# Reactivity Patterns of Imidazole, Oxazole, and Thiazole As Reflected by the Polarization Justified Fukui Functions

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Ⓢ *Supporting Information*

ABSTRACT: The concept of the polarization justified Fukui functions has been tested for the set of model molecules: imidazole, oxazole, and thiazole. Calculations of the Fukui functions have been based on the molecular polarizability analysis, which makes them a potentially more sensitive analytical tool as compared to the classical density functional theory proposals, typically built on electron density only. Three selected molecules show distinct differences in their reactivity patterns, despite very close geometry and electronic structure. The maps of the polarization justified Fukui functions on the molecular plane correctly identify important features of the molecules: the site for the preferential electrophilic attack in imidazole (−NH, see the TOC image) and oxazole (5-C), as well as uniquely aromatic character of the thiazole molecule and the acidic forms XH^+ of all three species.
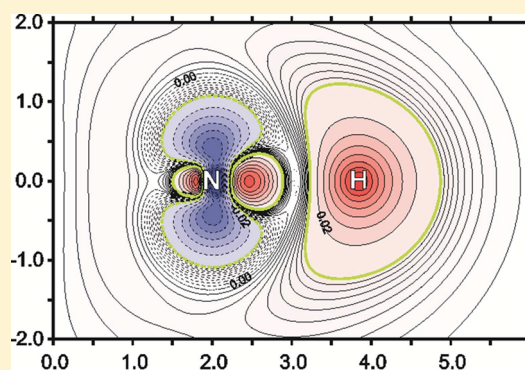
I. INTRODUCTION

The Fukui functions (FF) have been well recognized potential theoretical reactivity indicators in the conceptual density functional theory (CDFT).[1,2] Rigorously, they are defined as the derivative of the electron density $\rho(\mathbf{r})$ over the number of electrons N, or equivalently, the functional derivative of the chemical potential μ over the external potential $\nu(\mathbf{r})$:

$$f(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_\nu = \left(\frac{\delta \mu}{\delta \nu(\mathbf{r})}\right)_N \tag{1}$$

The FF have been traditionally calculated from the density function of a molecule and its ions at the level of two commonly used alternative methods: $f^{EG}(\mathbf{r}) \cong \rho(\mathbf{r})/N$ (electron gas approximation[1,3]) or $(f^\pm(\mathbf{r})) \cong (1/2)[\rho^-(\mathbf{r}) - \rho^+(\mathbf{r})])$ (finite difference approximation; ρ^- and ρ^+ stand for the density functions of respective ions). Neither of these approaches provides adequate description of the molecular reactivity, though.[4] The fundamental difficulty is in the insufficient information contained in the resulting FF. The $f^{EG}(\mathbf{r})$ function contains information on the equilibrium density only, while in the calculation of the $f^\pm(\mathbf{r})$ function, the density of the ionic states of a molecule is used, with no relation to the density of the neutral species. The common remedy is to explore the electrophilic FF $((f^-(\mathbf{r})) = (\partial\rho(\mathbf{r})/\partial N)_\nu^-)$ and nucleophilic FF $((f^+(\mathbf{r})) = (\partial\rho(\mathbf{r})/\partial N)_\nu^+)$ in order to describe the appropriate sensitivity of a molecule.[4] The concept of the polarization justified Fukui functions (PJFF) proposed in this laboratory[5−7] overcomes the difficulty in differentiating the local quantity (electron density) over the number of electrons (N) by using the second part of the definition (eq 1). The similar idea was explored by Ayers et al.;[8]

the $f^-(\mathbf{r})$ and $f^+(\mathbf{r})$ Fukui functions have been deduced from the change in Kohn−Sham orbital energies induced by perturbations in molecular external potential. The analytic approach to the Fukui functions in the recent work by Flores-Moreno et al.[9] is based on the classical approach (eq 1, first part).

