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Chemical Reactivity Descriptors for Ambiphilic Reagents: Dual Descriptor, Local Hypersoftness, and Electrostatic Potential

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The second-order response of the electron density with respect to changes in electron number, known as the dual descriptor, has been established as a key reactivity indicator for reactions like pericyclic reactions, where reagents accept and donate electrons concurrently. Here we establish that the dual descriptor is also the key reactivity indicator for ambiphilic reagents: reagents that can act either as electrophiles or as nucleophiles, depending on the reaction partner. Specifically, we study dual atoms (which are proposed to act, simultaneously, as an electron acceptor and an electron donor), dual molecules (which react with both electrophiles and nucleophiles, generally at different sites), and dual ion−molecule complexes (which react with both cations and anions). On the basis of our analysis, the dual atom (an Al(I) that has been purported to be dual in the literature) is actually pseudodual in the sense that it does not truly accept electrons from a nucleophiles; rather, it serves as a conduit through which an electrophile can donate electrons to the attached aromatic ring. For understanding dual ion−molecule complexes, it helps to understand that the dual descriptor makes a key contribution to the long-range portion of the quadratic hyperpolarization. In all cases, a complete description of the reactivity of the ambiphilic reagent requires considering both an orbital-based descriptor of electron transfer (the dual descriptor or the local hypersoftness) and the electrostatic potential. The local hypersoftness strongly resembles the dual descriptor.

I. Introduction

Ambiphilic chemical reagents cannot be classified either as electrophiles (electron acceptors, Lewis acids) or as nucleophiles (electron donors, Lewis bases). Instead, ambiphilic reagents act as either electrophiles or nucleophiles, depending on the reaction partner. Some ambiphilic reagents even accept (electrophilic behavior) and donate (nucleophilic behavior) electrons at the same time.

The classical tools of chemical reactivity theory do not seem to apply in a straightforward way to ambiphilic reagents. The regioselectivity of an electrophile can be ascertained by locating the site where the reagent is most likely to accept electrons. In molecular orbital theory, this site is associated with a large absolute value of the lowest unoccupied molecular orbital (LUMO), $\phi_{\mathrm{LUMO}}(\mathbf{r})$. Similarly, the regioselectivity of a nucleophiles can be ascertained by locating the site with a large absolute value of the highest occupied molecular orbital (HOMO), $\phi_{\mathrm{HOMO}}(\mathbf{r})$.[1−5] In classical frontier molecular orbital theory, then, there is no single reactivity indicator that can describe the regioselectivity of ambiphilic reagents, which react as *both* electrophiles and nucleophiles.

In the density-functional theory approach to phenomenological chemical reactivity theory (chemical DFT),[6−9] the reactive site of an electrophile is associated with a large positive value of the Fukui function from above,[10−12]

$$f^{+}(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)^{+}_{v(\mathbf{r})} = \rho_{N+1}(\mathbf{r}) - \rho_{N}(\mathbf{r}) \tag{1}$$

The superscript "+" on the derivative indicates that the derivative is taken from above; this is essential because the derivative from above and the derivative from below,

$$f^{-}(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)^{-}_{v(\mathbf{r})} = \rho_{N}(\mathbf{r}) - \rho_{N-1}(\mathbf{r}) \tag{2}$$

are not equal when the number of electrons is an integer, owing to the derivative discontinuity of the energy,[13,14] density, and other molecular properties.[15,16] In chemical DFT, the Fukui function from below, $f^{-}(\mathbf{r})$, is the key regioselectivity indicator for nucleophiles.

The finite difference approximation in eqs 1 and 2 is exact in principle,[12] but it is only approximate for approximate density functionals.[17−22] Because most density functional approximations are more accurate at the integers than in between them, the finite difference approximation seems to be more accurate[23] than techniques based on explicit differentiation of the density.[24−29] The link between the chemical DFT description and the frontier MO theory description is clear when one approximates the Fukui functions using the frontier molecular orbitals,

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$$\begin{aligned} f^{-}(\mathbf{r}) &= |\phi_{\mathrm{HOMO}}(\mathbf{r})|^2 \\ f^{+}(\mathbf{r}) &= |\phi_{\mathrm{LUMO}}(\mathbf{r})|^2 \end{aligned} \tag{3}$$

These approximations are sufficient except for the (seemingly rare[30−36]) cases where orbital relaxation effects are important.

Recent work reveals that the dual descriptor,[37]

$$f^{(2)}(\mathbf{r}) = \left(\frac{\partial^2 \rho(\mathbf{r})}{\partial N^2}\right)_{v(\mathbf{r})} \tag{4}$$

is useful for reactions in which a reagent simultaneously accepts and donates electrons.[38−42] The prototypical example is pericyclic reactions, where electrons flow simultaneously into and out of the reacting molecules/molecular fragments.[40,43] This suggests that the dual descriptor may be an appropriate tool for studying ambiphilic reagents, which can both donate and accept electrons (although they rarely do so simultaneously). Several other reactivity descriptors—notably the “multiphilic” reactivity descriptor of Padmanabhan et al.,[44−46] the electrophilicity access of Roy et al.,[47] the “local hardness” of Meneses et al.,[48] and the initial hardness response of De Proft et al.[49,50]—are closely related to the dual descriptor. Together with Patricia Pérez, two of the present authors recently performed a chemical DFT study of boron-based ambiphilic reagents.[51]

For an isolated molecule with between $N_0 - 1$ and $N_0 + 1$ electrons, where N_0 is an integer, the dual descriptor is[16]

$$\begin{aligned} f^{(2)}(\mathbf{r}) &= \delta(N - N_0)(\rho_{N_0+1}(\mathbf{r}) - 2\rho_{N_0}(\mathbf{r}) + \rho_{N_0-1}) \\ &= \delta(N - N_0)(f^{+}(\mathbf{r}) - f^{-}(\mathbf{r})) \end{aligned} \tag{5}$$

