrophiles with multiple reactive sites is certainly governed by reactivity effects that go beyond the nucleophilicity/electrophilicity of the reactive sites, and some of these reactivity trends may plausibly be classified as manifestations of a local HSAB principle. On the other hand, finding an appropriate mathematical definition for the local hardness and softness—that is, the hardness (softness) of an atom in a molecule or of an active site—is very challenging,[20, 21, 26-43] and certainly much more challenging, and much more controversial, than the (nevertheless still debated) corresponding definitions for the global hardness and softness.[9, 21, 44-53] If a suitable definition could be found, however, then chemical predictions could be made by noting that hard reactive sites of an

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electrophile would prefer to bind to hard reactive sites of a nucleophile, while soft reactive sites of an electrophile would prefer to bind to soft reactive sites of a nucleophile.

In this paper, we will approach the problem of defining the local hardness using the density-functional-theory (DFT) approach to chemical reactivity, an approach often called conceptual DFT.[54-60] In conceptual DFT, the global hardness is defined as[44]

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

where E is the electronic energy, N is the number of electrons, and $v(\mathbf{r})$ is the external (i.e., nuclear-electron) potential. As a working approximation, one usually invokes a quadratic model for the energy, $E = a + bN + cN^2$, and computes the hardness as the difference of the system's ionization potential and its electron affinity,[44]

$$\eta = I - A \tag{2}$$

The quadratic model is not the only one that is acceptable,[61-63] but it can be heuristically justified.[32] (In particular, the linear model (wherein the energy is a piecewise linear function interpolating the values of the energy for integer numbers of electrons) is more rigorous, and is unambiguously correct for exact calculations of isolated chemical systems.[64-68])

To resolve the hardness at a pointwise level, we first note that the chemical hardness can be rewritten as

$$\eta = \left(\frac{\partial \mu}{\partial N} \right)_{v(\mathbf{r})}, \tag{3}$$

where $\mu = \left(\partial E / \partial N \right)_{v(\mathbf{r})}$ is the electronic chemical potential. The local hardness is then defined as the change in chemical potential induced by a change in the number of electrons in the volume element centered at $\mathbf{r}$, $\delta\rho(\mathbf{r})d\mathbf{r}$, is then[28, 29]

$$\eta(\mathbf{r}) = \left(\frac{\delta \mu}{\delta \rho(\mathbf{r})} \right)_{v(\mathbf{r})}. \tag{4}$$

The constrained functional derivative in Eq. (4) is highly ambiguous, as can be seen from the chain rule,

$$\left(\frac{\partial \mu}{\partial N}\right)_{v(\mathbf{r})} = \int \left(\frac{\delta \mu}{\delta \rho(\mathbf{r})}\right)_{v(\mathbf{r})} \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_{v(\mathbf{r})} d\mathbf{r}$$
$$\eta = \int \eta(\mathbf{r}) f(\mathbf{r}) d\mathbf{r} \tag{5}$$

where the Fukui function is defined as $f(\mathbf{r}) = \left(\partial \rho(\mathbf{r}) / \partial N\right)_{v(\mathbf{r})}$.[69-72] *Any function* $\eta(\mathbf{r})$*, that satisfies Eq. (5) is an acceptable definition of the local hardness.*[32] Eq. (5) is the equation for a hyperplane, so $\eta(\mathbf{r})$ is any element in the space of potential-like functions that has codimension one. Moreover, the space of potential-like functions (ergo the space of acceptable choices for $\eta(\mathbf{r})$) strictly includes $\mathbb{L}^{\infty}(\mathbb{R}^3)$, and therefore has no countable basis set.[32, 56, 73, 74]

There are many choices for the local hardness in the literature that are consistent with Eq. (5). One, often called the frontier local hardness,[37, 38] is simply to choose $\eta_f(\mathbf{r}) = \eta$; this choice is mathematically elegant but useless for the purposes of the local HSAB principle, since it predicts that every location in a molecule has the same reactivity. (A skeptic may invoke this definition to deny the existence of the local HSAB principle.) Another choice, call the unconstrained local hardness,[30] $\eta_u(\mathbf{r}) = \delta\mu / \delta\rho(\mathbf{r})$ is mathematically defined but, at least for finite systems like atoms and molecules, it is infinitely ill-conditioned numerically, and therefore computationally impracticable (but see ref. [33]).[40, 75] Our ambition is to select a local hardness measure using information theory.[76, 77] Information theory is often used to select, among many possible distributions, the "most unbiased" choice, given the constraints that a distribution must satisfy. In the case of the local hardness, the constraint is Eq. (5).

