

## Conceptual Density-Functional Theory for General Chemical Reactions, Including Those That Are Neither Charge- nor Frontier-Orbital-Controlled. 1. Theory and Derivation of a General-Purpose Reactivity Indicator

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**Abstract:** A new general-purpose reactivity indicator is derived. Unlike existing indicators, this indicator can describe the reactivity of molecules that lie between the electrostatic (or charge) control and electron-transfer (or frontier-orbital) control paradigms. Depending on the parameters in the indicator, it describes electrostatic control (where the electrostatic potential is the appropriate indicator), electron-transfer control (where the Fukui function's potential is the appropriate indicator), and intermediate cases (where linear combinations of the electrostatic potential and the Fukui function's potential are appropriate indicators). Our analysis gives some insight into the origins of the local hard/soft–acid/base principle. The “minimum Fukui function” rule for hard reagents also emerges naturally from our analysis: if (1) a reaction is strongly electrostatically controlled and (2) there are two sites that are equally favorable from an electrostatic standpoint, then the most reactive of the electrostatically equivalent sites is the site with the smallest Fukui function. An analogous electrostatic potential rule for soft reagents is also introduced: if (1) a reaction is strongly electron-transfer-controlled and (2) there are two sites where the Fukui function's potential are equivalent, then the most reactive of the Fukui-equivalent sites will be the one with greatest electrostatic potential (for electrophilic attack on a nucleophile) or smallest electrostatic potential (for nucleophilic attack on an electrophile).

### I. Introduction

Many qualitative and semiquantitative methods have been developed for predicting how and whether a reaction will take place. Perhaps the most popular method of prediction is frontier molecular orbital theory (FMO).<sup>1</sup> This method uses the shapes and symmetries of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) to indicate whether a reaction will occur. If the

HOMO of the electron donor and the LUMO of the electron acceptor have the same shape and phase, then electron transfer from the HOMO of the first molecule to the LUMO of the second can occur, often forming a bond between the reagents. Kenichi Fukui and Roald Hoffmann shared the 1981 Nobel Prize in chemistry for precisely this: showing that the shape<sup>2–5</sup> (Fukui et al.) and phase<sup>6–10</sup> (Hoffmann et al.) of the HOMO and LUMO orbitals are indicative of chemical reactivity.

A primary limitation of the frontier molecular orbital theory approach is that it presupposes the validity of the orbital model and thus fails to incorporate the effects of electron correlation or orbital relaxation. This motivated the

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definition of a “Fukui function” in the context of density-functional theory (DFT), a function that encapsulates the essence of FMO<sup>11–14</sup> but, in principle, includes both electron correlation<sup>11,15</sup> and orbital relaxation.<sup>12,16</sup> The Fukui function from below,  $f^-(r)$ , is defined as the change in density that one observes when one goes from  $N$  to  $N - 1$  electrons (with the nuclear positions fixed); in simple molecular orbital theory, this would give precisely the density of the HOMO orbital. A similar function,  $f^+(r)$ , can be defined as the difference between the electron densities of the  $N + 1$  and  $N$  electron systems; this is analogous to the LUMO orbital density.

The Fukui function is labeled according to whether the system is acting as an electron acceptor or an electron donor.  $f^+(r)$  says where an electron (received from a perfect electron donor) will add to the molecule.  $f^-(r)$  says where an electron given to an electron acceptor (a perfect one, if you like) will come from. Electron donors tend to attack the molecule where  $f^+(r)$  is large because this is where the molecule “wants electrons.” Electron acceptors tend to attack the molecule where  $f^-(r)$  is large because this is where the molecule has electrons that it is “willing to give up.”<sup>11,13</sup> This reasoning, of course, is only valid when the transition state lies early enough on the reaction path for the reacting fragments to still resemble the isolated reagents.<sup>13</sup> The fact that conceptual DFT tends to work even when the transition state is not especially early may be attributed to the empirically observed utility of “hill-climbing” methods for locating transition states.<sup>17,18</sup>

In 1989, Dewar<sup>19</sup> listed several nucleophiles where FMO failed to describe electrophilic aromatic substitution, including isoquinoline, 10-hydroxy-10,9-borazarophenanthrene, and 10-methyl-10,9-borazarophenanthrene. We attempted to explain the reactivity of these molecules using the tools of conceptual DFT, but it does not seem possible to describe the reactivity of these molecules without considering *both* electron-transfer effects *and* electrostatic interactions. This spurred us to develop a new reactivity indicator that combines the Fukui function and the electrostatic potential. The indicator we developed provides a general-purpose model for chemical reactivity. The purpose of this paper is to derive and discuss this reactivity indicator. The second paper in this series will discuss the application of the indicator to Dewar’s problematic molecules.<sup>20</sup>

Before deriving the general-purpose reactivity indicator, we present a brief overview of FMO and conceptual DFT in section II. The new reactivity indicator is then derived, step-by-step, in section III. Our model provides a unified picture of chemical reactivity and elucidates, among other things, the “minimum Fukui function rule.”<sup>21,22</sup> Section IV summarizes our findings.

## II. Theoretical Background

**A. Overview of Frontier Molecular Orbital Theory.** FMO arises as a simplification of the treatment proposed by Coulson and Longuet-Higgins,<sup>23–26</sup> who used second-order perturbation theory to describe the interactions between the filled molecular orbitals of one reactant and the empty

molecular orbitals of the other. The interaction energy between the fragments is then

$$E_{AB}^{\text{FMO}} = 2 \left( \sum_{i \in O_A} \sum_{b \in U_B} \frac{|\langle \phi_i^{(A)} | \hat{h}_{AB} | \phi_b^{(B)} \rangle|^2}{\epsilon_i^{(A)} - \epsilon_b^{(B)}} + \sum_{j \in O_B} \sum_{a \in U_A} \frac{|\langle \phi_j^{(B)} | \hat{h}_{AB} | \phi_a^{(A)} \rangle|^2}{\epsilon_j^{(B)} - \epsilon_a^{(A)}} \right) \quad (1)$$

Here,  $\{\phi_i^{(A)}\}$  and  $\{\phi_j^{(B)}\}$  are the molecular orbitals of fragments A and B;  $\{\epsilon_i^{(A)}\}$  and  $\{\epsilon_j^{(B)}\}$  are their respective orbital energies;  $O_A$  and  $O_B$  are the sets of occupied molecular orbitals, and  $U_A$  and  $U_B$  are the sets of unoccupied (virtual) orbitals in fragments A and B, respectively.  $\hat{h}_{AB}$  denotes the one-electron Hamiltonian for the “supermolecule” (A + B; e.g., the Fock operator in Hartree–Fock or the Kohn–Sham Hamiltonian in DFT). The numerators in eq 1 are analogous to resonance integrals in Hückel theory.

In general, the most important terms in eq 1 are those with the smallest denominator. This suggests ignoring terms that do not depend on the frontier molecular orbitals, so that

$$E_{AB}^{\text{FMO}} \approx 2 \left( \frac{|\langle \phi_{\text{HOMO}}^{(A)} | \hat{h}_{AB} | \phi_{\text{LUMO}}^{(B)} \rangle|^2}{\epsilon_{\text{HOMO}}^{(A)} - \epsilon_{\text{LUMO}}^{(B)}} + \frac{|\langle \phi_{\text{HOMO}}^{(B)} | \hat{h}_{AB} | \phi_{\text{LUMO}}^{(A)} \rangle|^2}{\epsilon_{\text{HOMO}}^{(B)} - \epsilon_{\text{LUMO}}^{(A)}} \right) \quad (2)$$

If A (the Lewis acid) is the electron acceptor and B (the Lewis base) is the electron donor, then we expect that  $\epsilon_{\text{LUMO}}^{(A)}$  is small and  $\epsilon_{\text{HOMO}}^{(B)}$  is large. By this argument, the second term in eq 2 should be larger than the first term. Neglecting the first term gives

$$E_{AB}^{\text{FMO}} \approx 2 \left( \frac{|\langle \phi_{\text{HOMO}}^{(B)} | \hat{h}_{AB} | \phi_{\text{LUMO}}^{(A)} \rangle|^2}{\epsilon_{\text{HOMO}}^{(B)} - \epsilon_{\text{LUMO}}^{(A)}} \right) \quad (3)$$

This equation is the essential basis for the frontier molecular orbital theory. It is only valid when the neglected terms in eq 1 (and especially the neglected first term in eq 2) are negligible.<sup>19</sup> The numerator of eq 3 is a sort of “generalized resonance integral”, and so, one can infer, by the usual arguments (e.g., from the justification of the Wolfsberg–Helmholz approximation<sup>27</sup>), that a large overlap between electron-donating and electron-accepting orbitals is favorable. This result can also be inferred from a Hölder inequality:

$$\begin{aligned} |\langle \phi_{\text{HOMO}}^{(B)} | \hat{h}_{AB} | \phi_{\text{LUMO}}^{(A)} \rangle|^2 &\leq \|\hat{h}_{AB}\|^2 \|\phi_{\text{HOMO}}^{(B)} \phi_{\text{LUMO}}^{(A)}\|^2 \\ &= \|\hat{h}_{AB}\|^2 \left\{ \int |\phi_{\text{HOMO}}^{(B)}(r)|^* \phi_{\text{LUMO}}^{(A)}(r) dr \right\}^2 \quad (4) \end{aligned}$$

**B. The Fukui Function.** As mentioned before, because the Fukui function contains similar information to the frontier molecular orbitals, it can be used to provide a DFT-based alternative to the standard rationalization of FMO theory. The Fukui function,  $f(r)$ , is defined as<sup>11–13</sup>

$$f(r) = \left[ \frac{\delta \mu}{\delta v(r)} \right]_N = \left[ \frac{\partial \rho(r)}{\partial N} \right]_v \quad (5)$$

Here,  $\mu$  is the electronic chemical potential (equal to minus

the electronegativity),  $v(r)$  is the “external” potential due to the atomic nuclei,  $\rho(r)$  is the electron density, and  $N$  is the number of electrons. The equality between the functional derivative of the chemical potential and the ordinary derivative of the electron density arises as a “Maxwell relation.”<sup>28</sup>

The slope of  $\rho(r)$  as a function of  $N$  has discontinuities,<sup>29–31</sup> and so, the derivative must be evaluated from above and below (and averaged if necessary). This results in a Fukui function appropriate for describing nucleophilic attack<sup>11</sup>

$$f^+(r) = \left[ \frac{\partial \rho(r)}{\partial N} \right]_{v(r)}^+ \quad (6)$$

and a Fukui function appropriate for describing electrophilic attack

$$f^-(r) = \left[ \frac{\partial \rho(r)}{\partial N} \right]_{v(r)}^- \quad (7)$$