The Dirac delta function in this equation arises from the derivative discontinuity. When molecules interact with and share electrons with their surroundings, the derivative discontinuity disappears.[52] The simplest possible finite-difference equations for the Fukui function and the dual descriptor are then

$$\begin{aligned} f^{0}(\mathbf{r}) &\approx \frac{\rho_{N_0+1}(\mathbf{r}) - \rho_{N_0-1}(\mathbf{r})}{2} = \frac{f^{+}(\mathbf{r}) + f^{-}(\mathbf{r})}{2} \\ &\approx \frac{|\phi_{\mathrm{LUMO}}(\mathbf{r})|^2 + |\phi_{\mathrm{HOMO}}(\mathbf{r})|^2}{2} \end{aligned} \tag{6}$$

$$\begin{aligned} f^{(2)}(\mathbf{r}) &\approx \rho_{N_0+1}(\mathbf{r}) - 2\rho_{N_0}(\mathbf{r}) + \rho_{N_0-1}(\mathbf{r}) = f^{+}(\mathbf{r}) - f^{-}(\mathbf{r}) \\ &\approx |\phi_{\mathrm{LUMO}}(\mathbf{r})|^2 - |\phi_{\mathrm{HOMO}}(\mathbf{r})|^2 \end{aligned} \tag{7}$$

Note that the first line of eq 7 is just eq 5, without the Dirac delta function.

When a molecule interacts and interchanges electrons with its surroundings, the number of electrons in the molecule fluctuates. For this reason, the number of electrons is not a natural variable for solution-phase chemistry. When chemical reagents are represented as open systems, it is more useful to use the electronic chemical potential[53] to control the average number of electrons on a fragment.[54] The analogue of the dual descriptor is the local hypersoftness,[40,55]

$$s^{(2)}(\mathbf{r}) = \left(\frac{\partial^2 \rho(\mathbf{r})}{\partial \mu^2}\right)_{v(\mathbf{r})} = \frac{f^{(2)}(\mathbf{r})}{\eta^2} + \frac{\eta^{(2)} f(\mathbf{r})}{\eta^3} \tag{8}$$

In this equation,

$$\begin{aligned} \eta &= \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\mathbf{r})} \approx E_{N_0+1} - 2E_{N_0} + E_{N_0-1} = I - A \\ &\approx \varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}} \end{aligned} \tag{9}$$

is the chemical hardness of Parr and Pearson[56−58] and

$$\begin{aligned} \eta^{(2)} &= \left(\frac{\partial^3 E}{\partial N^3}\right)_{v(\mathbf{r})} \approx E_{N_0+1} - 3E_{N_0} + 3E_{N_0-1} - E_{N_0-2} \\ &\approx \varepsilon_{\mathrm{LUMO}} - 2\varepsilon_{\mathrm{HOMO}} + \varepsilon_{\mathrm{HOMO-1}} \end{aligned} \tag{10}$$

is the hyperhardness of Fuentealba and Parr.[59] The hyperhardness is usually small because the energy, E, often has a nearly quadratic dependence on the number of electrons (cf. the rationalization in ref 60). The quantity $(\partial^2\rho(\mathbf{r})/\partial N^2)_{v(\mathbf{r})}$ also appeared in Fuentealba and Parr’s paper,[59] but they did not give any interpretation for it.

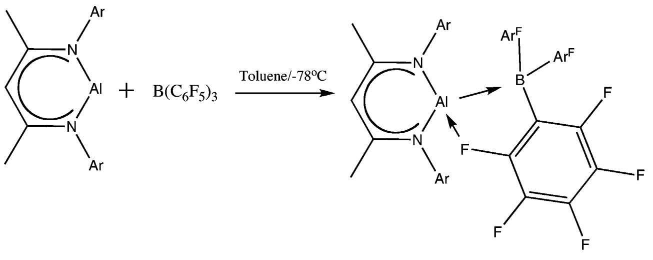
The interpretations of $f^{(2)}(\mathbf{r})$ and $s^{(2)}(\mathbf{r})$ are similar: they are positive in electrophilic regions and negative in nucleophilic regions. For isolated molecules, $f^{(2)}(\mathbf{r})$ and $s^{(2)}(\mathbf{r})$ should give similar reactivity descriptions. (However, we know of only one previous computation of $s^{(2)}(\mathbf{r})$, and that computation neglected the second term in eq 8.[61] Our calculations support this approximation: it is fine to omit the second term.) For comparing the reactivity of different molecules, it is better to use $s^{(2)}(\mathbf{r})$.[40] This is especially important when molecules of different size are compared: in the thermodynamic limit, $s^{(2)}(\mathbf{r})$ is “intensive” (like the electron density), but $f^{(2)}(\mathbf{r})$ is subintensive and tends to zero strongly (as N^{-2}!) with increasing molecular size.

The goal of this paper is to explore the extent to which the dual descriptor suffices to describe three different types of ambiphilic reagents. The first reagent we consider is the Al(I) compound **1**; when this compound reacts with $B(C_6F_5)_3$, the aluminum has been proposed to serve simultaneously as an electron donor (to boron) and an electron acceptor (from fluorine). The next reagent we consider, 2,6-dichloropyridine, reacts with either electrophiles or nucleophiles, but not with both at the same time. Finally, we consider 2,5-dichloropyrazine; this compound forms ion−molecule complexes with both anions (nucleophiles) and cations (electrophiles).