The canonical heterocyclic structure of imidazole has been selected as a model for this present study, with X being NH (imidazole), O (oxazole), and (S) thiazole.
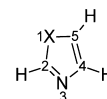
All three molecules are planar and isosteric. Basic properties of the selected molecules are well-known; despite the structural identity, they differ remarkably in their reactivity. The most notable example is in proton affinity at 3-N atom, indicated by the experimental pK_a values in water for the conjugate NH acids: imidazole, 7.1;[10] oxazole, 0.8;[11] and thiazole, 2.52.[11] The reactivity of the ring atoms toward electrophilic and nucleophilic agents is amply described in organic chemistry literature.[10−12] Thiazole is considered to be aromatic, oxazole has little aromatic character[11] and appears to be least reactive of all. Bromination is easy for imidazole (at 2-C), somewhat more difficult for thiazole (at 5-C), and unknown for oxazole.[10] The rate of alkilation at the nitrogen (3-N) is decreasing in the order imidazole, thiazole, and oxazole, as 900:15:1,[10] in line with the decrease of the pK_a. The preferential site for the electrophilic attack in imidazole is at the

nitrogen (1-N); electrophilic substitution is also observed at 5-C and 4-C, never at 2-C.[12] The preferential site for the electrophilic substitution in oxazole is 5-C, then 4-C, and the nucleophilic agents attack the 2-C position only.[11] Electrophiles attack thiazole also at 5-C; reaction with nucleophiles is rare (at 2-C). The most pronounced features of this set of molecules appear to be (i) proton affinity and (ii) much different character of 5-C and 2-C positions.

The first computational study of the Fukui function of imidazole is due to Lopez and Mendez.[13] The authors demonstrated how the condensed Fukui functions ($f(\mathbf{r})$ integrated over some atomic basins) support their concept of the new resonance structure, explaining the high nucleophilic reactivity of 2-C carbon in neutral or basic conditions. Other structures have not yet been the subject of a conceptual DFT analysis, to the best of our knowledge.

II. METHODS

The polarization justified Fukui function is determined from the local polarization function (the computable vector):

$$\boldsymbol{\alpha}(\mathbf{r}) \equiv -(\partial\rho(\mathbf{r})/\partial\boldsymbol{\varepsilon})_N \qquad (2)$$

The effect of the density function responding to an external perturbation (uniform electric field $\boldsymbol{\varepsilon}$) is now included directly in the new FF.[5−7] This approach, originally proposed for atoms, has recently been extended to molecules[14] leading to the explicit formulation of the local softness $s(\mathbf{r}) = [\partial\rho(\mathbf{r})/\partial\mu]_v$:

$$s(\mathbf{r}) = \frac{\boldsymbol{\alpha}(\mathbf{r})\cdot[\mathbf{r} - \mathbf{M}_e^{(N)}] - b\rho(\mathbf{r})[\mathbf{M}_e - N\mathbf{r}]\cdot[\mathbf{r} - M_e^{(N)}]}{(1 - c)[\mathbf{r} - \mathbf{M}_e^{(N)}]^2} \qquad (3)$$

where vectors $\boldsymbol{\alpha}(\mathbf{r})$, $\mathbf{M}_e$, and $\mathbf{M}_e^{(N)}$ are the local polarization (eq 2), the electronic part of the dipole moment, and its derivative over N, respectively. The Fukui function $f(\mathbf{r})$ is just the local softness divided by the result of integration thereof ($S = \int s(\mathbf{r})d\mathbf{r} = (I-A)^{-1}$, the inverse global hardness; I and A are ionization energy and electron affinity, respectively). By introducing a constant K

$$K = (I - A)(1 - c) \qquad (4)$$

the computable result for the unique Fukui function in a molecule reads:

$$f(\mathbf{r}) = \frac{1}{K[\mathbf{r} - \mathbf{M}_e^{(N)}]^2}\{\boldsymbol{\alpha}(\mathbf{r}) - b\rho(\mathbf{r})[\mathbf{M}_e - N\mathbf{r}]\}\cdot$$
$$[\mathbf{r} - \mathbf{M}_e^{(N)}] \qquad (5)$$