The role of information-theory in this treatment can be understood by considering the analogous way that information theory is used to resolve the ambiguity in the definition of an atom in a molecule (AIM).[45, 78, 79] In AIM, the constraint is that the sum of AIM densities must equal the total density. Just as the definition of an AIM is inherently ambiguous, the concept of local hardness is inherently ambiguous; there are therefore many ways to define AIMs[78, 80-84] and local hardness indicators,[32] and information theory is only one possible approach. There are even several different approaches to AIM based on information theory.[45, 78, 79, 85-87] Similarly, while we are choosing to use information theory as a tool to resolve the ambiguity in the local hardness, neither the use of information theory, nor the particular information-theoretic approach we take, is mandated by the mathematical structure or chemical context of the local hardness concept.

In section II we will derive a pointwise local hardness based on the idea that the local hardness of an atom should maximally resemble the local hardness of the free electron gas. In section III we will derive a condensed local hardness, which is tested for pyridines in section IV.

II. Information-Theoretic Pointwise Local Hardness

Information theory is a method for finding the least-biased probability distribution function, subject to some constraints.[76] In practice, the framework can be slightly generalized, allowing one to find the best choice of nonnegative, normalizable function.[88] In light of (5), we select $p(\mathbf{r}) = \eta(\mathbf{r}) f(\mathbf{r})$ as our function. Since this function is assumed to be nonnegative, at any location in space where the Fukui function is negative,[89-95] the local hardness defined in this approach will be nonpositive. Information theory then guides us to a suitable definition for the local hardness, namely,

$$\underbrace{\min}_{\left\{p(\mathbf{r}) \middle| \eta = \int p(\mathbf{r}) d\mathbf{r}\right\}} \int p(\mathbf{r}) \ln\left(\frac{p(\mathbf{r})}{p_0(\mathbf{r})}\right) d\mathbf{r} \quad . \tag{6}$$

The Lagrangian for this optimization is

$$\Lambda[p;\lambda] = \int p(\mathbf{r}) \ln\left(\frac{p(\mathbf{r})}{p_0(\mathbf{r})}\right) d\mathbf{r} - \lambda\left(\int p(\mathbf{r}) d\mathbf{r} - \eta\right) \tag{7}$$

and so the solution is,

$$p(\mathbf{r}) = \frac{\eta}{\int p_0(\mathbf{r}) d\mathbf{r}} p_0(\mathbf{r}). \tag{8}$$

Rearranging, one obtains

$$\begin{aligned} \eta(\mathbf{r}) &= \frac{\eta}{f(\mathbf{r}) \int p_0(\mathbf{r}) d\mathbf{r}} p_0(\mathbf{r}) \\ &= \frac{p_0(\mathbf{r})}{s(\mathbf{r}) \int p_0(\mathbf{r}) d\mathbf{r}} \end{aligned} \tag{9}$$

where $s(\mathbf{r}) = f(\mathbf{r})/\eta = \left(\partial\rho(\mathbf{r})/\partial\mu\right)_{v(\mathbf{r})}$ is the local softness. If $p_0(\mathbf{r})$ is based on an acceptable definition for the local hardness (e.g., $p_0(\mathbf{r}) = \eta f(\mathbf{r})$), then the same local hardness will be recovered. However, if $p_0(\mathbf{r})$ is based on an approximate model for the local hardness, then the resulting local hardness will be chosen so that $\eta(\mathbf{r}) f(\mathbf{r})$ in the true system is as close as possible to $\eta(\mathbf{r}) f(\mathbf{r})$ in the model.

How should we choose $p_0(\mathbf{r})$? Notice that because $p_0(\mathbf{r})$ is divided by its integral, the normalization of $p_0(\mathbf{r})$ does not matter—we need only determine $p_0(\mathbf{r})$ to within a constant of proportionality. The simplest choice is to choose $p_0(\mathbf{r})$ for the noninteracting uniform electron gas. In that case, the Fukui function is a constant (specifically, a generalized function equal to zero everywhere, but integrating to one) and the unconstrained local hardness is

$$\frac{\delta\mu}{\delta\rho} = \frac{\delta\varepsilon_F}{\delta\rho} = \frac{\delta\left(\tfrac{1}{2}\left(3\pi^2\right)^{2/3}\rho^{2/3}\right)}{\delta\rho} = \frac{\left(3\pi^2\right)^{2/3}}{3}\rho^{-1/3} \qquad (10)$$