II. Computational Methods

The geometry of each molecule was optimized using the PBE exchange−correlation density functional[62] and the 6-31+G(d) basis set. There is good agreement with the experimental/theoretical structure in every case.[63,64] The molecular orbitals and electron densities required to compute the dual descriptor and the dual local softness were obtained from single point calculations on the previous optimized structure using two different functionals (PBE and B3LYP)[62,65−68] and the 6-31++G(d) basis. The global properties (hardness, chemical potential, dipole moment, etc.) and local properties (electron density, HOMO and LUMO, and atomic charges, etc.) were not sensitive to the choice of functional and basis set. The plots of the dual descriptor and the local hypersoftness in this paper are computed using the

SCHEME 1



1

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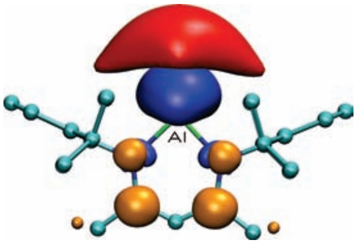


Figure 1. Dual descriptor and electrostatic potential of compound **1**. Blue: isosurface of $f^{(2)}(\mathbf{r}) = -0.004$ au, indicating regions of the molecule that donate electrons. Orange: isosurface $f^{(2)}(\mathbf{r}) = 0.004$ au, indicating regions of the molecule that accept electrons. Red: isosurface $\Phi(\mathbf{r}) = -0.035$ au, indicating regions of the molecule that attract positively charged moieties, like the boron center.

frontier orbital approximation. The plots from the density differences were similar, but slightly more difficult to interpret because of the characteristic, but chemically unimportant, orbital-relaxation-induced oscillations near the nodal surfaces of the HOMO and the LUMO.[32,35,40] All computations were performed using *Gaussian 2003*.[69]

III. Results and Analysis

A. Pseudodual Behavior of an Aluminum(I) Compound. Very recently, there has been interest in compounds in which aluminum is in the +1 oxidation state. Unlike the majority of aluminum compounds, where Aluminum is in the +3 oxidation state and thus behaves as a hard Lewis acid, the aluminum atom in Al(I) compounds is not especially electrophilic and can potentially act as a Lewis base.[70−72]

In 2000 Cui et al. synthesized the first stable bicoordinated aluminum compound **1**;[63] on the basis of the similarity between **1** and a carbene, it was hypothesized that this compound might react as both a Lewis acid and a Lewis base. According to ab initio calculations, the Al(I) center has a lone pair that it can donate, supporting the idea that **1** can act as a Lewis base. In addition, there is a region of electron depletion near the Al(I) center, in the direction of the ring. This electron-deficient region is a potential reactive site for Lewis acids.[63]

In 2007, the dual reactivity of **1** was confirmed by Yang et al., who showed that **1** reacts with $B(C_6F_5)_3$ to form **2** (Scheme 1), a compound with a donor−acceptor aluminum−boron and an acceptor−donor aluminum−fluorine bond. The boron aligns with aluminum in the plane of ring, whereas the fluorine−aluminum bond is almost perpendicular to the plane of the aluminum-containing ring.[73] We consider two possible explanations for the structure observed by Yang et al.

i. Genuine Dual Reactivity. The Al(I) center accepts and donates electrons directly. If this is the case, we expect to see (a) a large (in absolute value) negative value of the dual descriptor near Al in the plane of the ring pointing outward toward the reactive site with Boron and (b) a large positive value of the dual descriptor above Al, perpendicular to the plane of the ring.

ii. Pseudodual Reactivity. The Al(I) center serves as a conduit through which electrons are transferred from the Fluorine to the aromatic ring. In this case, the aromatic ring is the ultimate electron acceptor. In this situation one still expects to see the negative-valued dual descriptor pointing out from the ring toward the boron site. However, the positive values of the dual descriptor will not be on the aluminum atom, but elsewhere on the ring.

The dual descriptor, $f^{(2)}(\mathbf{r})$, of **1** is plotted in Figure 1. The negative-valued region of the dual descriptor is centered on Al and is concentrated on the exterior of the ring, "pointing toward" the reactive site with boron. There are no appreciable positive regions of the dual descriptor on the aluminum atom; this suggests that the Al(I) center is pseudodual. Electrons are donated by the fluorine, pass through the (relatively nonelectronegative) Al atom, and accumulate in the π-cloud of the other atoms in the aromatic ring.

To clarify the driving forces for this reaction, in Figure 1 we plot the negative contours of the electrostatic potential,[74,75]

$$\Phi(\mathbf{r}) = \sum_{\alpha} \frac{Z_\alpha}{|\mathbf{r} - \mathbf{R}_\alpha|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}\, d\mathbf{r}' \qquad (11)$$

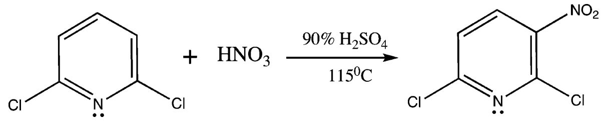
Regions where $\Phi(\mathbf{r})$ is negative are attractive to cations and repulsive to anions; regions where $\Phi(\mathbf{r})$ is positive are attractive to anions and repulsive to cations. Electrostatic attraction/repulsion is long-ranged compared to the electron-transfer effects characterized by the dual descriptor. Specifically, for a neutral reagent with a nonzero dipole moment, electrostatic effects decay as $1/R^3$, while electron-transfer effects decay exponentially with increasing distance between reagents. The orientation in which reagents initially approach each other is often determined by $\Phi(\mathbf{r})$.