If one writes the electron density as a function of the Kohn–Sham orbitals,  $\phi_i(r)$ , and orbital occupation numbers,  $n_i$ ,

$$\rho(r) = \sum_{i=1}^{\infty} n_i |\phi_i(r)|^2 \quad (8)$$

$$n_i = \begin{cases} 1 & i \leq \text{HOMO} \\ 0 & i \geq \text{LUMO} \end{cases} \quad (9)$$

then, from eqs 6 and 7, one has<sup>12,32</sup>

$$f^+(r) = |\phi_{\text{LUMO}}(r)|^2 + \sum_{i=1}^{\text{HOMO}} \left( \frac{\partial |\phi_i(r)|^2}{\partial N} \right)_{v(r)}^+ \quad (10)$$

$$f^-(r) = |\phi_{\text{HOMO}}(r)|^2 + \sum_{i=1}^{\text{HOMO}} \left( \frac{\partial |\phi_i(r)|^2}{\partial N} \right)_{v(r)}^- \quad (11)$$

The link to frontier molecular orbital theory is obtained by neglecting the orbital relaxation terms, so that

$$f^+(r) \approx |\phi_{\text{LUMO}}(r)|^2 \quad (12)$$

$$f^-(r) \approx |\phi_{\text{HOMO}}(r)|^2 \quad (13)$$

**C. Theoretical Description of Electrostatic and Electron-Transfer Effects.** We have not yet provided a mathematical reason, comparable to eq 3, for interpreting the Fukui function as a reactivity indicator. To do this, consider how the energy of a molecule changes in response to an attacking electrophile. The attacking electrophile will take electrons from the molecule ( $\Delta N_{\text{molecule}} < 0$ ). Additionally, the electrons that remain in the molecule will be perturbed by the presence of the reagent: that is, the electrons in the nucleophile will feel an additional external potential due to the electrons and nuclei of the electrophile. When these two effects are combined, the change in the total energy of the

molecule undergoing attack is

$$\begin{aligned} \Delta U = & \int \frac{\delta V_{nn}[v]}{\delta v(r)} \Delta v(r) \, dr + \left( \frac{\partial E}{\partial N} \right)_{v(r)}^- \Delta N \\ & + \int \left\{ \frac{\delta E_v[v;N]}{\delta v(r)} \right\}_N \Delta v(r) \, dr \\ & + \left\{ \int \left[ \frac{\partial}{\partial N} \left( \frac{\delta E_v[v;N]}{\delta v(r)} \right) \right]_{v(r)}^- \Delta v(r) \, dr \right\} \Delta N + \dots \end{aligned} \quad (14)$$

Here, we are using  $U$  to denote the potential energy surface for the atomic nuclei. Within the Born–Oppenheimer approximation,  $U = E + V_{nn}$ ; that is,  $U$  is sum of the electronic energy and the nuclear–nuclear repulsion energy.

The terms in eq 14 represent (a) the change in nuclear–nuclear repulsion energy, (b) the change in electronic energy due to electron transfer, (c) the change in electronic energy due to the change in external potential, and (d) the cross term linking electron transfer to changes in external potential. We will work within an exact formulation for the isolated system (e.g., the zero-temperature grand canonical ensemble<sup>29</sup>), so second- and higher-order derivatives with respect to the number of electrons vanish.<sup>29,30</sup> We are neglecting terms including higher-order responses to the external potential even though the first term (which models the polarization of the system by the approaching electrophile) might be important. Polarization effects are commonly neglected in the DFT-based approach to chemical reactivity. This is mostly because it is difficult to compute the polarizability kernel;<sup>33</sup> the success of DFT-based reactivity methods even when the polarization term is neglected suggests that the approximation in eq 14 is often sufficient for qualitative considerations. This success may be rationalized by noting that the dominant contribution to polarization arises from induced dipoles on the atomic centers, and the resulting interaction is short-ranged and weak<sup>34</sup> compared to the interaction from atomic charges. As such, the polarization contribution will ordinarily be an order of magnitude smaller than the energetic contributions from the molecular electrostatic potential, so it is often negligible for qualitative and semiquantitative purposes. Further evidence for this assertion comes from the broad (but not universal!) success of classical molecular dynamics that do not include polarization.

Subject to the approximations inherent in eq 14, the change in the energy of the nucleophile due to the approaching electrophile is

$$\begin{aligned} \Delta U_{\text{nucleophile}} = & (-I_{\text{nucleophile}}) \Delta N \\ & - \int \left( \sum_{\alpha \in \text{nucleophile}} [Z_{\alpha} \delta(r - R_{\alpha})] - \rho_{\text{nucleophile}}(r) \right. \\ & \left. - \Delta N f_{\text{nucleophile}}^-(r) \right) \Delta v(r) \, dr \end{aligned} \quad (15)$$

Here,  $I_{\text{nucleophile}}$  is the vertical ionization potential of the molecule,  $\{Z_{\alpha}\}$  and  $\{R_{\alpha}\}$  denote the nuclear charges and their positions, respectively, and the summation is over all of the atomic nuclei in the nucleophile. Because the first term in

eq 15 depends only on  $\Delta N$  and not on the position of the electrophile, the second term controls the regioselectivity of the reaction.

There is an exact model for  $\Delta v(r)$ , but it is not useful for computational purposes.<sup>35,36</sup> For reactants that are far apart, exchange and correlation between electrons on different subsystems should be negligible, so we can approximate  $\Delta v(r)$  with minus the electrostatic potential of the attacking reagent.<sup>35,36</sup> The resulting model for the change in external potential at the point  $r_p$  is

$$\begin{aligned}\Delta v(r_p) &\approx \\ & - \int \frac{\sum_{\beta \in \text{electrophile}} Z_{\beta} \delta(r - R_{\beta}) - [\rho_{\text{electrophile}}(r) + (-\Delta N) f_{\text{electrophile}}^{+}(r)]}{|r - r_p|} dr \\ & = -\Phi_{\text{electrophile}}(r_p) - \Delta N \int \frac{f_{\text{electrophile}}^{+}(r)}{|r - r_p|} dr\end{aligned}\quad (16)$$

The first term in the third line is the electrostatic potential of the isolated electrophile, and the second term is the correction to the electrostatic potential from electron transfer to the electrophile. In our model,  $\Delta N < 0$  is the change in the number of electrons on the nucleophilic substrate, so the change in electron number for the electrophilic reagent is  $-\Delta N$ , which is greater than zero. This sign convention anticipates the second paper of this series,<sup>20</sup> where we will use these results to describe where nucleophiles are most susceptible to electrophilic attack.

Just as the energy of the nucleophile is changed by the approaching electrophile, the energy of the electrophile is changed by the presence of the nucleophile. In analogy to eq 15, one has

$$\begin{aligned}\Delta U_{\text{electrophile}} &= (-A_{\text{electrophile}})(-\Delta N) \\ & - \int \left[ \sum_{\beta \in \text{electrophile}} Z_{\beta} \delta(r - R_{\beta}) - \rho_{\text{electrophile}}(r) \right. \\ & \quad \left. - (-\Delta N) f_{\text{electrophile}}^{+}(r) \right] \Delta v(r) dr\end{aligned}\quad (17)$$

Here, the change in external potential is due to the electrons and nuclei in the nucleophile. Again, we approximate the change in external potential with the negative electrostatic potential of the nucleophile as corrected for electron transfer

$$\begin{aligned}\Delta v(r_p) &\approx \\ & - \int \frac{\sum_{\alpha \in \text{nucleophile}} Z_{\alpha} \delta(r - R_{\alpha}) - [\rho_{\text{nucleophile}}(r) + \Delta N f_{\text{nucleophile}}^{-}(r)]}{|r - r_p|} dr \\ & = -\Phi_{\text{nucleophile}}(r_p) + \Delta N \int \frac{f_{\text{nucleophile}}^{-}(r)}{|r - r_p|} dr\end{aligned}\quad (18)$$

The replacement of  $\Delta N$  in eqs 15 and 16 with  $-\Delta N$  in eqs 17 and 18 is dictated by charge conservation: electrons are

transferred from the nucleophile to the electrophile. Equations 16 and 18 lead to the identification of the electrostatic potential

$$\Phi(r_p) = \int \frac{\sum_{\beta \in \text{electrophile}} Z_{\beta} \delta(r - R_{\beta}) - \rho(r)}{|r - r_p|} dr \quad (19)$$

and the Fukui potential

$$v^f(r_p) = \int \frac{f(r)}{|r - r_p|} dr \quad (20)$$

as key reactivity indicators. Clearly, the Fukui potential is only relevant in cases where electron transfer is important. The Fukui potential also plays a key role in the reactivity model proposed by Berkowitz.<sup>37</sup>

Combining eqs 15 and 17 and correcting for the double counting of interactions gives a model for the interaction energy between the nucleophilic substrate and the electrophilic reagent:

$$\begin{aligned}U_{\text{int}} &= (A_{\text{electrophile}} - I_{\text{nucleophile}}) \Delta N \\ & + \int \left( \sum_{\alpha \in \text{nucleophile}} Z_{\alpha} \delta(r - R_{\alpha}) - \rho_{\text{nucleophile}}(r) \right) \Phi_{\text{electrophile}}(r) dr \\ & + \Delta N \int [f_{\text{electrophile}}^{+}(r) \Phi_{\text{nucleophile}}(r) - f_{\text{nucleophile}}^{-}(r) \Phi_{\text{electrophile}}(r)] dr \\ & - (\Delta N)^2 \iint \frac{f_{\text{nucleophile}}^{-}(r) f_{\text{electrophile}}^{+}(r')}{|r - r'|} dr dr'\end{aligned}\quad (21)$$