The resulting

$$p_0(\mathbf{r}) \propto \rho^{-1/3}(\mathbf{r}) \qquad (11)$$

diverges exponentially in the asymptotic tail of an atom or molecule. The resulting expression for the local hardness is an indeterminant form, and one can merely say,

$$\eta^{\text{UEG-based}}(\mathbf{r}) \propto \frac{1}{f(\mathbf{r})\rho^{1/3}(\mathbf{r})}. \qquad (12)$$

The exponential divergence of the local hardness is arguably correct, at least for a model based on the unconstrained local hardness, but it is not very useful.[33]

One could try to refine this model by using expressions from a model for the inhomogeneous electron gas, e.g., the Airy gas or the Mathieu gas.[96-99] Those models could be used to obtain gradient-corrected functionals for the Fermi level, $\varepsilon_F\left(\rho,\nabla\rho,\nabla^2\rho,\ldots\right)$, which could then be used to derive more complicated models for the local hardness. The resulting models would be much more complicated, but because one expects that the uniform-electron-gas term persists (but augmented by some gradient corrections), it seems unlikely that these approaches would remove the exponential divergence in Eq. (12).

Almost any model for the reference function, $p_0(\mathbf{r})$, is acceptable. Using the (nearly) uniform electron gas as a reference seems advisable because the appropriate definition for the local hardness for this system is relatively unambiguous. We remain hopeful, however, that by finding a different reference function, the local hardness definition in Eq. (9) could be made more useful.

III. Information-Theoretic Condensed Local Hardness

It is more natural for many chemists to think in terms of the chemical reactivity of an atom or functional group in a molecule, rather than in the chemical reactivity of a specific position in space. This picture is obtained when one computes the atom-condensed reactivity indicators in the DFT framework.[91, 100] The pseudo-probability distribution function for the local hardness is then,

$$p_A = \eta_A f_A, \qquad (13)$$

where η_A and f_A are the condensed local hardness and condensed Fukui function[100] of the atom (or functional group) *A*. The defining property of the condensed local hardness is (compare Eq. (5))

$$\eta = \sum_{A=1}^{N_{\text{atoms}}} \eta_A f_A = \sum_{A=1}^{N_{\text{atoms}}} p_A \qquad (14)$$

Treating Eq. (13) as a discrete probability distribution one has, in direct analogy to Eq. (6),

$$\underbrace{\min}_{\left\{ \{p_A\} \middle| \eta = \sum_{A=1}^{N_{\text{atoms}}} p_A \right\}} \sum_{A=1}^{N_{\text{atoms}}} p_A \ln\left(\frac{p_A}{p_A^0}\right) \qquad (15)$$

with Lagrangian

$$\Lambda\left(\{p_A\},\lambda\right) = \sum_{A=1}^{N_{\text{atoms}}} p_A \ln\left(\frac{p_A}{p_A^0}\right) - \lambda\left(\sum_{A=1}^{N_{\text{atoms}}} p_A - \eta\right). \qquad (16)$$

The minimum occurs when

$$0 = \frac{\partial \Lambda}{\partial p_A} = \ln\left(\frac{p_A}{p_A^0}\right) + 1 - \lambda \qquad (17)$$

and so at the solution, the ratio of the pseudo-distribution functions to the prior distribution function is the same for all atoms,

$$\frac{p_A}{p_A^0} = \frac{p_B}{p_B^0} \qquad (18)$$

Rewriting this as

$$\frac{p_A}{p_A^0} p_B^0 = p_B, \qquad (19)$$

summing over *B*,

$$\frac{p_A}{p_A^0}\sum_{B=1}^{N_{\text{atoms}}} p_B^0 = \sum_{B=1}^{N_{\text{atoms}}} p_B = \eta, \tag{20}$$

and rearranging gives,

$$p_A = p_A^0 \frac{\eta}{\sum_{B=1}^{N_{\text{atoms}}} p_B^0}. \tag{21}$$

The second equality in Eq. (20) follows from the defining relation of the condensed local hardness, Eq. (14). The condensed local hardness is then

$$\eta_A = \frac{p_A^0}{f_A}\frac{\eta}{\sum_{B=1}^{N_{\text{atoms}}} p_B^0} \tag{22}$$

or, using the definition of the condensed local softness, $s_A = f_A / \eta$,[26]

$$\eta_A = \frac{1}{s_A}\frac{p_A^0}{\left(\sum_{B=1}^{N_{\text{atoms}}} p_B^0\right)}. \tag{23}$$