Because the $-C_6F_5$ groups are strongly electron withdrawing, the boron atom in $B(C_6F_5)_3$ is positively charged. The negatively charged region outside the aromatic ring, near Al, guides the boron atom into the plane of the aromatic ring, aligning it with the lone pair of electron of the Al. Once the Al−B distance is short enough, electron transfer from the lone pair of Al to the empty p-orbital of B begins to occur, in accord with the positive value of the dual descriptor on Al site. Electron donation from Al raises the charge and electronegativity of Al and decreases the electronegativity of $B(C_6F_5)_3$; this, along with the steric constraints imposed by the incipient Al−B bond, causes fluorine to align above Al. In accord with the pseudodual nature of the Al atom, electrons are funneled through the F−Al bond to the (more electronegative) carbon and nitrogen atoms in the ring.

B. Reagent-Specific Regioselectivity in 2,6-Dichloropyridine. Pyridines are generally unreactive with respect to electrophilic aromatic substitution, with reaction rates that are typically 18−20 orders of magnitude slower than benzene.[76,77] Electrophilic aromatic substitution reactions are performed in acidic conditions. Because pyridines are bases, they are protonated (or, in aprotic media, form salts) under such conditions, and it is very difficult to perform an electrophilic substitution on a positively charged reagent.

2,6-Dichloropyridine is an exception where the neutral molecule undergoes electrophilic substitution; see Scheme 2.[76,77] The electron-withdrawing chlorine atoms reduce the basicity of the nitrogen atom enough so that the molecule is not protonated, even under acidic conditions. (The pK_a of protonated

SCHEME 2: Electrophilic Substitution (Nitration) of Neutral 2,6-Dichloropyridine



2,6-dichloropyridine is −2.86!)[78] 2,6-Dichloropyridine is a dual molecule because it undergoes both electrophilic aromatic substitution (at C3 and C5, as shown in Scheme 2) and nucleophilic aromatic substitution (at C4). Therefore we expect the dual descriptor to be positive at C4 and negative at C3 and C5. Figure 2 confirms this expectation.

The dual descriptor also predicts that, like C3 and C5, the chlorine atoms are nucleophilic. Like C4, the nitrogen atom is electrophilic. Reactivity on Cl can be dismissed because Cl is outside the ring: Cl is a possible leaving group, but not a site for electrophilic substitution reactions. Nucleophilic attack on the nitrogen atom cannot occur because the electrostatic potential is negative at the nitrogen reactive site: this negative region repels nucleophiles, which are generally negatively charged.

The negative electrostatic potential near the nitrogen atom indicates that very hard acids (e.g., the proton) will react with 2,6-dichloropyridine at the nitrogen site, rather than at C3/C5. This is in fact observed: to the extent that it is protonated at all, 2,6-dichloropyridine is protonated on the nitrogen. It reacts with very strong oxidizing agents like trifluoroperacetic acid to form 2,6-dichlorpyridine *N*-oxide, in which the nitrogen atom serves as an electron donor (to obtain a formal charge of +5).[79,80] This reemphasizes the importance of considering both charge effects (encapsulated by the electrostatic potential and dominant for hard reagents) and electron-transfer effects (encapsulated by the Fukui functions and the dual descriptor, and dominant for soft reagents) when describing chemical reactivity.[58,81−87] It is rare that either the dual descriptor or the electrostatic potential, alone, can fully explain the chemical reactivity of a reagent.

We also computed the local hypersoftness for 2,6-dichloropyridine. When computing the local hypersoftness, one confronts the problem of choosing which Fukui function should be used in the second term of eq 8. On formal grounds, one should probably use the average Fukui function, $f^0(\mathbf{r})$, since the way it is computed is analogous to the dual descriptor and the hardness. However, one may argue that $f^+(\mathbf{r})$ is a more appropriate choice for molecules that are primarily electrophiles and that $f^-(\mathbf{r})$ is a more appropriate choice for molecules that are primarily nucleophiles. Figure 3 shows the results for all three alternatives. The plots are almost indistinguishable from each other, and also from the plot of the dual descriptor (Figure 2), because $\eta^{(2)}/\eta \ll 1$ and the first term in eq 8 is dominant. This is commonly true: the local hypersoftness and the dual descriptor are also very similar for the other molecules considered in this paper.

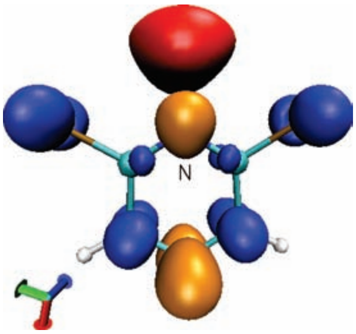


Figure 2. Dual descriptor and electrostatic potential of 2,6-dichloropyridine. Blue: isosurface of $f^{(2)}(\mathbf{r}) = -0.004$ au, indicating regions of the molecule that donate electrons and are susceptible to electrophilic attack. Orange: isosurface $f^{(2)}(\mathbf{r}) = 0.004$ au, indicating regions of the molecule that accept electrons and are susceptible to nucleophilic attack. Red: isosurface $\Phi(\mathbf{r}) = -0.035$au, indicating regions of the molecule that attract positively charged reagents.

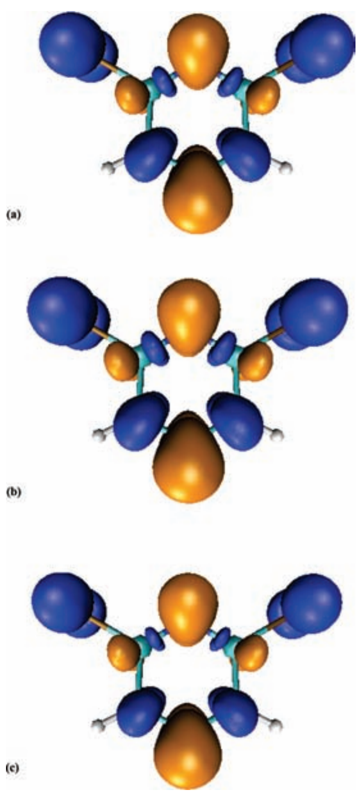


Figure 3. Local hypersoftness of 2,6-dichloropyridine. In blue the isosurface of $s^{(2)}(\mathbf{r}) = -0.02$ au, in orange the isosurface $s^{(2)}(\mathbf{r}) = 0.02$ au. The sites enclosed by the blue surface readily give electrons, whereas the sites enclosed by the orange surface readily accept electrons. (a) Using $f^0(\mathbf{r})$ in eq 8. (b) Using $f^+(\mathbf{r})$. (c) Using $f^-(\mathbf{r})$.