The first term in this equation is a constant and does not affect site selectivity. The next term reflects the electrostatic interactions between electrophiles and nucleophiles: because the active sites of electrophiles are usually positively charged while the reactive sites of nucleophiles are usually negatively charged, this term is usually negative. That is, electrostatic effects are usually attractive. This is in marked contrast to the terms in the third line of eq 21. Because  $\Delta N < 0$ , if  $f_{\text{electrophile}}^{+}(r) > 0$  at the reactive site of the electrophile and the reactive site of the nucleophile is negatively charged [so that  $\Phi_{\text{nucleophile}}(r) < 0$ ], then the first term in the third line of eq 21 is usually positive. Similarly, the second term in the third line of eq 21 is usually positive because  $f_{\text{nucleophile}}^{-}(r) > 0$  at the active site of the nucleophile and the active site of the electrophile is usually positively charged [so that  $\Phi_{\text{electrophile}}(r) > 0$ ]. The third line of eq 21, then, reflects the fact that charge transfer from the nucleophile to the electrophile helps to equalize the charges of the reagents, which reduces the electrostatic attraction between them. The fourth line of eq 21 will generally be negative. The expression in the fourth line plays a key role in the theory of electron transfer proposed by Berkowitz.<sup>37</sup> Of all the terms in eq 21, this is the term that most closely resembles the results from frontier molecular orbital theory. In fact, an expression very similar to eq 4 can be derived:



$$\begin{aligned}
& \iint \frac{f_{\text{nucleophile}}^-(r) f_{\text{electrophile}}^+(r')}{|r - r'|} dr dr' \\
& \leq \left\| \frac{1}{|r - r'|} \right\| \left\| \int f_{\text{nucleophile}}^-(r) f_{\text{electrophile}}^+(r) dr \right\| \\
& \approx \left\| \frac{1}{|r - r'|} \right\| \left\| \int |\phi_{\text{HOMO}}^{(\text{B})}(r)|^2 |\phi_{\text{LUMO}}^{(\text{A})}(r)|^2 dr \right\| \\
& \leq \left\| \frac{1}{|r - r'|} \right\| \left\| \int [\phi_{\text{HOMO}}^{(\text{B})}(r)]^* \phi_{\text{LUMO}}^{(\text{A})}(r) dr \right\|^2 \\
& \leq \left\| \frac{1}{|r - r'|} \right\| \left\| \int |\phi_{\text{HOMO}}^{(\text{B})}(r)|^* \phi_{\text{LUMO}}^{(\text{A})}(r)| dr \right\|^2 \quad (22)
\end{aligned}$$

Reactants will approach each other in a way that minimizes the interaction energy. That is, the more negative the interaction energy, the stronger the attraction between reagents and the greater their susceptibility to reaction. Coulson and Longuet-Higgins used perturbation theory and molecular orbital theory to derive a formula for the interaction energy between two separated reagents; this led them to eq 1. Equation 21 is just a density-functional-theory-inspired reformulation of perturbation theory about the separated reagent limit. Reactivity indicators based on these formulas might be unreliable when the transition state occurs late in the reaction, because in those cases the molecular geometry in the transition state may not resemble the isolated reagents.

Some readers may find it surprising that the electrostatic potential enters into eq 21 in such a natural way. Traditionally, the electrostatic potential has not been considered a reactivity index associated with conceptual DFT.<sup>38</sup> However, it is evident from the preceding analysis that, whenever the change in the potential energy surface due to the external potential is addressed<sup>35</sup>

$$\int \left( \frac{\delta U}{\delta v(r)} \right)_N \delta v(r) dr \quad (23)$$

the electrostatic potential enters into conceptual DFT in a very natural way. Evaluating expressions like eq 23 requires evaluating the functional derivative of the nuclear–nuclear repulsion energy with respect to changes in the external potential. Evaluating that functional derivative is a nontrivial mathematical exercise; details can be found in Appendix A. This analysis helps provide a theoretical foundation for recent work relating “conventional” DFT-based reactivity indicators to the electrostatic potential.<sup>39,40</sup>

### III. A General-Purpose Model for Chemical Reactivity

**A. The Reactive Site Interaction Model.** In general, the regioselective preferences of a nucleophile undergoing electrophilic attack are preserved across a broad range of electrophilic partners. Because the specific identity of the electrophile is not critical, we can replace the electrophile with a “model perturbation”.<sup>14,35,41</sup> Presuming that the reactivity is dominated by the properties at the active site, we will represent the electrostatic potential of the electrophile as the electrostatic potential due to the charge on the reactive site

$$\Phi_{\text{electrophile}}(r) \approx \frac{q_{\text{electrophile}}^{(0)}}{|r - R_{\text{electrophile}}|} \quad (24)$$

and, similarly, replace the Fukui function with its “condensed” value<sup>42,43</sup>

$$\begin{aligned}
f_{\text{electrophile}}^+(r) & \approx f_{\text{electrophile}}^{(+)} \delta(r - R_{\text{electrophile}}) \\
& = (q_{\text{electrophile}}^{(0)} - q_{\text{electrophile}}^{(+)}) \delta(r - R_{\text{electrophile}}) \quad (25)
\end{aligned}$$

Here,  $q_{\text{electrophile}}^{(0)}$  and  $q_{\text{electrophile}}^{(+)}$  denote the effective charges on the reactive site of the electrophile and the electrophile with an additional electron, respectively. If the Fukui function is approximated by eq 25, then the equation for the Fukui potential becomes

$$v_{\text{electrophile}}^+(r) \approx \frac{f_{\text{electrophile}}^{(+)}}{|r - R_{\text{electrophile}}|} = \frac{q_{\text{electrophile}}^{(0)} - q_{\text{electrophile}}^{(+)}}{|r - R_{\text{electrophile}}|} \quad (26)$$

Models based on eqs 24–26 should be accurate for atomic cations (where  $q_{\text{electrophile}}^{(0)} = f_{\text{electrophile}}^{(+)} = 1$ ) and reasonable for molecular electrophiles, though in that case, it will be important that the “effective charge” and “effective condensed Fukui function” on the reactive site might not equal the atomic quantities but might instead represent a partial sum over several atoms in the vicinity of the reactive site. With that caveat, this model should be reasonably realistic whenever the reagents are very far apart, so that the overlaps between their electron distributions and Fukui functions are negligible. When these approximations are used, the interaction energy between a nucleophile and a model electrophile whose reactive site is (a) located at the point  $r_p$ , (b) has charge  $q_{\text{electrophile}}^{(0)}$ , and (c) has condensed Fukui function  $f_{\text{electrophile}}^{(+)}$  becomes

$$\begin{aligned}
U_{\text{int}}(r_p) & \approx (A_{\text{electrophile}} - I_{\text{nucleophile}}) \Delta N \\
& + (q_{\text{electrophile}}^{(0)} + \Delta N f_{\text{electrophile}}^{(+)}) \Phi_{\text{nucleophile}}(r_p) \\
& - \Delta N (q_{\text{electrophile}}^{(0)} + \Delta N f_{\text{electrophile}}^{(+)}) v_{\text{nucleophile}}^-(r_p) \quad (27)
\end{aligned}$$

This “single reactive site interaction model” is easily generalized to cases where multiple reactive sites need to be considered: simply sum over the effective charges and effective condensed Fukui functions<sup>42</sup> on all of the relevant sites

$$\begin{aligned}
U_{\text{int}} & \approx (A_{\text{electrophile}} - I_{\text{nucleophile}}) \Delta N \\
& + \sum_{\beta \in \text{electrophile}} \sum_{\alpha \in \text{nucleophile}} \frac{(q_{\beta}^{(0)} + \Delta N f_{\beta}^{(+)}) q_{\alpha}^{(0)}}{|R_{\alpha} - R_{\beta}|} \\
& - \Delta N \sum_{\beta \in \text{electrophile}} \sum_{\alpha \in \text{nucleophile}} \frac{(q_{\beta}^{(0)} + \Delta N f_{\beta}^{(+)}) f_{\alpha}^{(-)}}{|R_{\alpha} - R_{\beta}|} \quad (28)
\end{aligned}$$

Again, a smaller (more negative)  $U_{\text{int}}$  represents greater attraction between reagents and indicates greater reactivity.

Insofar as we are modeling the attacking reagent with a point charge, these expressions for  $U_{\text{int}}(r_p)$  are similar to the indicator of Brønsted–Lowry acidity introduced in ref 35, though the Taylor series expansion in that work includes

higher-order terms in the external potential and does not include the electron-transfer contribution. The present model is not restricted to charges of unit magnitude and, in that sense, is more like the single-interaction-site point-charge model that recently was used to elucidate the hard/soft–acid/base (HSAB) principle.<sup>44</sup> More generally, models resembling this one are commonly encountered when the so-called perturbative perspective on conceptual density-functional theory is utilized.<sup>14,33,35,41,43,45</sup> This sort of analysis, with its fundamental link to the Taylor series expansion to the energy and the use of “model perturbations” to define reactivity indicators, grew out of the work of De Proft, Liu, Nalewajski, Parr, and Senet, among others.<sup>28,46–50</sup>

**B. Deriving a General-Purpose Reactivity Indicator for Nucleophiles.** Equation 27 provides the basis for a general-purpose reactivity indicator for nucleophiles. Note, first of all, that the key parameter

$$\tilde{\kappa} \equiv q_{\text{electrophile}}^{(0)} + \Delta N f_{\text{electrophile}}^{(+)} \quad (29)$$

modulates the electrostatic and Fukui function contributions to the interaction energy. Insert the definition of  $\tilde{\kappa}$  into eq 27, and note that the first term in eq 27 does not depend on the position,  $r_p$ . One obtains

$$\tilde{\Xi}_{\Delta N \leq 0}^{\tilde{\kappa}}(r_p) \equiv \tilde{\kappa} [\Phi_{\text{nucleophile}}(r_p) - \Delta N v_{\text{nucleophile}}^-(r_p)] \quad (30)$$

which is a regioselectivity indicator for electrophilic attack. A nucleophile will be most reactive in places where  $\tilde{\Xi}_{\Delta N \leq 0}^{\tilde{\kappa}}(r_p)$  is small (most negative) because electrophilic attack at those sites is energetically favorable.

Equation 30 uses the reaction site interaction model to provide simple approximations to the complicated integral expressions in eq 21. But this is *too* simple. In particular, the reactive site interaction model is more accurate for some integrals than it is for others. The model typically underestimates the integrals because interactions between the asymptotic tails of the electron densities and the Fukui functions are neglected. Moreover, this error is largest for the integrals containing Fukui functions (which are concentrated on the periphery of the reagents). This implies that the reactive site interaction model is better at describing the interaction of the electrophile with the electrostatic potential (which contains the potential due to the electron density) than it is at describing the interaction of the electrophile with the Fukui potential. If we correct eq 30 for the errors associated with the reaction site interaction model, then we obtain an expression with the form

$$\tilde{\Xi}_{\Delta N \leq 0}^{\tilde{\kappa}}(r_p) \equiv (\tilde{\kappa} + \epsilon_p) \Phi_{\text{nucleophile}}(r_p) - (\tilde{\kappa} + \epsilon_p) \Delta N v_{\text{nucleophile}}^-(r_p) \quad (31)$$

Here,  $\epsilon_p$  corrects for the errors incurred by the reactive-site approximation for the electron density and  $\epsilon_f$  corrects for the error incurred by the reactive-site approximation for the Fukui function. According to the preceding arguments

$$\epsilon_f < \epsilon_p \quad (32)$$

Usually, both  $\epsilon_f$  and  $\epsilon_p$  are negative. Appendix B provides a full accounting of the error terms.

We cannot evaluate these error terms within the context of the reactive site interaction model. It is certainly true that the errors are small when the molecules are far apart and that the error “correction” terms dominate when the molecules are close together. When the molecules are in van der Waals contact, one suspects that the error terms make significant corrections to  $\tilde{\kappa}$ .