How should one choose p_A^0? The simplest choice is to choose the value of p_A for an isolated atom. For an isolated atom, the normalization condition on the Fukui function implies that the condensed Fukui function is exactly one, and Eq. (13) therefore implies that p_A^0 is the hardness of the isolated atom, $p_A^0 = \eta_A^0$. One then has,

$$\eta_A = \frac{1}{s_A}\frac{\eta_A^0}{\left(\sum_{B=1}^{N_{\text{atoms}}} \eta_B^0\right)} = \frac{\eta}{f_A}\frac{\eta_A^0}{\left(\sum_{B=1}^{N_{\text{atoms}}} \eta_B^0\right)} \tag{24}$$

It is not coincidental that Eq. (24) has the same structure as the formulas for the atomic populations in Hirshfeld-like population analysis.[78, 84, 101]

Owing to the derivative discontinuity of the energy and its derivatives at integer numbers of electrons,[64, 65, 67, 68] Eq. (24) can be replaced by three separate local hardnesses,

$$\eta_A^{\pm,0} = \frac{1}{s_A^{\pm,0}} \frac{\eta_A^0}{\left(\sum_{B=1}^{N_{\text{atoms}}} \eta_B^0\right)} = \frac{\eta}{f_A^{\pm,0}} \frac{\eta_A^0}{\left(\sum_{B=1}^{N_{\text{atoms}}} \eta_B^0\right)}. \tag{25}$$

These are appropriate for nucleophilic attack, η_A^+, electrophilic attack, η_A^-, and radical attack, η_A^0, respectively.

The local hardness is high when (a) the reference atom is hard and (b) when the condensed Fukui function is small (but not negative) on the reactive site. Notice that the oft-denigrated notion[18, 102] that hard reagents react where the Fukui function is minimal recurs in this context.[103] Said differently, the local hardness is big when the local softness is small, but this effect is increased/decreased when the reference-hardness of the atom/functional group is large/small.

One can use the condensed local hardnesses in Eq. (24) to define a new reference for the pointwise local hardness by replacing the condensed Fukui function in Eq. (24) with the pointwise Fukui function,

$$p_0(\mathbf{r}) = \left(\sum_{A=1}^{N_{\text{atoms}}} \eta_A \frac{\eta}{f_A(\mathbf{r})} \frac{\eta_A^0}{\sum_{B=1}^{N_{\text{atoms}}} \eta_B^0} \right) f(\mathbf{r}) \tag{26}$$

Unfortunately this distribution is only integrable if all of the atomic Fukui functions decay asymptotically slower than the molecular Fukui function, which occurs only if the chemical potential of the molecule is greater that the chemical potential of all of its composing atoms[72, 104] (in contradiction to the chemical potential equalization postulate[61, 105-108]). So Eq. (26) suffers from the same sort of ill-conditioning that we observed when the reference distribution was taken from the uniform electron gas.

IV. Numerical Tests

To test this new approach to the local hardness we examined several weakly-basic substituted pyridines. Using the Gaussian program,[109] we optimized the geometry of the molecules using the B3LYP functional[110-112] and the 6-311++G(d,p) basis set.[113-115] To facilitate finding symmetry-broken solutions (especially for charged pyridines) we performed unrestricted calculations and did not allow spatial symmetry to be used in any of our calculations. The cations (N–1 electron systems) were then computed at the geometry of the neutral pyridines. Condensed Fukui functions[91, 100, 116, 117] were computed as differences of atomic charges from natural population analysis (NPA)[118] and CHELPG.[119] To perform the CHELPG analysis, the radius of the Br atom was set to be 1.85 Angstroms. In CHELPG, we added the charges of Hydrogen atoms to those of the nearest non-Hydrogen atom in order to accurately represent the total charge on a specific molecular site; for NPA this combination does not seem to be helpful or necessary. We did not consider Mulliken population analysis[120-123] because it is unreliable for this large and diffuse basis set.[124]

The way that local properties[125-128] and condensed reactivity indicators are computed is mathematically ambiguous,[129] but for the purposes of this paper we used the computationally facile response-of-molecular-fragment approach,[129] which allows the Fukui functions from above (f_A^+, for nucleophilic attack), below (f_A^-, for electrophilic attack), and their average (f_A^0, for radical attack) to be computed from the atomic charges of a molecule. Specifically, one has[100]

$$\begin{aligned} f_A^+ &= q_A - q_A^- \\ f_A^- &= q_A^+ - q_A \\ f_A^0 &= \tfrac{1}{2}\left(q_A^+ - q_A^-\right) = \tfrac{1}{2}\left(f_A^+ + f_A^-\right) \end{aligned} \tag{27}$$