Note that the $[\mathbf{r} - \mathbf{M}_e^{(N)}]$ and $[\mathbf{M}_e - N\mathbf{r}]$ vectors (eq 5) are translationally invariant, while the $\mathbf{M}_e^{(N)}$ and $\mathbf{M}_e$ alone are not. Constants b and c are internal parameters of the method, the calculation scheme for the PJFF allows for their direct determinations. They stem from the adopted approximation for the softness kernel:[5,7]

$$s(\mathbf{r}, \mathbf{r}') = \left[\frac{\delta\rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right]_\mu$$
$$= (1 - c)s(\mathbf{r})\delta(\mathbf{r} - \mathbf{r}') - bN\rho(\mathbf{r})\delta(\mathbf{r} - \mathbf{r}')$$
$$+ b\rho(\mathbf{r})\rho(\mathbf{r}') + cSf(\mathbf{r})f(\mathbf{r}') \qquad (6)$$

The derivative of the electronic dipole moment was calculated by the finite difference method, based on the results for the

respective molecular cation and anion. The $\mathbf{M}_e^{(N)}$ value in eq 5 serves as an additional computable global parameter; taking a derivative of a local quantity over N is no longer necessary.

The Fukui functions have been calculated by eq 5. The electron density has been calculated by the Gaussian03 code,[15] the DFT B3LYP method using the aug-cc-pvqz basis set. The local polarizability vector $\boldsymbol{\alpha}(\mathbf{r})$ (eq 2) has been calculated by the finite field procedure. The electron dipole polarizability for each molecule was obtained by the numerical integration of diagonal elements of the local $\boldsymbol{\alpha}(\mathbf{r})\mathbf{r}$ tensorial product and served for the purpose of testing, whether the calculation scheme and the basis set properly reproduce the polarizability of the system.

III. RESULTS

The calculated energies and electron dipole polarizabilities, as well as the respective reference data are collected in Table 1. The

Table 1. Calculated Molecular Parameters and the Respective Reference Values (All in Atomic Units): I, Ionization Energy; A, Electron Affinity; $\langle\alpha\rangle$, Electron Dipole Polarizability; and $|M|$, the Dipole Moment

molecule	imidazole	oxazole	thiazole
I (ref 11)	0.3226	0.3612	0.3490
$I-A$ (calcd)	0.2630	0.2837	0.2362
$\langle\alpha\rangle$ (calcd)	45.760	41.049	56.451
$|M|$ (ref 10)	1.456	0.590	0.633
$|M|$ (calcd)	1.491	0.605	0.577
$b\ 10^3$	5.664	14.636	−26.680
K	7.698	11.634	−22.048
c	−1.025	−2.300	6.207
$(\overline{\partial u_{NL}/\partial\mu})_v$	0.506	0.697	1.192

calculated parameters that appear in the working approximation are also shown in Table 1. They are well in accord with the results initially obtained for a set of diatomic molecules; parameter b in all molecules is exceedingly small, but not unimportant (cf. ref 14).

The last entry in Table 1 represents an important quantity resulting in this computational scheme: the average value of the derivative of the nonlocal part of the electronic potential $u_{NL}(\mathbf{r})$. Assuming the electrostatic part to be dominant in the electronic potential $u_{NL}(\mathbf{r})$,[14] the derivative represents the average Fukui potential:[16]

$$\left\langle\left[\frac{\partial u_{NL}(\mathbf{r})}{\partial\mu}\right]_v\right\rangle \approx S\left\langle\int\frac{f(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}d\mathbf{r}'\right\rangle \qquad (7)$$

The small positive numbers for that derivative corroborate the above assumption.[14] The planar maps of the Fukui functions resulting in this work are presented in Figure 1.