Our goal is to derive a *qualitative* indicator of chemical reactivity. Note that (i)  $\tilde{\kappa} \equiv q_{\text{electrophile}}^{(0)} + \Delta N f_{\text{electrophile}}^{(+)}$  has units of electric charge because the charge and the condensed Fukui function of the electrophile’s reactive site both have units of electric charge. (ii)  $\tilde{\kappa}$  is of order unity if one measures it in terms of the magnitude of charge on the electron,  $e$ . This is because  $e$  is the natural unit for expressing the charge and the condensed Fukui function of the electrophile’s reactive site. (iii) We can eliminate the unknown error terms by introducing a new scale of electric charge, with the new unit of charge defined by

$$1 = \frac{\epsilon_p - \epsilon_f}{2} \quad (33)$$

We then define

$$\kappa = \tilde{\kappa} + \epsilon_p - 1 \quad (34)$$

This definition “sets the zero” of a scale for  $\kappa$ . Specifically,  $\kappa = 0$  occurs when electrostatic and electron-transfer effects are perfectly balanced.

Using these relations, we can eliminate the unknown error terms from eq 31. This results in a general-purpose regioselectivity indicator for nucleophiles:

$$\Xi_{\Delta N \leq 0}^{\kappa}(r_p) \equiv (\kappa + 1) \Phi_{\text{nucleophile}}(r_p) - (\kappa - 1) \Delta N v_{\text{nucleophile}}^-(r_p) \quad (35)$$

There is another way to derive eq 35: starting with eq 31, choose the unit of energy and the zero of energy so that the unknown error terms are eliminated. (Notice, however, that the energy scale one defines depends on what position,  $r_p$ , in the molecule is being considered.)

Equation 35 is our general-purpose reactivity indicator. Because  $\Xi_{\Delta N \leq 0}^{\kappa}(r_p)$  is a qualitative measure of the interaction energy of the nucleophile with an electrophile at the point  $r_p$ , the nucleophile will be most reactive where  $\Xi_{\Delta N \leq 0}^{\kappa}(r_p)$  is most negative.

Equation 35 is the most conceptually transparent form for our indicator. However, for computational applications, we find it convenient to compute the indicator from the electrostatic potential of the nucleophile,  $\Phi_{\text{nucleophile}}^{(0)}(r)$ , and the electrostatic potential of the nucleophile with one electron removed,  $\Phi_{\text{nucleophile}}^{(-)}(r)$ :

$$\Xi_{\Delta N \leq 0}^{\kappa}(r_p) = [1 + \kappa + \Delta N(\kappa - 1)] \Phi_{\text{nucleophile}}^{(0)}(r_p) - \Delta N(\kappa - 1) \Phi_{\text{nucleophile}}^{(-)}(r_p) \quad (36)$$

When this expression is used, our reactivity indicator can be evaluated using any popular quantum chemistry package.

Remember that  $\Xi_{\Delta N \leq 0}^{\kappa}(r_p)$  models the interaction energy, so the nucleophile is most reactive where  $\Xi_{\Delta N \leq 0}^{\kappa}(r_p)$  has the smallest (most negative) values.

The key to deriving eq 36 is to note that the Fukui potential (and the Fukui function) can be computed from the electrostatic potentials of the nucleophile,  $\Phi_{\text{nucleophile}}^{(0)}(r)$  and the electrostatic potential of the nucleophile with one electron removed,  $\Phi_{\text{nucleophile}}^{(-)}(r)$ . Specifically,

$$\begin{aligned} v_{\text{nucleophile}}^{f-}(r) &\equiv \int \frac{f_{\text{nucleophile}}^{(-)}(r)}{|r - r_p|} dr \\ &= \int \frac{\rho_{\text{nucleophile}}^{(0)}(r) - \rho_{\text{nucleophile}}^{(-)}(r)}{|r - r_p|} dr \\ &= \Phi_{\text{nucleophile}}^{(-)}(r_p) - \Phi_{\text{nucleophile}}^{(0)}(r_p) \\ f_{\text{nucleophile}}^{(-)}(r) &= \frac{1}{4\pi} \nabla^2 [\Phi_{\text{nucleophile}}^{(0)}(r) - \Phi_{\text{nucleophile}}^{(-)}(r)] \quad (37) \end{aligned}$$

Equation 35 or, equivalently, eq 36 is our general-purpose reactivity model for nucleophiles. Because of the way we have accommodated the error terms in eq 31, this is only a qualitative model for reactivity. One could derive other models with qualitatively similar behavior but somewhat different functional forms. We selected this form because it has an appealing symmetry and because it is easy to interpret (using eq 35) and apply (using eq 36).

$\Xi_{\Delta N \leq 0}^{\kappa}(r_p)$  depends on two parameters,  $\Delta N$  (measuring the extent of electron donation) and  $\kappa$  (measuring the relative importance of electrostatic effects and electron-transfer effects).  $\kappa = 1$  corresponds to pure electrostatic control;  $\kappa = -1$  corresponds to pure electron-transfer (or Fukui-function) control.  $\kappa = 0$  corresponds to a perfect balance between electrostatic and electron-transfer control.

The change of units that accompanies the elimination of the error terms means that  $\kappa \neq \tilde{\kappa}$ . However, if the error terms are not too big,  $\kappa$  will be approximately proportional to  $\tilde{\kappa}$ . We denote this  $\kappa \approx \tilde{\kappa}$ . This insight gives us a working approximation for  $\kappa$  (cf. eq 29), namely,

$$\kappa \approx q_{\text{electrophile}}^{(0)} + \Delta N f_{\text{electrophile}}^{(+)} \quad (38)$$

When the charge on the electrophile is very large, we still expect to see electrostatically controlled reactivity. Similarly, when the charge on the electrophile's reactive site is small compared with the extent of electron transfer to the reactive site ( $q_{\text{electrophile}}^{(0)} \leq |\Delta N| f_{\text{electrophile}}^{(+)}$ ), the reaction is electron-transfer controlled.

Like  $\tilde{\kappa}$ ,  $\kappa$  has units of electric charge and has order of magnitude unity. Equation 38 is an approximate proportionality, and it is useful for elucidating how a nucleophile's reactivity depends on the charge and condensed Fukui function of an electrophile's reactive site. However, eq 38 is not a quantitative formula for  $\kappa$ . Determining the value of  $\kappa$  that is most appropriate for a given reaction is sensitive to (a) the inherent errors in the reactive site interaction model and (b) molecular polarization and other effects that are neglected in this analysis. However, eq 38 should be sufficient to indicate whether  $\kappa$  is "large and positive", "small

and positive", "almost zero", "small and negative, or "large and negative." Section III.F. contains a detailed discussion of each of these cases.

**C. A General-Purpose Reactivity Indicator for Electrophiles.** There is clearly an analogous indicator for electrophiles. Specifically, one has

$$\Xi_{\Delta N \geq 0}^{\kappa}(r_p) \equiv -(\kappa + 1) \Phi_{\text{electrophile}}(r_p) + \Delta N(\kappa - 1) v_{\text{electrophile}}^{f+}(r_p) \quad (39)$$

where the Fukui potential for the electrophile is given by

$$\begin{aligned} v_{\text{electrophile}}^{f+}(r) &\equiv \int \frac{f_{\text{electrophile}}^{+}(r)}{|r - r_p|} dr \\ &= \int \frac{\rho_{\text{electrophile}}^{(+)}(r) - \rho_{\text{electrophile}}^{(0)}(r)}{|r - r_p|} dr \\ &= \Phi_{\text{electrophile}}^{(0)}(r_p) - \Phi_{\text{electrophile}}^{(+)}(r_p) \\ f_{\text{electrophile}}^{+}(r) &= \frac{1}{4\pi} \nabla^2 [\Phi_{\text{electrophile}}^{(+)}(r) - \Phi_{\text{electrophile}}^{(0)}(r)] \quad (40) \end{aligned}$$

The appropriate values of  $\kappa$  are the same as before:  $\kappa \geq 1$  (electrostatic control),  $\kappa \leq -1$  (electron-transfer control), and  $-1 < \kappa < 1$  (intermediate). Corresponding to eq 38, we can say that  $\kappa$  is approximately proportional to  $-q_{\text{nucleophile}}^{(0)} - \Delta N f_{\text{nucleophile}}^{(-)}$ . Here,  $q_{\text{nucleophile}}^{(0)}$  is the charge on the reactive site of the nucleophile and is typically negative.  $f_{\text{nucleophile}}^{(-)}$  is the condensed Fukui function from below at the reactive site of the nucleophile. It would be shocking to observe a negative value for  $f_{\text{nucleophile}}^{(-)}$ .<sup>43,51-55</sup>

**D. The Condensed General-Purpose Reactivity Indices.** Because local reactivity indicators vary on a point-by-point basis, it is often convenient to "condense" their values to atomic sites.<sup>42,43</sup> A condensed indicator related to  $\Xi_{\Delta N}^{\kappa}(r_p)$  follows directly from the fitting of the electrostatic potential to atomic charges. Specifically, the electrostatic potential can be expanded in an asymptotic series of atomic multipoles. Truncating the multipole expansion after the monopoles yields an expression for the electrostatic potential in terms of atomic charges

$$\begin{aligned} \Phi_{\text{nucleophile}}^{(0)}(r) &\sim \sum_{\alpha \in \text{nucleophile}} \frac{q_{\text{nucleophile},\alpha}^{(0)}}{|r - R_{\alpha}|} \\ \Phi_{\text{nucleophile}}^{(-)}(r) &\sim \sum_{\alpha \in \text{nucleophile}} \frac{q_{\text{nucleophile},\alpha}^{(-)}}{|r - R_{\alpha}|} \quad (41) \end{aligned}$$

These expressions are not very accurate close to the molecule. For example, these expressions do not reproduce the correct singularity at the atomic nuclei. However, the relevant values of a local reactivity indicator occur far from the molecule, on a "reactivity surface" that represents how closely two reagents can approach each other and still retain their separate identities. Not only do expressions like eq 41 suffice for this purpose, condensed expressions are actually preferable because they "average over" the irrelevant fine structure of the spatially varying indicators.<sup>43</sup>

“Condensed” expressions for the Fukui potential are easily constructed from eqs 37, 40, and 41

$$v_{\text{nucleophile}}^{f^-}(r) \sim \sum_{\alpha \in \text{nucleophile}} \frac{f_{\text{nucleophile},\alpha}^-}{|r - R_\alpha|}$$

$$f_{\text{nucleophile},\alpha}^- = q_{\text{nucleophile},\alpha}^{(-)} - q_{\text{nucleophile},\alpha}^{(0)} \quad (42)$$

$$v_{\text{electrophile}}^{f^+}(r) \sim \sum_{\alpha \in \text{electrophile}} \frac{f_{\text{electrophile},\alpha}^+}{|r - R_\alpha|}$$

$$f_{\text{electrophile},\alpha}^+ = q_{\text{electrophile},\alpha}^{(0)} - q_{\text{electrophile},\alpha}^{(+)} \quad (43)$$