Consistent with the constraint of constant external potential, the N-1 and N+1 electron states are computed at the optimal geometry of the N-electron system. For systems where the N-electron state, the N-1 electron state, and the N+1 electron state are nondegenerate,[130] the condensed Fukui function, like the Fukui function itself, must be normalized to one,

$$1 = \int f(\mathbf{r})\, d\mathbf{r} = \sum_{A=1}^{N_{\text{atoms}}} f_A . \tag{28}$$

The molecular hardness was computed from the ionization potential and electron affinity of the molecule using Eq. (2). The hardnesses of the neutral reference atoms were taken from ref. [131], but we did not use metastable anions to compute the hardness. (That is, negative electron affinities were replaced by zero.) This model for the hardness of an atom in a molecule is theoretically ill-founded, but it is a pragmatic choice given the difficulty of computing the hardness of an N-electron atom embedded in a molecular environment.

We chose to study substituted pyridines because when a substituted pyridine is a very weak base (i.e. when the pyridinium ion is highly acidic), it is susceptible to electrophilic attack at both the nitrogen atom (by a hard acid) and at positions 3 and 5 on the pyridine ring (meta to the nitrogen atom, by a soft acid).[132-134] All of the pyridines we consider are very weak bases; as shown in Table 1, the pK_a's of their corresponding pyridinium ions are less than 1.

The data in Table 1 is similar to what one normally expects for ambident nucleophiles: the hard nucleophilic site (the nitrogen atom) has the largest negative charge. Similarly, the soft nucleophilic sites (Carbons 3 and 5) have the highest value of the Fukui function from below. This reinforces the general consensus that the electrostatic potential (atomic charges) control reactivity by hard reagents while the frontier orbitals (condensed Fukui functions) control reactivity by soft reagents.[8, 18, 19, 102, 135, 136]

Remarkably, the information-theoretic condensed local hardness measure from Eq. (25) also captures these trends. It predicts that the nitrogen atom is much harder than the other sites on the ring in almost all cases. The one exception is for 2-bromopyridine with the CHELPG population analysis. In that case Carbon 4 is predicted to be harder than the nitrogen atom; this spurious result occurs because of the very small (but positive) Fukui function on that atom. Natural population analysis (NPA) seems to give consistently reliable results.

Notice that the results from the information-theoretic condensed local hardness are better than what is obtained by merely invoking the “minimum Fukui function” rule. The form in Eq. (25) indicates that an atom/functional group with a high reference-state hardness and a small Fukui function is more reactive than an atom/functional group with a lower reference-state hardness and an equally small Fukui function. Here we observe that this measure gives predictions similar to the charge on the atom. Insofar as electronegative elements tend to have high ionization potential, high hardness, and a propensity to accumulate electrons, this is not surprising. Further tests are needed before this information-theoretical local hardness measure can be considered generally useful, however.

It is somewhat disappointing that none of these reactivity indicators predict the correct trend in pK_a. Only the information-theoretic local hardness gives extreme values for 2,6-dichloropyridine, consistent with the fact this reagent is a significantly weaker base than the other reagents. However, the information-theoretic local hardness fails to recognize that 2-fluoropyridine is also an extremely weak base. Finding a first-principles quantitative structure-activity relationship that can predict the pK_a trend for pyridinium ions is a topic of active investigation in our laboratory and we hope that the information-theoretic local hardness, in combination with other reactivity indicators, may prove useful in this regard.

V. Summary

We have suggested that information theory can be used to resolve the inherent ambiguity in the local hardness. To demonstrate this idea, we derived two new approaches to the local hardness. In section II, an approach to the pointwise local hardness was derived. The resulting form of the local hardness has an exponential divergence far from a molecule, which is reasonable in light of recent numerical and analytical results. In section III an analogous argument is used to derive an information-theoretic condensed local hardness. This local hardness measure is large when the Fukui function is small and positive, and therefore gives some support to the oft-denigrated concept that low values of the Fukui function are indicative of hard reactive sites.[103] The idea that minimal values of the Fukui function indicate hard reactive sites contradicts the “dμ big is good” rule of Parr and Yang,[56] and also Klopman’s rule which indicates that hard reagents tend to react in the location of greatest charge.[135] However, our tests show that the condensed local hardness definition from Eq. (25) can, at least in some families of molecules, identify the atom with the highest charge.