The characteristic feature of the PJFF maps depicted in Figure 1 are large regions of positive values accompanied by small bays of negative $f(\mathbf{r})$ clearly visible in Figure 1a. Earlier approximations typically resulted in positive values of $f(\mathbf{r})$;[4] arguments have been presented that the Fukui function indices condensed to atoms must not have negative values.[17,18] Theoretical arguments by Bultinck et al.[19] proved that regions of negative $f(\mathbf{r})$ function are not impossible, they have not yet been systematically studied, though. The result for atoms[5,6,18] demonstrated the regions of negative $f(\mathbf{r})$ near atomic nucleus for the results of nonrelated computational procedures; this has been substantiated by the strong theoretical arguments given by Ayers et al.[18]
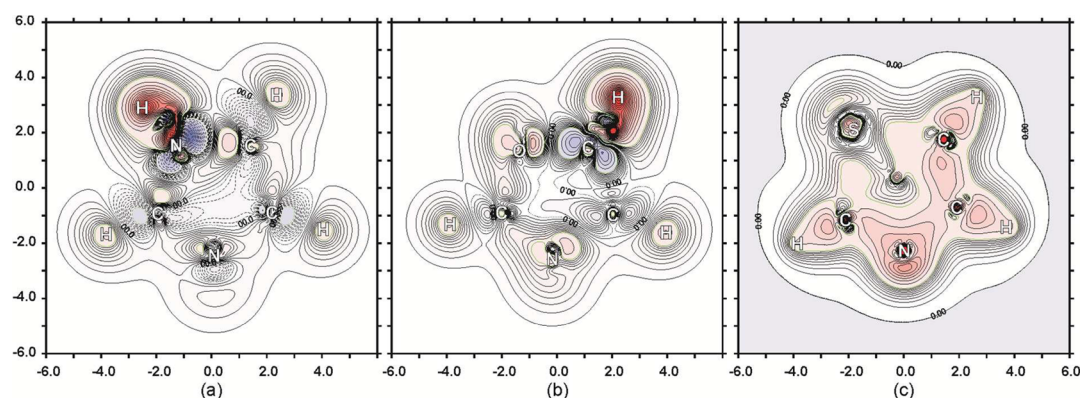
Figure 1. Polarization justified Fukui functions in the molecular plane (distance in a.u.; negative values, dashed lines): (a) imidazole; (b) oxazole; and (c) thiazole.
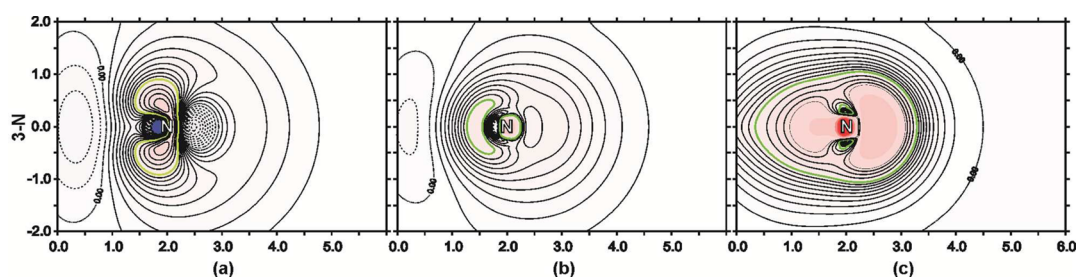