$f_\alpha^\pm$  are called the condensed Fukui functions.<sup>42</sup> We can now write asymptotic expressions for the reactivity indicators proposed in this paper. For nucleophiles,

$$\Xi_{\Delta N \leq 0}^\kappa(r_p) \sim \sum_{\alpha \in \text{nucleophile}} \frac{\Xi_{\Delta N \leq 0,\alpha}^\kappa}{|r - R_\alpha|}$$

$$\Xi_{\Delta N \leq 0,\alpha}^\kappa = (\kappa + 1)q_{\text{nucleophile},\alpha}^{(0)} - \Delta N(\kappa - 1)f_{\text{nucleophile},\alpha}^-$$

$$= [1 + \kappa + \Delta N(\kappa - 1)]q_{\text{nucleophile},\alpha}^{(0)} - \Delta N(\kappa - 1)q_{\text{nucleophile},\alpha}^{(-)} \quad (44)$$

For electrophiles,

$$\Xi_{\Delta N \geq 0}^\kappa(r_p) \sim \sum_{\alpha \in \text{electrophile}} \frac{\Xi_{\Delta N \geq 0,\alpha}^\kappa}{|r - R_\alpha|}$$

$$\Xi_{\Delta N \geq 0,\alpha}^\kappa = -(\kappa + 1)q_{\text{electrophile},\alpha}^{(0)} + \Delta N(\kappa - 1)f_{\text{electrophile},\alpha}^+$$

$$= [\Delta N(\kappa - 1) - \kappa - 1]q_{\text{electrophile},\alpha}^{(0)} - \Delta N(\kappa - 1)q_{\text{electrophile},\alpha}^{(+)} \quad (45)$$

Nucleophiles will be susceptible to electrophilic attack at the atomic sites where  $\Xi_{\Delta N \leq 0,\alpha}^\kappa$  is small, and ideally negative. Electrophiles will be susceptible to nucleophilic attack at the atomic sites where  $\Xi_{\Delta N \geq 0,\alpha}^\kappa$  is small.

**E. Single-Parameter Variants of the General-Purpose Reactivity Indicator.** Because our general-purpose reactivity indicator,  $\Xi_{\Delta N}^\kappa(r)$ , depends on two parameters ( $\kappa$  and  $\Delta N$ ), it is sometimes difficult to visualize the wealth of information it contains. In some contexts, then, it would be convenient to use a variant of  $\Xi_{\Delta N}^\kappa(r)$  that depended only on the amount of electron transfer, because that is easily computed using electronegativity equalization schemes. Because the appropriate value of  $\kappa$  varies depending on the amount of electron transfer, one could introduce a one-parameter model by setting

$$\kappa \approx \begin{cases} 1 + 2(\Delta N) & \Delta N \leq 0 \\ 1 - 2(\Delta N) & \Delta N \geq 0 \end{cases} \quad (46)$$

This model correctly predicts electrostatic control when  $\Delta N \approx 0$  and electron-transfer control when  $\Delta N \approx \pm 1$ . Using eq 46, one obtains one-parameter models for the reactivity of nucleophiles

$$\Xi_{\Delta N \leq 0}^{1+2\Delta N}(r_p) = 2[(1 + \Delta N) \Phi_{\text{nucleophile}}(r_p) - (\Delta N)^2 v_{\text{nucleophile}}^f(r_p)] \quad (47)$$

and electrophiles

$$\Xi_{\Delta N \geq 0}^{1-2\Delta N}(r_p) \equiv 2[(\Delta N - 1) \Phi_{\text{electrophile}}(r_p) - (\Delta N)^2 v_{\text{electrophile}}^f(r_p)] \quad (48)$$

While these single-parameter models are simpler than their two-parameter counterparts, our preliminary investigations indicate that, in molecules with multiple reactive sites, the single-parameter models sometimes fail to identify one or more reactive sites. For this reason, we will focus on the more general two-parameter models.

#### F. General-Purpose Reactivity Indicators: Discussion.

We now discuss the interpretation of the general-purpose reactivity indicators for nucleophiles

$$\Xi_{\Delta N \leq 0}^\kappa(r) \equiv (\kappa + 1) \Phi_{\text{nucleophile}}(r) - \Delta N(\kappa - 1) v_{\text{nucleophile}}^f(r) \quad (49)$$

and electrophiles

$$\Xi_{\Delta N \geq 0}^\kappa(r) \equiv -(\kappa + 1) \Phi_{\text{electrophile}}(r) + \Delta N(\kappa - 1) v_{\text{electrophile}}^f(r) \quad (50)$$

These indicators are designed to reproduce the qualitative features of the molecular interaction energy expression that we derived in section II.C, namely,

$$U_{\text{int}} = (A_{\text{electrophile}} - I_{\text{nucleophile}})\Delta N$$

$$+ \int [\sum_{\alpha \in \text{nucleophile}} Z_\alpha \delta(r - R_\alpha) - \rho_{\text{nucleophile}}(r)] \Phi_{\text{electrophile}}(r) dr$$

$$+ \Delta N \int [f_{\text{electrophile}}^+(r) \Phi_{\text{nucleophile}}(r) - f_{\text{nucleophile}}^-(r) \Phi_{\text{electrophile}}(r)] dr$$

$$- (\Delta N)^2 \iint \frac{f_{\text{nucleophile}}^-(r) f_{\text{electrophile}}^+(r')}{|r - r'|} dr dr' \quad (51)$$

Negative values of the interaction energy,  $U_{\text{int}}$ , are associated with favorable interactions between the electrophile and the nucleophile. Similarly, molecules will be most highly reactive where  $\Xi_{\Delta N}^\kappa(r)$  is the smallest.

In accord with a suggestion by Langenaeker and co-workers,<sup>56</sup> each of our reactivity indicators is a linear combination of an appropriate reactivity index for hard–hard interactions (the electrostatic potential) and an appropriate reactivity index for soft–soft interactions (the Fukui function). The relative importance of these two contributions is controlled by the extent of charge transfer and the charge on the reactive site of the attacking reagent, as it should be. These are the key ingredients that make  $\Xi_{\Delta N}^\kappa(r_p)$  a true general-purpose reactivity indicator: it can model the extreme cases of electrostatic and electron-transfer control, but it can also model the “in-between” cases. We will now explore each of these cases in more detail. In the interest of specificity and brevity, the following discussion is focused on the reactivity of nucleophiles. The results for electrophiles are broadly similar.



**Case 1: Electrostatically Controlled Reactions;  $\kappa \geq 1$ .** Electrostatically controlled (also called charge-controlled) reactions are typified by the following: (a) The reagents have large charges [so  $q_{\text{electrophile}}^{(0)} \gg 0$  and  $\Phi_{\text{nucleophile}}(r_p) \ll 0$ ]. (b) Reactivity does not necessarily occur in places where the Fukui functions are large. ( $f_{\text{electrophile}}^{(+)}$  may not be very big.) (c) The charge transfer between reagents is minimal ( $\Delta N \approx 0$ ). Under these conditions,  $\kappa$  is greater than, or approximately equal to, 1. We call the case  $\kappa = 1$  “pure electrostatic control” and the case  $\kappa > 1$  “strong electrostatic control.”

**Case 1A: Pure Electrostatic Control;  $\kappa = 1$ .** When  $\kappa = 1$

$$\Xi_{\Delta N \leq 0}^{\kappa=1}(r_p) = 2\Phi_{\text{nucleophile}}(r_p) \quad (52)$$

Thus, for purely electrostatically controlled reactions, the appropriate reactivity indicator is the electrostatic potential. Furthermore, using the condensed version of the indicator

$$\Xi_{\Delta N \leq 0, \alpha}^{\kappa=1} = 2q_{\text{nucleophile}, \alpha}^{(0)} \quad (53)$$

we infer that, in the limit of pure electrostatic control, nucleophiles react at the most negatively charged atomic site. (For electrophiles, the most reactive sites are those where the electrostatic potential/atomic charge is most positive.)

**Case 1B: Strong Electrostatic Control;  $\kappa > 1$ .** When  $\kappa > 1$ , the second term in eq 49 is usually very small because  $\kappa - 1 < \kappa + 1$  and because the extent of electron transfer is very small ( $\Delta N \approx 0$ ). For this reason, there can be no doubt that the most appropriate reactivity indicator for electrostatically controlled reactions is the electrostatic potential.<sup>22,57</sup>

What happens if there are two sites that are equivalent from an electrostatic perspective? Because  $-\Delta N(\kappa - 1) > 0$  whenever  $\kappa > 1$ ,  $\Xi_{\Delta N \leq 0}^{\kappa > 1}$  will be smallest in those places where the Fukui potential is the smallest. Insofar as the Fukui potential is smallest in places where the Fukui function is also small, this suggests that, *for reactions that are strongly electrostatically controlled, if there are two reactive sites with the same electrostatic favorability, then the site with minimum Fukui function is the most favorable.* This rule can also be derived from the condensed version of our indicator. In that case, *for electrophilic attack occurring under conditions associated with strong electrostatic control of chemical reactivity, a nucleophile possessing two sites with equal negative charge will be most reactive at the site with the smallest condensed Fukui function.* These rules might be called “minimum Fukui function tie-breaking rules” because they indicate that, if a reaction is strongly electrostatically controlled and there are two sites with equivalent electrostatic properties (and also other properties, notably including polarizability), then minimizing the Fukui function serves as a “tie breaker” between the two equivalent sites.

In 1995, Li and Evans proposed that hard–hard interactions occur where the Fukui function is small.<sup>21</sup> This counterintuitive result started a debate in the literature.<sup>22,58–60</sup> Our analysis establishes that it is true that sometimes having a small value for the Fukui function is favorable for

reactivity, but the conditions under which this rule is valid are rather limited. There might be cases where the minimum Fukui function tie breaker is decisive in determining the reactivity. However, the second term in eq 49 is usually *much smaller* than the first term, so the minimum Fukui function tie breaker will *only* be operative when two hard reagents interact (so that  $\Delta N \approx 0$ ), the electrophile is highly charged (so that  $q_{\text{electrophile}}^{(0)}$ , and thus  $\kappa$ , is large), and the nucleophile has two reactive sites with *very similar* electrostatic profiles. Unless the possible reaction sites are very similar electrostatically, the weak dependence of  $\Xi_{\Delta N \leq 0}^{\kappa > 1}$  on the Fukui function will not be decisive.