C. Ion−Molecule Complexes with 2,5-Dichloropyrazine. Most aromatic compounds form ion−molecule complexes either with cations (cation−π) complexes or with anions (anion π−complexes).[88−90] In both cases, the dominant interactions seem to be ion-induced polarization and electrostatic effects, with electron transfer generally playing a smaller role.[64,89,91,92] Interestingly, some aromatic compounds are "dual" and form stable complexes with both cations and anions.[64,90−93] One such compound, 2,5-dichloropyrazine, is selected for study here.

In 2004, Garau et al. used MP2 calculations to determine the binding energies of a series of aromatic compounds with Na^+ and F^-.[64] For 2,5-dichloropyrazine (DCP), they found that both complexes, DCP$\cdots Na^+$ and DCP$\cdots F^-$ were stable, with binding energies of −2.87 and −13.98 kcal/mol, respectively. The ion−ring distances of the two compounds are very similar, 2.62 and 2.51 Å, respectively. In both cases, the extent of electron transfer, computed using the quantum theory of atoms-in-molecules[94,95] (AIM) was negligible, $|\Delta N| < 0.03$ electrons. They performed an energy decomposition analysis using the molecular interaction polarized potential (MIPp)[96,97] and noted that the electrostatic contribution to binding is +7.0 kcal/mol for Na^+ and −6.5 kcal/mol for F^-. This difference is consistent with Figure 5, which shows that $\Phi(\mathbf{r}) > 0$ on the aromatic ring, and largely explains the difference in binding between Na^+ and F^-. The polarization interaction energies of

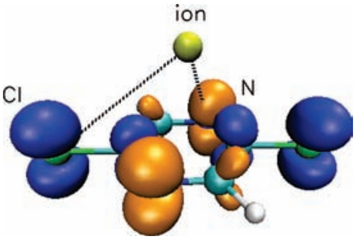


Figure 4. Dual descriptor of 2,5-dichloropyrazine. Blue: isosurface $f^{(2)}(\mathbf{r}) = -0.003$ au, indicating regions of the molecule that readily donate electrons. Orange: isosurface $f^{(2)}(\mathbf{r}) = 0.003$ au, indicating regions of the molecule that readily accept electrons. The dashed lines represent the most important stabilizing interactions between the ion (F^- or Na^+) and the molecule.

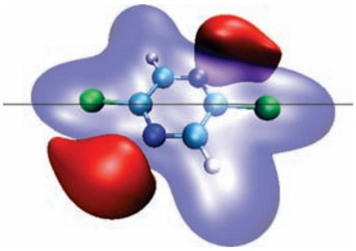


Figure 5. Electrostatic potential of 2,5-dichloropyrazine. Blue: isosurface of $\Phi(\mathbf{r}) = 0.015$ au. Red: isosurface $\Phi(\mathbf{r}) = -0.015$ au.

the -11.4 kcal/mol for Na^+ and -10.4 kcal/mol for F^- make the dominant contribution to binding but do not explain the preference for F^-.[64] It is not surprising that polarization is the dominant term: DCP is a relatively soft molecule and Na^+ and F^- are both hard reagents. Often, in hard/soft interactions, neither electron transfer (which is dominant in soft/soft interactions) nor electrostatics (which is dominant in hard/hard interactions) dominates.

MIPp is based on a decomposition of the interaction energy with a *classical* ion, so there is no electron-transfer contribution in MIPp analysis. Effectively, the electron-transfer contribution is combined with the polarization contribution; electron transfer (e.g., of NaCl to Na^+Cl^-) is viewed as extreme polarization. An order of magnitude estimate for the "true" electron transfer can be obtained from the typical orbital energy difference between donor and acceptor orbitals (ca. 0.2 hartree); this gives, as an order-of-magnitude estimate for the molecular stabilization from electron transfer, 100 kcal/mol per electron transferred. We estimate, then, that less than 5 kcal/mol of the binding energy can be attributed to electron transfer. "True" polarization—that is, deformation of the electron density clouds of DCP and the ions—must be important in binding.

The dual descriptor and the electrostatic potential for DCP are plotted in Figure 4. Consistent with its dual-binding nature, there are both positive and negative regions of both the electrostatic potential and the dual descriptor on the aromatic ring. There are multiple favorable interactions for both cations and anions, as explicitly shown in the case of the dual descriptor.

The Fukui function and the dual descriptor are also related to polarization. The "true" polarization energy of the molecule can be computed from the linear and higher-order responses of the electron density to a perturbing potential,

$$\Delta E_{\text{pol}} = \frac{1}{2}\int\int\left(\frac{\delta\rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right)_N \Delta v(\mathbf{r})\,\Delta v(\mathbf{r}')\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' + \frac{1}{6}\int\int\int\left(\frac{\delta^2\rho(\mathbf{r})}{\delta v(\mathbf{r}'')\,\delta v(\mathbf{r}')}\right)_N \Delta v(\mathbf{r})\,\Delta v(\mathbf{r}')\,\Delta v(\mathbf{r}'')\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}'\,\mathrm{d}\mathbf{r}'' + \cdots \tag{12}$$

For the polarization of DCP, $\Delta v(\mathbf{r})$ is the additional "effective external potential" that electrons in DCP feel due to the presence of the electrons and nuclei of the ion.[98] This "embedding potential"[99−101] can be computed exactly,[102,103] but for reagents that are far apart, it can be approximated by the electrostatic potential of the approaching reagent.[98] When the system is considered as a whole, $\Delta v(\mathbf{r})$ is the change in external potential that occurs when the DCP and the ion approach each other.