Figure 2. Polarization justified Fukui functions in the perpendicular plane around the 3-N atom (distance in a.u.; negative values, dashed lines): (a) imidazole; (b) oxazole; and (c) thiazole.
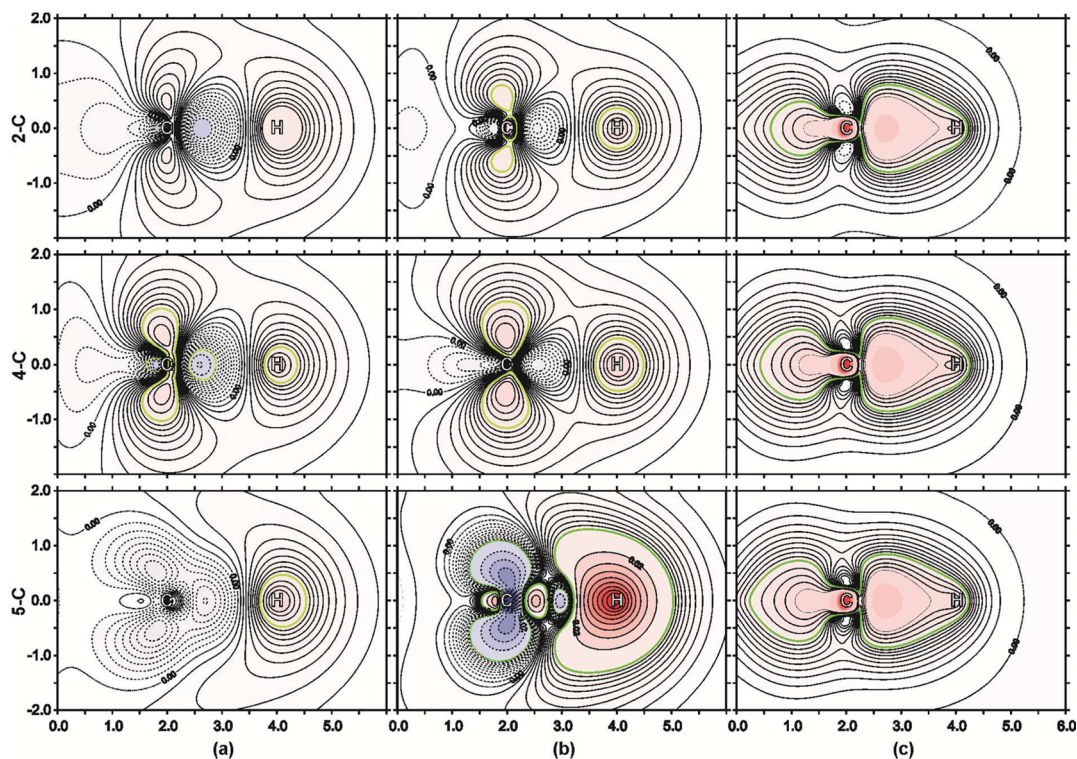

Figure 3. Polarization justified Fukui functions in the perpendicular plane along the C−H bond for the ring atoms 2-C, 4-C, and 5-C (distance in a.u.; negative values, dashed lines): (a) imidazole; (b) oxazole; and (c) thiazole.

There are two regions of the negative Fukui function for the imidazole ring systems under study. The broad basin of very small negative $f(\mathbf{r})$ at the ring center in imidazole (Figure 1a) may be attributed to the insufficient accuracy of the computations.

Small regions of considerable magnitude $f(\mathbf{r})$ are observed near heavy nuclei as expected. In imidazole, they tend to be broad enough to be seen in the ring plane (Figure 1a) as well as in the perpendicular plane (Figure 2a for N atom; Figure 3a for C

atoms). In oxazole, these regions are hardly seen in the molecular plane,;they are very clear, though smaller, in the perpendicular plane (Figure 3b). In thiazole, these regions are not observed (Figure 3c); the traces of very small negative $f(\mathbf{r})$ in thiazole are beyond a reasonable discussion. Appearance of the negative $f(\mathbf{r})$ has been rationalized by Ayers et al.[18] with simple chemical arguments: adding an electron to a LUMO will cause a decrease of the density near its node, due to the screening effect of the added electron on the remaining ones, hence $d\rho(\mathbf{r})/dN < 0$. It is remarkable to see that this appealing argument holds also for the PJFF's, calculated with no relation to adding/subtracting electrons: the underlying physical effect here is the density polarization in external field. Evidently, PJFF's very properly reflect the nonuniform character of the density in molecules (for the electron gas $f(\mathbf{r}) \approx const > 0$). Thiazole is nearly aromatic; the difference between its uniform density system and strongly polarized system (imidazole) and the moderately polarized molecule (oxazole) is reflected by the PJFF's maps.