Even when it appears that the tie-breaking rule should apply, it may not. Because the dependence on the Fukui function is so weak, some of the interactions that were neglected in our model might be more important for determining the nucleophile’s reactivity. The most important of these neglected interactions is probably the polarizability. Consider the Berkowitz–Parr formula for the polarizability kernel<sup>33,61</sup>

$$\left( \frac{\delta E}{\delta v(r) \delta v(r')} \right)_N = \left( \frac{\delta E}{\delta v(r) \delta v(r')} \right)_\mu + \left( \frac{\partial N}{\partial \mu} \right)_{v(r)} f(r) f(r') \quad (54)$$

or the approximate formula for the polarizability kernel based on the Kohn–Sham noninteracting reference system<sup>33,62</sup>

$$\begin{aligned} \left( \frac{\delta E}{\delta v(r) \delta v(r')} \right)_N &\approx \sum_i \sum_{j \neq i} \frac{n_j - n_i}{\epsilon_j - \epsilon_i} \phi_i^*(r) \phi_j(r) \phi_j^*(r') \phi_i(r') \\ &\approx \frac{\begin{bmatrix} -\phi_{\text{HOMO}}^*(r) \phi_{\text{LUMO}}(r) \phi_{\text{LUMO}}^*(r') \phi_{\text{HOMO}}(r') \\ -\phi_{\text{LUMO}}^*(r) \phi_{\text{HOMO}}(r) \phi_{\text{HOMO}}^*(r') \phi_{\text{LUMO}}(r') \end{bmatrix}}{\epsilon_{\text{HOMO}} - \epsilon_{\text{LUMO}}} \quad (55) \end{aligned}$$

From these formulas, it is clear that a molecule tends to be most polarizable where the Fukui function (eq 54) and the frontier orbitals (eq 55) have a large amplitude. Given that strong electrostatic control will only occur for highly charged electrophiles, the second-order response to the change in external potential might not be especially small. Consequently, polarization effects may well cancel out, or even reverse, the predictions that would be obtained by naïvely applying the minimum Fukui function tie breaker.

The idea that the minimum Fukui function might correspond to the most reactive site goes against conventional wisdom, but it can be simply explained using the fundamental equation for the interaction energy, eq 51. Note that (i) the first line of this equation is a constant and does not influence regioselectivity. (ii) The second line of eq 51 models the electrostatic attraction between the electrophile and the nucleophile. If we are in a “tie-breaking” situation, this term is the same for electrophilic attack at both reactive sites. Thus, although the electrostatic interaction in the second line of this equation makes the biggest contribution to the interaction energy, it does not determine the regioselectivity. (iii) Recall from our discussion of eq 51 that both terms on the third line are positive. (iv) The first term on the third line of eq 51 does not distinguish between electrostatically equivalent sites on the nucleophile. (v) The term on the fourth

line of eq 51 is negligible. If we are in a strongly electrostatically controlled regime, the extent of electron transfer is small, and so, the  $(\Delta N)^2$  term is entirely negligible. (The term on the fourth line might be important if a “second tie breaker” was needed, though.)

The remaining term in eq 51 must determine the regioselectivity. This term—the second term on the third line of eq 51—can be rewritten as

$$-\Delta N \int f_{\text{nucleophile}}^-(r) \Phi_{\text{electrophile}}(r) dr \quad (56)$$

Equation 56 models how electron transfer quenches the electrostatic attraction between the nucleophile and the electrophile. The quenching arises because, after the nucleophile donates electrons to the electrophile, the electron density on the nucleophile decreases by  $\Delta N f_{\text{nucleophile}}^-(r)$ . Because the reactive sites of the nucleophile are less negatively charged after the electron transfer, the electrostatic attraction between the nucleophile and the electrophile is weaker after electron transfer than it was before. If electron transfer quenches the electrostatic attraction at one interaction site more than the other [ $f_{\text{nucleophile}}^-(r_1) > f_{\text{nucleophile}}^-(r_2)$ ], then the second interaction site—the one with “minimum Fukui function”—will be the most favorable reactive site.

It should be stressed, again, that *the minimum Fukui function rule is a “tie-breaking” rule; it is not a general-purpose reactivity rule.* The minimum Fukui function rule applies only when (1) the reaction is a strongly electrostatically controlled reaction (the term in the fourth line of eq 51 must be negligible!); (2) multiple reactive sites are equivalent electrostatically (the first term in eq 51 and the first term on the third line in eq 51 must fail to distinguish between the reactive sites.); (3) the Fukui-function term (the second term on the third line in eq 51) is more important than the effects, like polarization, that are neglected by our model.

A minimum Fukui function tie breaker is also operative in strongly electrostatically controlled nucleophilic attacks on electrophiles. In that case, it is the first term on the third line in eq 51 that determines the regioselectivity.

**Case 2: Electron-Transfer-Controlled Reactions;**  $\kappa \leq -1$ . Electron-transfer-controlled (also called Fukui-function-controlled and frontier-orbital-controlled) reactions are typified by the following: (a) The reactive sites have small charges (so  $q_{\text{electrophile}}^{(0)} \approx 0$  and  $\Phi_{\text{nucleophile}}(r_p) \approx 0$ ). (b) Reactivity occurs where the Fukui functions are large ( $f_{\text{electrophile}}^{(+)} \gg 0$ ). (c) Electron transfer between reagents is significant ( $\Delta N \approx -1$ ). Under these conditions,  $\kappa$  is less than, or approximately equal to,  $-1$ . We call the case  $\kappa = -1$  “pure electron-transfer control” and the case  $\kappa < -1$  “strong electron-transfer control.”

**Case 2A: Pure Electron-Transfer Control;  $\kappa = -1$ .** When  $\kappa = -1$

$$\Xi_{\Delta N \leq 0}^{\kappa=-1}(r_p) = 2\Delta N v_{\text{nucleophile}}^-(r_p) \quad (57)$$

Thus, for pure electron-transfer-controlled reactions, the appropriate reactivity indicator is the Fukui function’s potential. Because  $\Delta N < 0$ , the preferred reactive site is the location where the Fukui potential is the largest. Because

the Fukui potential is usually large in the same places that the Fukui function is large, electron-transfer-controlled reactions tend to occur where the Fukui function is large.

For the condensed version of the general-purpose reactivity indicator

$$\Xi_{\Delta N \leq 0, \alpha}^{\kappa=-1} = 2\Delta N f_{\text{nucleophile}, \alpha}^- \quad (58)$$

On the basis of this, we infer that, for pure electron-transfer control, the atomic site with the largest condensed Fukui function is the most reactive. The situation for electrophiles is essentially the same, but in that case, it is the Fukui function from above,  $f_{\text{electrophile}, \alpha}^+$ , that is relevant.

**Case 2B: Strong Electron-Transfer Control;  $\kappa < -1$ .** When  $\kappa < -1$ , the magnitude of the first term in eq 49 is usually much smaller than the second term because  $|\kappa - 1| > |\kappa + 1|$  and the nucleophile is not highly charged in electron-transfer-controlled reactions ( $q_{\text{nucleophile}, \alpha}^{(0)} \approx 0$ ). For this reason, there can be no doubt that the most appropriate reactivity indicator for electron-transfer-controlled reactions is the Fukui potential or, alternatively, the Fukui function.<sup>22,57</sup>

What happens if there are two sites that have equivalent values of the Fukui potential? Because  $\kappa + 1 < 0$  whenever  $\kappa < -1$ ,  $\Xi_{\Delta N \leq 0}^{\kappa < -1}$  will be smallest in those places where the electrostatic potential,  $\Phi_{\text{nucleophile}}(r_p)$ , is the largest. That is, reactivity will be favored at the more positive (or less negative) reactive sites. This counterintuitive electrostatic potential tie breaker is the analogue of the minimum Fukui function tie breaker for strongly electron-transfer-controlled reactions.

For nucleophiles, the “electrostatic potential tie-breaking rule” states that, *if an electrophilic attack reaction on a nucleophile is strongly electron-transfer-controlled and if there are two reactive sites with the same Fukui potential, then the site with the greatest electrostatic potential is the most favorable.* This principle can be restated in terms of condensed reactivity indicators: *for electrophilic attack occurring under conditions associated with strong electron-transfer control of the chemical reactivity, a nucleophile possessing two sites with equal condensed Fukui functions will be the most reactive at the site with the greatest charge.*

The analogous tie-breaking rule for electrophiles is, *if a nucleophilic attack reaction on an electrophile is strongly electron-transfer-controlled and if there are two reactive sites with the same Fukui potential, then the site with the smallest electrostatic potential is the most favorable.* The condensed version of this rule is, *for nucleophilic attack occurring under conditions associated with strong electron-transfer control of the chemical reactivity, an electrophile possessing two sites with equal condensed Fukui functions will be the most reactive at the site with the least charge.*

Just as we did for the minimum Fukui function tie breaker, we can elucidate the origins of the electrostatic potential tie breaker by studying the fundamental equation for the interaction energy, eq 51. Note that (i) the first line of this equation is a constant and does not influence regioselectivity. (ii) The fourth line of this equation models electron transfer from the nucleophile to the electrophile. Although this term usually dominates the regioselectivity, when we are in a “tie-

breaking” situation, the Fukui potential of the nucleophile is the same at both reactive sites. Consequently, this term does not determine the regioselectivity. (iii) Because the nucleophile’s Fukui potential is similar at the two reactive sites, the second term on the third line does not contribute to the regioselectivity preference. (iv) Because we are in the strong electron-transfer-control limit, neither the electrophile nor the nucleophile are highly charged. The second line of eq 51 models electrostatic effects, but if magnitudes of the atomic charges on the electrophile and the atomic charges on the nucleophile are both small, the mutual attraction between these charges

$$E_{\text{int}}^{\text{electrostatic}} \approx \sum_{\alpha \in \text{nucleophile}} \sum_{\beta \in \text{electrophile}} \frac{q_{\text{nucleophile},\alpha} q_{\text{electrophile},\beta}}{|R_{\alpha} - R_{\beta}|} \quad (59)$$

should be very small.

The remaining term in eq 51

$$\Delta N \int f_{\text{electrophile}}^{+}(r) \Phi_{\text{nucleophile}}(r) dr \quad (60)$$

must determine the regioselectivity. As electrons move from the nucleophile to the electrophile, the electron density on the electrophile increases by  $-\Delta N f_{\text{electrophile}}^{+}(r)$ . This causes the atomic charges on the electrophile to become less positive (or more negative) and decreases the electrostatic attraction between the nucleophile and the electrophile. (Because the electrophile was not highly charged to begin with, it is even conceivable that, after electron transfer, some key sites on the electrophile might be negatively charged. This corresponds to the extreme case where the electron transfer is so dramatic that the polarity of the nucleophile–electrophile bond is reversed.) Given a choice between two reactive sites with  $\Phi_{\text{nucleophile}}(r_1) > \Phi_{\text{nucleophile}}(r_2)$ , the most favorable site will be the first site, because this site is associated with a more favorable (or at least a less unfavorable) electrostatic interaction with the electrophile.