The long-range behavior of the density-response functions are closely related to the Fukui function and the dual descriptor. Consider the famous Berkowitz−Parr identity,[104]

$$\begin{aligned}\left(\frac{\delta\rho(\mathbf{r})}{\delta v(\mathbf{r})}\right)_N &= \left(\frac{\delta\rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right)_\mu + \left(\frac{\partial\rho(\mathbf{r})}{\partial\mu}\right)_{v(\mathbf{r})}\left(\frac{\delta\mu}{\delta v(\mathbf{r})}\right)_N \\ &= \left(\frac{\delta\rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right)_\mu + \frac{f(\mathbf{r})\,f(\mathbf{r}')}{\eta}\end{aligned} \tag{13}$$

It follows from the nearsightedness of the electron density with respect to changes in external potential at constant chemical potential (and thus, in the absence of electron transfer) that $(\delta\rho(\mathbf{r})/\delta v(\mathbf{r}'))_\mu$ decays exponentially as $|\mathbf{r} - \mathbf{r}'|$ grows large.[105,106] So the dominant long-range term in the polarization energy is given by the Fukui function. Because $f^{(2)}(\mathbf{r}) \approx f^+(\mathbf{r}) - f^-(\mathbf{r})$, the dual descriptor can only be large in places where one of the Fukui functions is large; the dual descriptor thus captures information about the susceptibility of the molecule to polarization. The Berkowitz−Parr-like identify for the quadratic response is derived in the appendix; the result is

$$\begin{aligned}\chi_N^{(2)}(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3) = {} & \chi_\mu^{(2)}(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3) - (s^{(2)}(\mathbf{r}_1,\mathbf{r}_2)\,f(\mathbf{r}_3) \\ & + s^{(2)}(\mathbf{r}_1,\mathbf{r}_3)\,f(\mathbf{r}_2) + s^{(2)}(\mathbf{r}_2,\mathbf{r}_3)\,f(\mathbf{r}_1)) \\ & + \eta^{-2}(f^{(2)}(\mathbf{r}_1)\,f(\mathbf{r}_2)\,f(\mathbf{r}_3) + f(\mathbf{r}_1)\,f^{(2)}(\mathbf{r}_2)\,f(\mathbf{r}_3) \\ & + f(\mathbf{r}_1)\,f(\mathbf{r}_2)\,f^{(2)}(\mathbf{r}_3)) + 4\eta^{-3}\eta^{(2)}f(\mathbf{r}_1)\,f(\mathbf{r}_2)\,f(\mathbf{r}_3)\end{aligned} \tag{14}$$

The dominant term in the long-range portion of the quadratic response contains the dual descriptor. This emphasizes again that the dual descriptor indicates the susceptibility of a molecule to polarization by a distant reagent.

For well-separated reagents, the first term in eq 13 is negligible. The second term does not distinguish between attractive and repulsive interactions because

$$\begin{aligned}&\frac{1}{2\eta}\int\int f(\mathbf{r})\,\Delta v(\mathbf{r})\,f(\mathbf{r}')\,\Delta v(\mathbf{r}')\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' \\ &\quad = \frac{1}{2\eta}\left(\int f(\mathbf{r})\,\Delta v(\mathbf{r})\,\mathrm{d}\mathbf{r}\right)^2 \geq 0\end{aligned} \tag{15}$$

is never negative. In contrast, the quadratic polarization response does provide insight into attractive vs repulsive interactions. For systems that are far apart, the first two terms in eq 14 should be negligible. The last term is small whenever $\eta^{(2)}/\eta \ll 1$, which is usually the case. The decisive factor is thus

$$\int f^{(2)}(\mathbf{r})\,\Delta v(\mathbf{r})\,\mathrm{d}\mathbf{r} \tag{16}$$

If this factor is negative when the ion approaches DCP, that is indicative of an attractive interaction.

Parts a and b of Figure 6 plot the dual descriptor for DCP···$Na^+$and DCP···F^-, respectively. Consistent with our expectations, the vicinity of Na^+ is mostly electron accepting and the vicinity of F^- is mostly electron donating. The greater delocalization of the dual descriptor onto F^- is consistent with the observation that in orbital-based population analysis schemes (e.g., natural population analysis), significant charge transfer from F^- to DCP is observed. (Very little charge transfer is observed in AIM, however, which is a density-based population analysis method.) The delocalization of the dual descriptor onto F^- is indicative of “extreme” polarization associated with pseudoelectron transfer from the fluorine into the region between DCP and F^-; this is a favorable (attractive) interaction.

As the nucleus of the ion moves toward DCP, $\Delta v(\mathbf{r}) = -Z/|\mathbf{r} - \mathbf{R}| + Z/|\mathbf{r} - \mathbf{R} - \mathrm{d}\mathbf{R}|$ is a dipole directed along the ion−molecule axis. According to eq 16, a favorable interaction will occur if a positive lobe of $f^{(2)}(\mathbf{r})$ is directed preferentially toward the ion. This explains the favorable polarization interaction with Na^+. The same analysis for interaction with F^- is inconclusive because there the dual descriptor resembles a dipole orthogonal to the ion−molecule axis. For F^-, the pseudoelectron transfer is decisive instead.