Specifically, the proposed local hardness measure was able to recognize that the nitrogen atom, and not carbon 3 and/or 5, was the hard reactive site in weakly basic substituted pyridines. This finding is surprising because the new local hardness formula, Eq. (25), depends only on frontier-electron effects in the molecule and its composing atoms, and has no information about the electrostatic features of the molecule, which are supposed to be dominant in hard-hard interactions.

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Table 1. Reactivity parameters for some substituted pyridines that are very weakly basic. The pK_a of the corresponding pyridinium ion is listed in the table, along with their charges, Fukui function from below, and the information-theoretic local hardness in Eq. (25). The nitrogen atom is listed in **bold** to indicate that this is where a hard reagent should attack; carbons 3 and 5 are shown in *italics* to indicate that this is where a soft reagent should attack. Carbons that are unreactive because they are already substituted are shaded gray.

	Site on Ring	q_A (NPA)	f_A^- (NPA)	η_A^- (NPA)	q_A (CHELPG)	f_A^- (CHELPG)	η_A^- (CHELPG)
2-bromopyridine (pK_a = 0.99)	**Nitrogen**	**-0.47**	**0.03**	**1.37**	**-0.60**	**0.04**	**0.97**
	Carbon-2	0.15	0.03	0.89	0.50	-0.09	-0.32
	Carbon-3	*-0.26*	*0.13*	*0.22*	*-0.21*	*0.20*	*0.14*
	Carbon-4	-0.15	-0.01	-5.20	0.25	0.03	1.08
	Carbon-5	*-0.25*	*0.17*	*0.16*	*-0.25*	*0.21*	*0.13*
	Carbon-6	0.07	0.09	0.29	0.45	0.16	0.17
2-hydroxypyridine (pK_a = 0.75)	**Nitrogen**	**-0.53**	**0.06**	**0.57**	**-0.74**	**0.09**	**0.39**
	Carbon-2	0.53	0.07	0.32	0.87	-0.03	-0.93
	Carbon-3	*-0.28*	*0.17*	*0.14*	*-0.30*	*0.27*	*0.09*
	Carbon-4	-0.15	-0.01	-1.84	0.25	-0.03	-0.93

	Carbon-5	*-0.28*	*0.22*	*0.11*	*-0.26*	*0.31*	*0.07*
	Carbon-6	0.07	0.10	0.23	0.43	0.13	0.19
2-chloropyridine (pK_a = 0.72)	**Nitrogen**	**-0.43**	**0.03**	**1.38**	**-0.60**	**0.05**	**0.82**
	Carbon-2	0.27	0.06	0.43	0.55	-0.05	-0.52
	Carbon-3	*-0.11*	*0.15*	*0.19*	*-0.21*	*0.23*	*0.12*
	Carbon-4	-0.16	-0.01	-2.88	0.25	0.00	-21.47
	Carbon-5	*-0.06*	*0.19*	*0.15*	*-0.25*	*0.26*	*0.11*
	Carbon-6	0.18	0.11	0.25	0.44	0.16	0.17
2-fluoropyridine (pK_a = -0.44)	**Nitrogen**	**-0.48**	**0.04**	**1.10**	**-0.64**	**0.09**	**0.44**
	Carbon-2	0.61	0.12	0.22	0.82	0.02	1.53
	Carbon-3	*-0.29*	*0.19*	*0.15*	*-0.29*	*0.30*	*0.09*
	Carbon-4	-0.15	-0.02	-1.64	0.26	-0.04	-0.71
	Carbon-5	*-0.26*	*0.22*	*0.12*	*-0.25*	*0.33*	*0.08*
	Carbon-6	0.06	0.15	0.19	0.42	0.15	0.18
2,6-dichloropyridine (pK_a = -	**Nitrogen**	**-0.48**	**0.02**	**2.13**	**-0.54**	**0.02**	**2.12**
	Carbon-2	0.21	0.04	0.63	0.51	-0.02	-1.32

	Carbon-3	*-0.26*	*0.16*	*0.17*	*-0.20*	*0.23*	*0.12*
	Carbon-4	-0.14	-0.02	-1.86	0.23	0.01	1.90
	Carbon-5	*-0.26*	*0.16*	*0.17*	*-0.19*	*0.23*	*0.13*
	Carbon-6	0.21	0.04	0.63	0.50	-0.02	-1.75

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A definition of the local hardness, suitable for application in the local hard/soft acid/base principle, is derived by applying information theory.