**Case 3: Joint Electrostatic and Electron-Transfer Control,  $-1 < \kappa < 1$ .** When  $\kappa$  is between  $-1$  and  $+1$ , a nucleophile will be most reactive at places where the electrostatic potential is negative or the Fukui potential is big.

When  $\kappa$  is close to  $+1$  or the extent of electron transfer is small ( $\Delta N \approx 0$ ), reactivity preferences are predominately determined by the electrostatic potential. However, when two sites have similar electrostatic potentials, the most reactive site will be the site with the *largest* value of the Fukui potential. This should be contrasted with the extreme case of strong electrostatic control ( $\kappa > 1$ ), where the site with the smallest value of the Fukui potential was the most favorable.

When  $\kappa$  is close to  $-1$  and the extent of electron transfer is large ( $\Delta N \approx -1$ ), reactivity preferences are predominately determined by the Fukui function. However, when two sites have similar Fukui functions, the site with the minimum electrostatic potential will be favored. This should be contrasted with the extreme case of strong electron-transfer control ( $\kappa < -1$ ), where the site with maximum electrostatic potential would be favored.

In the intermediate regime, where  $\kappa \approx 0$ , the importance of electrostatic effects and electron-transfer effects are nearly balanced. In such cases, a reactive site that is negatively charged and has a reasonably positive value for the Fukui function might be favored over an uncharged site with a larger Fukui function. Similarly, such a site might be favored over an even more negatively charged site if that site was associated with a negligible value for the Fukui function.

Joint electrostatic and electron-transfer control seems to be one of the most common situations in chemical reactivity. For example, one might expect that the protonation of aminoethanol,  $(\text{H}_2\text{N})\text{H}_2\text{CCH}_2\text{OH}$ , would be strongly electrostatically controlled: the proton is the prototypical hard acid,<sup>63</sup> and aminoethanol is not an especially soft base. It is observed that the electrostatic potential around the oxygen atom and that around the nitrogen atom are about the same.<sup>41</sup> Assuming strong electrostatic control, one would then infer that protonation occurs on the oxygen atom, because this is the site with minimum Fukui function. This is not the case; protonation occurs on the nitrogen atom, where the Fukui function is the largest.<sup>41</sup> Thus, even in cases where strong electrostatic control might be expected, one frequently observes joint electrostatic and electron-transfer control.

It is interesting to notice what happens if one neglects the error-correction terms in eq 31 and returns to the oversimplified reactivity indicator in eq 30. In that model,  $\tilde{\kappa} > 0$  corresponds to strong electrostatic control and  $\tilde{\kappa} < 0$  corresponds to strong electron-transfer control of the reactivity. This shows that, in a single reactive site interaction model, the possibility of joint electrostatic and electron-transfer control of the reactivity arises *because* the point-charge representation of the electrophile provides a more accurate approximation to the electrostatic effects (involving the electrostatic potential of the nucleophile) than it does to the electron-transfer effects (involving the Fukui potential of the nucleophile). If this was not the case, then eq 32 would not be valid. If this equation was not valid, then every reaction would be either strongly electrostatically controlled or strongly electron-transfer-controlled and a simple indicator like  $\tilde{\epsilon}_{\Delta N \leq 0}^{\tilde{\kappa}}(r_p)$  (cf. eq 31) would be qualitatively correct. However, joint electrostatic and electron-transfer control is commonly observed, while situations that require the minimum-Fukui function and electrostatic potential tie-breaker rules are uncommon. This observation provides experimental evidence for the validity of eq 32 and strongly supports the error analysis in Appendix B.

**G. Implications for the Local HSAB Principle.** Our analysis provides a measure of support for the local hard/soft–acid/base principle.<sup>44b,64–67</sup> The local hard/soft–acid/base principle indicates that ambidentate ligands react with soft reagents in locations where the local softness is large and hard reagents in places where the local softness is small. [The local softness is just the global softness,  $S$ , times the Fukui function,  $s(r) = Sf(r)$ .] Our analysis indicates that soft reagents ( $\kappa \approx -1$ ) should react with the molecule in the places where the Fukui function (and thus the local softness) is the largest. For hard reagents, the Fukui function is not an important indicator, and reactions could occur where the Fukui function is small. Hard reagents might also react with



the molecule in places where the Fukui function is large, however, because large values of the Fukui function are neither favorable nor unfavorable in electrostatically controlled reactions. The (probably extremely rare) exception is strongly electrostatic-controlled ( $\kappa > 1$ ) reactions of molecules that have multiple electrostatically favorable sites. In that case, a small value of the Fukui function (and thus the local softness) would be preferred over a large value.

The overall picture is entirely consistent with the work of Klopman:<sup>57</sup> electrostatic effects [ $\Phi(r_p)$  is the appropriate reactivity indicator] are typically dominant in reactions between hard reagents (where charge transfer is minimal); electron-transfer effects [ $f^-(r_p)$  is the appropriate reactivity indicator] are typically dominant in reactions between soft reagents (where substantial charge transfer occurs). For the intermediate cases, both effects are important.

#### IV. Recapitulation

It seems desirable to review what we have accomplished. Starting from the Taylor expansion for the potential energy surface of interacting electrophiles and nucleophiles (eq 21), we developed a “reactive site interaction model” based on the assumption that the interaction between the electrophile and the nucleophile is dominated by the interaction between their active sites. This led to a simplified indicator for the regioselectivity of the nucleophile (eq 27). This model was then subjected to a detailed error analysis and parametrized to obtain our final indicators: eq 35 (for the regioselectivity of nucleophiles) and eq 39 (for the regioselectivity of electrophiles). These expressions could then be condensed into indicators for the reactivity of different atoms in the molecule, giving eq 44 (for nucleophiles) and eq 45 (for electrophiles).

All of our reactivity indicators represent models for the interaction energies between the electrophile and the nucleophile; because of this, highly reactive sites are associated with negative values of the reactivity indicator, which we denote  $\Xi_{\Delta N}^\kappa$ . This model interaction energy clearly depends on two parameters. The first parameter,  $\Delta N$ , is the amount of electron transfer.  $\Delta N$  could be computed from the chemical potential and the hardnesses of the reagents<sup>68</sup> or, alternatively, on the basis of a quantum mechanical calculation of the product state (when the product of the chemical reaction is known). The second parameter,  $\kappa$ , quantifies whether the reaction is electrostatically controlled ( $\kappa \geq 1$ ), electron-transfer-controlled ( $\kappa \leq -1$ ), or somewhere in between ( $-1 < \kappa < 1$ ). The relative values of  $\kappa$  for different reagents can be compared using the approximate proportionalities

$$\kappa_{\Delta N \leq 0} \approx q_{\text{electrophile}}^{(0)} + \Delta N f_{\text{electrophile}}^{(+)} \quad (61)$$

$$\kappa_{\Delta N \geq 0} \approx -(q_{\text{nucleophile}}^{(0)} + \Delta N f_{\text{nucleophile}}^{(-)}) \quad (62)$$

For highly charged electrophiles and small amounts of electron transfer,  $\kappa \approx 1$  (electrostatic control). For weakly charged nucleophiles and significant electron transfer,  $\kappa \approx -1$ .

In most cases, the  $\kappa \approx 1; |\Delta N| \approx 1$  case (electrostatic control and large amounts of electron transfer) is chemically irrelevant unless electrostatic effects are very, very strong. (This case could be important, for example, when the electrophile being reduced is a metal cation in a high oxidation state.) Similarly, the  $\kappa \approx -1; \Delta N \approx 0$  case (electron-transfer control and negligible amounts of electron transfer) is chemically irrelevant unless electrostatic effects are weak. The  $\kappa \approx 1; \Delta N \approx 0$  and  $\kappa \approx -1; |\Delta N| \approx 1$  cases are very important limiting cases; they are associated with “classic” electrostatic and electron-transfer control, respectively. Most chemical reactions fall between those extremes; in these “jointly electrostatically and electron-transfer-controlled” reactions, the present indicator is preferable to existing approaches.

Using this reactivity indicator, we were able to gain some insight into appropriate indicators for different types of reactions. In the strong electrostatic control limit,  $\kappa > 1$ , it is observed that, given two sites with similar electrostatic potential, the reactive site with the smallest Fukui function is favored. Similarly, in the strong electron-transfer-control limit,  $\kappa < 1$ , it is observed that, given two sites with similar Fukui potentials, the reactive site with the greatest electrostatic potential (if the molecule is a nucleophile) or the least electrostatic potential (if the molecule is an electrophile) is most reactive. Both of these results are counterintuitive, and it is reassuring that, in the cases of greatest chemical relevance, the electrostatic potential is the dominant indicator for electrostatically controlled reactions and the condensed Fukui function is the dominant indicator for electron-transfer-controlled reactions. When the reactivity is between these two extremes, the most reactive site will be determined by a balance between the most favorable electrostatic potential and the most favorable Fukui potential, as one would expect.

When applying this model, the key assumptions that were made during its derivation are important: (i) the reactive site interaction model, that is, we assumed that the attacking reagent can be modeled as a point charge with a specified condensed Fukui function, and (ii) neglect of the polarization and other terms from higher-order derivatives with respect to the external potential.

The first assumption is required for any reactivity indicator. Because we are seeking a qualitative reactivity indicator, it is imperative that our model depend only on the coarsest details of the attacking reagent. This is in keeping with experimental evidence: most molecules react at only one or two places, regardless of the choice of reagent. The “details” of the reagents cannot be very important for determining the reactivity of the molecule that is attacked.<sup>41</sup>

The second assumption is merely pragmatic. We hope to incorporate polarization effects in our future work, but it is difficult to concoct a simple atom-condensed reactivity indicator that depends on a two-point quantity like the polarizability kernel. In addition, we believe that the most useful reactivity indicators are those that are easily evaluated using the output of standard quantum chemistry programs. The present reactivity indicator is easily computed from the atomic charges, which is a standard feature in quantum chemistry codes. In contrast, we do not know any simple



way to extract a condensed polarizability kernel from the output file of a quantum chemistry program.