IV. Summary

The dual descriptor is a single reactivity indicator that predicts the regioselectivity of electrophilic and nucleophilic attack simultaneously. This is especially useful for ambiphilic molecules—molecules that are both electrophiles and nucleophiles—since it would ordinarily require two reactivity indicators ($\phi_{\mathrm{HOMO}}(\mathbf{r})$ and $\phi_{\mathrm{LUMO}}(\mathbf{r})$, or $f^-(\mathbf{r})$ and $f^+(\mathbf{r})$) to adequately describe these molecules’ reactivity. The dual descriptor is most appropriate for predicting reactions where there is significant electron transfer, and the predictions of the dual descriptor are most easily interpreted in those cases. When electron transfer is not significant, but the mutual polarization of the reagents is, the dual descriptor can still be useful because it contributes to a key term that determines the favorability of the polarization interaction. To obtain a complete picture of chemical reactivity, however, it is important to consider electrostatic interactions also. In cases where the dual descriptor and the electrostatic potential give opposing predictions of chemical reactivity, a detailed quantitative analysis is needed to determine which effect is dominant. Electrostatics is always dominant when the reagents are far apart, but electron-transfer effects (which are largely captured by the dual descriptor) often dominate when the reagents come close together.

Support for the preceding conclusions came from considering three, very different, systems.

1. The Al(I) center in **1** was identified as a pseudodual site because it serves as an electron donor (to Boron) but it is not the ultimate acceptor of electrons; instead it is a conduit through which electrons flow to the more electronegative atoms on ring. See section III.A for more details.

2. In 2,6-dichloropyridine, nucleophilic attack occurs on C4, and electrophilic attack occurs on C3 (or, equivalently, C5). A more nuanced understanding can be obtained by considering the electrostatic potential, which reveals that very hard electrophiles (where electrostatics dominates) tend to attack the nitrogen atom, rather than C3/C5, in accord with experimental findings. See section III.B for more details.

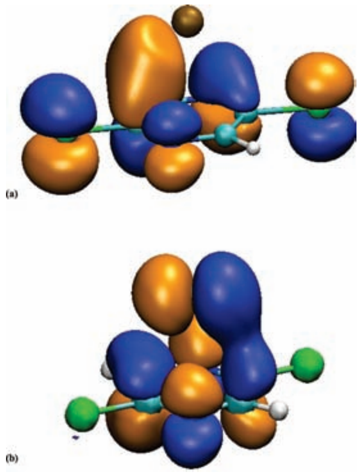


Figure 6. Dual descriptor for the ion−molecule complex of 2,5-dichloropyrazine with (a) Na^+ and (b) F^-. Blue: the isosurface $f^{(2)}(\mathbf{r}) = -0.004$ au, indicating regions that readily donate electrons. Orange: the isosurface $f^{(2)}(\mathbf{r}) = 0.004$ au, indicating regions that readily accept electrons.

3. In ion−molecule complexes of Na^+ or F^- with 2,5-dichloropyrazine (DCP), electrostatic forces are responsible for the fact that F^- binds more tightly than Na^+. In both ions, however, polarization interactions make a large (and, for Na^+, decisive) contribution to the stability of the complex. In DCP···F^-, the dual descriptor is delocalized over both fragments, indicative of incipient electron transfer. In DCP···Na^+ the dual descriptor has a form that is perhaps more typical for long-range polarization; in this case it is the sign of the factor in eq 16 that suggests a favorable polarization interaction.

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Appendix

We first define our notation. The *k*th-order constant-*N* and constant-μ response functions are written as

$$\begin{aligned}\chi_N^{(k)}(\mathbf{r}, \mathbf{r}') &= \left(\frac{\delta^k \rho(\mathbf{r})}{\delta v(\mathbf{r}_1)\,\delta v(\mathbf{r}_2)\cdots\delta v(\mathbf{r}_k)}\right)_N \\ \chi_\mu^{(k)}(\mathbf{r}, \mathbf{r}') &= \left(\frac{\delta^k \rho(\mathbf{r})}{\delta v(\mathbf{r}_1)\,\delta v(\mathbf{r}_2)\cdots\delta v(\mathbf{r}_k)}\right)_\mu\end{aligned} \tag{17}$$

In the following, we will economize our notation by always omitting superscripts (1) (e.g., $\chi_N^{(1)}(\mathbf{r}_1,\mathbf{r}_2) \rightarrow \chi_N(\mathbf{r}_1,\mathbf{r}_2)$). The global (hyper)softnesses are defined as[55]

$$S^{(k)} = \left(\frac{\partial^k N}{\partial \mu^k}\right)_{v(\mathbf{r})} \tag{18}$$

where $S = \eta^{-1}$ is the conventional global softness[107] and the first global hypersoftness is[55]

$$S^{(2)} = -\frac{\eta^{(2)}}{\eta^3} \tag{19}$$

The local (hyper)softnesses are defined by[55]

$$s^{(k)}(\mathbf{r}) = \left(\frac{\partial^k \rho(\mathbf{r})}{\partial \mu^k}\right)_{v(\mathbf{r})} = -\left(\frac{\delta S^{(k-1)}}{\delta v(\mathbf{r})}\right)_{\mu} \tag{20}$$

The conventional local softness is $s(\mathbf{r}) = Sf(\mathbf{r})$.[107] The (hyper)softness kernels are defined as[55]

$$s^{(k)}(\mathbf{r}_1,\mathbf{r}_2) = -\left(\frac{\delta s^{(k-1)}(\mathbf{r}_1)}{\delta v(\mathbf{r}_2)}\right)_{\mu} \tag{21}$$

with the conventional softness kernel defined as $s(\mathbf{r}_1,\mathbf{r}_2) = -\chi_{\mu}(\mathbf{r}_1,\mathbf{r}_2)$.[104] With this notation, the Berkowitz–Parr identity can be rewritten as[104]

$$\chi_N(\mathbf{r}_1,\mathbf{r}_2) = \chi_{\mu}(\mathbf{r}_1,\mathbf{r}_2) + s(\mathbf{r}_1)\, s(\mathbf{r}_2) S^{-1} \tag{22}$$