IV. DISCUSSION AND CONCLUSIONS

The chemical context of the results of this work needs recalling what are the consequences of the sign of $f(\mathbf{r})$ in some regions. In the calculation scheme for the PJFF, the number of electrons in a system is constant, and the second part of the $f(\mathbf{r})$ definition applies (eq 1). When positive point charge (e.g., proton) approaches to a molecule, it changes its chemical potential by $\Delta\mu$:

$$\Delta\mu = \int f(\mathbf{r})\Delta v(\mathbf{r})d\mathbf{r}$$

In the conceptual DFT formalism, the external potential due to the approaching point charge is 1: $\Delta v(\mathbf{r}) = -q/|\mathbf{r}-\mathbf{r}_q|$. With an electrophilic agent ($q > 0$), the contact region of positive $f(\mathbf{r})$ lowers its chemical potential ($\Delta\mu < 0$), thus extracting some density from other parts of the system, just as necessary for an electron donation to occur; the region of negative $f(\mathbf{r})$ should act in the same manner for a contact with a model nucleophilic agent ($q < 0$; $\Delta\mu > 0$). The higher positive FF of a group, the more impressive its role in the electrophilic substitution. This inductive effect will be enhanced by an electrostatic effect, if an atom or group in question bears negative charge. For the molecules under study, this appears to be the case of proton accepting 3-N atom, Figure 2. On the contrary, preferential electrophilic substitution at 1-N must be driven solely by the electrostatic effect; the role of negative $f(\mathbf{r})$ is immaterial (see the graphic abstract).

The result for thiazole properly reflects a uniform (aromatic) character of this ring system in contrast to the other two molecules (Figures 1 and 3). The same effect, positive only and much uniform maps of the PJFF's, has been demonstrated for the cationic species for all molecules under study: ImH$^+$, OxH$^+$, and ThH$^+$ (cf. Supporting Information); the PJFF's maps may well be explored as a potential aromaticity sensor.

In imidazole molecule, the NH entity shows extraordinarily high FF values, well in accord with the uniquely high reactivity of the molecule at this site. The difference between the carbon ring atoms can hardly be attributed to the features observed in Figure 1, though. The result for oxazole is surprising, as compared to the rest. The vicinity of 5-C atom looks very much like the N−H group in imidazole. Indeed, both sites are preferentially reactive to electrophiles. The imidazole NH proton is slightly acidic[11] ($pK_a = 14.52$), so should be the C−H proton at 5-C in oxazole. Since no experimental data have yet been reported for oxazole, the available data for furan are helpful. The experimentally

determined order of acidity is[20] water < furan < methanol, while for methanol,[21] $pK_a = 15.5$. Using the method of ref 20 leads to $pK_a = 14.75$ for 2-H position in furan, the closest possible estimation of the 5-H acidity in oxazole. The result is surprisingly close to the pK_a of imidazole and corroborates the predicting power of the PJFF. Neither $f^{EG}(\mathbf{r}) = \rho(\mathbf{r})/N$ nor $f^{\pm}(\mathbf{r}) = (1/2)[\rho^-(\mathbf{r}) - \rho^+(\mathbf{r})]$ approximations to the Fukui functions seem to reflect the variation of the ring atom properties that could be related to their observed properties (cf. Supporting Information). Although further studies are needed in order to understand the information hidden in the polarization justified Fukui functions, the present result demonstrates their potential in describing the subtle details of the electronic structure response to the external attacks. The primary target of further study is proton affinity/proton dissociation effects of molecules, as ample quantified data exist in this area.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Maps of the classical DFT FF for the molecules under study: $f^{\pm}(\mathbf{r}) \cong (1/2)[\rho^-(\mathbf{r}) - \rho^+(\mathbf{r})]$ (Figure 4); $f^{EG}(\mathbf{r}) \cong \rho(\mathbf{r})/N$ (Figure 5). Maps of the PJFF and the classical FF for the cations: ImH$^+$ (Figure 6), OxH$^+$ (Figure 7), and ThH$^+$ (Figure 8). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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