Using the same identity for functional derivatives that is used to derive the Berkowitz–Parr identity,[108]

$$\left(\frac{\delta \chi_N(\mathbf{r}_1,\mathbf{r}_2)}{\delta v(\mathbf{r}_3)}\right)_N = \left(\frac{\delta \chi_N(\mathbf{r}_1,\mathbf{r}_2)}{\delta v(\mathbf{r}_3)}\right)_{\mu} + \left(\frac{\partial \chi_N(\mathbf{r}_1,\mathbf{r}_2)}{\partial \mu}\right)_{v(\mathbf{r})} \left(\frac{\delta \mu}{\delta v(\mathbf{r}_3)}\right)_N \tag{23}$$

We want to write this equation in a form where the derivatives on the left-hand-side depend only on $v(\mathbf{r})$ and N, while the derivatives on the right-hand side depend only on $v(\mathbf{r})$ and μ. First, insert $f(\mathbf{r}_3) = s(\mathbf{r}_3)S^{-1}$ and the Berkowitz–Parr identity, eq 22, into eq 23, obtaining

$$\begin{aligned}\left(\frac{\delta \chi_N(\mathbf{r}_1,\mathbf{r}_2)}{\delta v(\mathbf{r}_3)}\right)_N &= \left(\frac{\delta \chi_{\mu}(\mathbf{r}_1,\mathbf{r}_2)}{\delta v(\mathbf{r}_3)}\right)_{\mu} + \left(\frac{\delta s(\mathbf{r}_1)\, s(\mathbf{r}_2) S^{-1}}{\delta v(\mathbf{r}_3)}\right)_{\mu} \\ &\quad + \frac{s(\mathbf{r}_3)}{S}\left(\left(\frac{\partial \chi_{\mu}(\mathbf{r}_1,\mathbf{r}_2)}{\partial \mu}\right)_{v(\mathbf{r})} + \left(\frac{\partial s(\mathbf{r}_1)\, s(\mathbf{r}_2) S^{-1}}{\partial \mu}\right)_{v(\mathbf{r})}\right)\end{aligned} \tag{24}$$

$$\begin{aligned}\chi_N^{(2)}(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3) &= \chi_{\mu}^{(2)}(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3) - S^{-1}(s^{(2)}(\mathbf{r}_1,\mathbf{r}_2)\, s(\mathbf{r}_3) \\ &\quad + s^{(2)}(\mathbf{r}_1,\mathbf{r}_3)\, s(\mathbf{r}_2) + s^{(2)}(\mathbf{r}_2,\mathbf{r}_3)\, s(\mathbf{r}_1)) \\ &\quad + S^{-2}(s^{(2)}(\mathbf{r}_1)\, s(\mathbf{r}_2)\, s(\mathbf{r}_3) + s(\mathbf{r}_1)\, s^{(2)}(\mathbf{r}_2)\, s(\mathbf{r}_3) \\ &\quad + s(\mathbf{r}_1)\, s(\mathbf{r}_2)\, s^{(2)}(\mathbf{r}_3)) - S^{-3}S^{(2)} s(\mathbf{r}_1)\, s(\mathbf{r}_2)\, s(\mathbf{r}_3)\end{aligned} \tag{25}$$

Using $s(\mathbf{r}) = \eta^{-1}f(\mathbf{r})$, eq 8, and eq 19 gives

$$\begin{aligned}\chi_N^{(2)}(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3) &= \chi_{\mu}^{(2)}(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3) - (s^{(2)}(\mathbf{r}_1,\mathbf{r}_2)\, f(\mathbf{r}_3) \\ &\quad + s^{(2)}(\mathbf{r}_1,\mathbf{r}_3)\, f(\mathbf{r}_2) + s^{(2)}(\mathbf{r}_2,\mathbf{r}_3)\, f(\mathbf{r}_1)) \\ &\quad + \eta^{-2}(f^{(2)}(\mathbf{r}_1)\, f(\mathbf{r}_2)\, f(\mathbf{r}_3) + f(\mathbf{r}_1)\, f^{(2)}(\mathbf{r}_2)\, f(\mathbf{r}_3) \\ &\quad + f(\mathbf{r}_1)\, f(\mathbf{r}_2)\, f^{(2)}(\mathbf{r}_3)) + 4\eta^{-3}\eta^{(2)} f(\mathbf{r}_1)\, f(\mathbf{r}_2)\, f(\mathbf{r}_3)\end{aligned} \tag{26}$$

The terms on the two lines contain derivatives of $\chi_{\mu}(\mathbf{r},\mathbf{r}')$, so they are also nearsighted. The term on the last line is usually much smaller than the term containing the dual descriptor because usually $|\eta^{(2)}/\eta| \ll 1$. So the dominant term in the long-range second-order density response depends upon the dual descriptor.

Equation 26 helps explain a paradox from ref 40. In the molecular-orbital theory of Diels–Alder reactions, the decisive term is related to long-range molecular polarization. In the corresponding interpretation based on density-functional theory, the decisive term depends on the dual descriptor, which seemingly pertains to electron transfer, rather than polarization. Since the net electron transfer between the diene and the dienophile in Diels–Alder reaction is sometimes small, the "polarization" picture seems more reasonable than the "electron-transfer" picture. Fortunately, the dual descriptor makes a decisive contribution to the long-range portion of the polarization; therefore one can interpret Diels–Alder reactions using DFT without invoking electron transfer.

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