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## Appendix A. Derivation of the Electrostatic Potential Contribution

The key formula is the expression for the nuclear–nuclear repulsion energy in ref 35

$$V_{nn}[v] = \frac{1}{32\pi^2} \int \int_{r \neq r'} \frac{[\nabla_r^2 v(r)][\nabla_{r'}^2 v(r')]}{|r - r'|} dr dr' \quad (63)$$

We can derive  $\delta V_{nn}[v]/\delta v(r)$  by finding the coefficient of  $\delta v(r)$  in the expression  $V_{nn}[v + \delta v] - V_{nn}[v]$ .

$$\begin{aligned} V_{nn}[v + \delta v] - V_{nn}[v] &= \frac{1}{32\pi^2} \left[ \int \int_{r \neq r'} \frac{\nabla_r^2 [v(r) + \delta v(r)] \nabla_{r'}^2 [v(r') + \delta v(r')]}{|r - r'|} dr dr' \right. \\ &\quad \left. - \int \int_{r \neq r'} \frac{\nabla_r^2 v(r) \nabla_{r'}^2 v(r')}{|r - r'|} dr dr' \right] \\ &= \left\{ \frac{1}{32\pi^2} \left[ \int \int_{r \neq r'} \frac{\nabla_r^2 \delta v(r) \nabla_{r'}^2 v(r')}{|r - r'|} dr dr' \right. \right. \\ &\quad \left. \left. + \int \int_{r \neq r'} \frac{\nabla_r^2 v(r) \nabla_{r'}^2 \delta v(r')}{|r - r'|} dr dr' \right] \right\} \\ &\quad + \left[ \frac{1}{32\pi^2} \int \int_{r \neq r'} \frac{\nabla_r^2 \delta v(r) \nabla_{r'}^2 \delta v(r')}{|r - r'|} dr dr' \right] \quad (64) \end{aligned}$$

The first term (in braces) represents the electrostatic interaction between the change in the external potential and the pre-existing charge density. The second term (in brackets) represents the self-repulsion energy of the perturbation. In an application such as ours, this term is neglected because it is already included in the energy expression for the attacking reagent. (If we included this term, we would make a “double-counting” error.) In any event, the term in brackets is second-order in the perturbing potential and will not contribute to the first functional derivative. Neglecting this term and noting that the two integrals in the braces have identical values, we can simplify eq 64 to

$$V_{nn}[v + \delta v] - V_{nn}[v] = \frac{1}{16\pi^2} \left( \int \int_{r \neq r'} \frac{\nabla_r^2 \delta v(r) \nabla_{r'}^2 v(r')}{|r - r'|} dr dr' \right) \quad (65)$$

This equation is simplified by writing the functional variation as a nested integration

$$\delta_v[V_{nn}, \delta v] = \frac{1}{16\pi^2} \int \nabla_{r'}^2 v(r') \left( \int \frac{\nabla_r^2 \delta v(r)}{|r - r'|} dr \right) dr' \quad (66)$$

and then simplifying the inner integral using Green’s theorem

$$\begin{aligned} \int \int \int \frac{1}{|r - r'|} [\nabla_r^2 \delta v(r)] dr &= \int \int \int \left( \nabla_r^2 \frac{1}{|r - r'|} \right) \delta v(r) dr \\ &\quad + \int \int \frac{1}{|r - r'|} [\nabla_r \delta v(r)] \cdot n da - \int \int \delta v(r) \left( \nabla_r \frac{1}{|r - r'|} \right) \cdot n da \quad (67) \end{aligned}$$

Our system is defined over all space, so in eq 67 we choose the surface to be a sphere infinitely far from the origin. We assume that the change in charge density associated with the change in external potential,  $\delta q(r) = -1/4\pi \nabla_r^2 \delta v(r)$ , is relatively localized, so that we can use the asymptotic form  $\delta v(r) \sim (\langle \delta q \rangle / r)$ . With this assumption, the surface integrals give

$$\begin{aligned} \lim_{r \rightarrow \infty} \int \int \frac{1}{|r - r'|} [\nabla_r \delta v(r)] \cdot n r^2 d\Omega &= \lim_{r \rightarrow \infty} \left[ \frac{1}{r} \frac{\partial \langle \delta q \rangle}{\partial r} \right] (4\pi r^2) = 0 \\ \lim_{r \rightarrow \infty} \int \int \delta v(r) \left( \nabla_r \frac{1}{|r - r'|} \right) \cdot n da &= \lim_{r \rightarrow \infty} \left[ \frac{\langle \delta q \rangle}{r} \frac{\partial}{\partial r} \left( \frac{1}{r} \right) \right] (4\pi r^2) = 0 \quad (68) \end{aligned}$$

Equation 68 shows that the surface terms vanish if  $\delta v(r)$  falls off to zero at infinity at least as fast as  $r^{-1}$ . We simplify the volume integral in eq 67 using Poisson’s equation for a point charge, obtaining

$$\begin{aligned} \int \int \int \left( \nabla_r^2 \frac{1}{|r - r'|} \right) \delta v(r) dr &= \int \int \int [-4\pi \delta(r - r')] \delta v(r) dr \\ &= -4\pi \delta v(r') \quad (69) \end{aligned}$$

Substitute eqs 68 and 69 into eq 67; then, substitute that result into eq 65 to obtain

$$V_{nn}[v + \delta v] - V_{nn}[v] = \frac{-1}{4\pi} \left[ \int \delta v(r') \nabla_{r'}^2 v(r') dr' \right] \quad (70)$$

The functional derivative is then

$$\begin{aligned} \frac{\delta V_{nn}[v]}{\delta v(r)} &= \frac{-1}{4\pi} \nabla_r^2 v(r) \\ &= -\rho_{nuc}(r) \quad (71) \end{aligned}$$

where  $-\rho_{nuc}(r) = -\sum_{\alpha} Z_{\alpha} \delta(r - R_{\alpha})$  is  $-1$  times the nuclear charge density.

It is now easy to see how the electrostatic potential arises as a reactivity indicator in density-functional theory. Consider the change in total energy due to adding a small point charge,  $q$ , at the point  $r_p$ :

$$\begin{aligned} \Delta(E + V_{nn}) &= \int \left[ \left( \frac{\delta E}{\delta v(r)} \right)_N + \frac{\delta V_{nn}}{\delta v(r)} \right] \frac{q}{|r - r_p|} dr \\ &= q \int \frac{\rho(r) - \sum_{\alpha} Z_{\alpha} \delta(r - R_{\alpha})}{|r - r_p|} dr \\ &= -q\Phi(r_p) \quad (72) \end{aligned}$$

## Appendix B. Error Analysis for the Reactive Site Interaction Model

This appendix performs an error analysis for the single reactive site interaction approximation to eq 21. The errors

incurred by replacing the integrals in eq 21 with the point charge representations in eq 27 are conveniently summarized using the following expressions:

$$-\epsilon_{(i)}\Phi_{\text{nucleophile}}(r_p) \equiv \int \left[ \sum_{\beta \in \text{electrophile}} Z_{\beta} \delta(r - R_{\beta}) - \rho_{\text{electrophile}}(r) - q_{\text{electrophile}}^{(0)} \delta(r - r_p) \right] \Phi_{\text{nucleophile}}(r) dr \quad (73)$$

$$\epsilon_{(ii)}\Phi_{\text{nucleophile}}(r_p) \equiv [f_{\text{electrophile}}^{+}(r) - f_{\text{electrophile}}^{(+)} \delta(r - r_p)] \Phi_{\text{nucleophile}}(r) dr \quad (74)$$

$$-\epsilon_{(iii)}v_{\text{nucleophile}}^{f-}(r_p) \equiv \int \left[ \sum_{\beta \in \text{electrophile}} Z_{\beta} \delta(r - R_{\beta}) - \rho_{\text{electrophile}}(r) - q_{\text{electrophile}}^{(0)} \delta(r - r_p) \right] v_{\text{nucleophile}}^{f-}(r) dr \quad (75)$$

$$\epsilon_{(iv)}v_{\text{nucleophile}}^{f-}(r_p) \equiv \int [f_{\text{electrophile}}^{+}(r) - f_{\text{electrophile}}^{(+)} \delta(r - r_p)] v_{\text{nucleophile}}^{f-}(r) dr \quad (76)$$

We now rationalize these forms. It is important to recognize that each of these integrals is really a Coulomb integral associated with the attractive forces that electrons feel toward nuclei and the repulsive forces they feel toward other electrons. For example, eq 74 could be rewritten as

$$\epsilon_{(ii)}\Phi_{\text{nucleophile}}(r_p) \equiv \int \int \frac{[f_{\text{electrophile}}^{+}(r) - f_{\text{electrophile}}^{(+)} \delta(r - r_p)] [\sum_{\alpha \in \text{nucleophile}} Z_{\alpha} \delta(r' - R_{\alpha}) - \rho_{\text{nucleophile}}(r')]}{|r - r'|} dr dr' \quad (77)$$

In an expression like this, it seems reasonable to assume that the largest error is associated with the approximation to the electron–electron repulsion-type term

$$-\int \int \frac{f_{\text{electrophile}}^{+}(r) \rho_{\text{nucleophile}}(r')}{|r - r'|} dr dr' \approx -\int \int \frac{f_{\text{electrophile}}^{+} \delta(r - r_p) \rho_{\text{nucleophile}}(r')}{|r - r'|} dr dr' \quad (78)$$

instead of with the approximation to the electron–nuclear attraction-type term

$$\int \int \frac{f_{\text{electrophile}}^{+}(r) [\sum_{\alpha \in \text{nucleophile}} Z_{\alpha} \delta(r' - R_{\alpha})]}{|r - r'|} dr dr' \approx \int \int \frac{f_{\text{electrophile}}^{+} \delta(r - r_p) [\sum_{\alpha \in \text{nucleophile}} Z_{\alpha} \delta(r' - R_{\alpha})]}{|r - r'|} dr dr' \quad (79)$$

Because the integrands in eq 78 are very large when  $r$  and  $r'$  are close together, the point charge approximation does not provide a good representation for the interaction between the asymptotic tails of  $\rho_{\text{nucleophile}}(r)$  and  $f_{\text{electrophile}}^{+}(r)$ . This suggests that (1) the left-hand side of eq 78 is less than the right-hand side and (2) the error in eq 78 is significantly bigger than the error in eq 79. Extending this argument to the other integrals in eqs 73–76, we see the following:

(a) In general, the left-hand side in eqs 73 and 76 should be positive. This implies that, in general,  $\epsilon_{(i)} > 0$  and  $\epsilon_{(iv)} > 0$ .

(b) In general, the left-hand side in eqs 74 and 75 should be negative. This implies that, in general,  $\epsilon_{(ii)} > 0$  and  $\epsilon_{(iii)} > 0$ .

The sign convention in eqs 73–76 is based on these observations. Recall that the electrostatic potential of a nucleophile is usually negative near a reactive site [ $\Phi_{\text{nucleophile}}(r_p) < 0$ ] while the potential due to the Fukui function is usually positive near a reactive site [ $v_{\text{nucleophile}}^{f-}(r_p) > 0$ ]. Referring back to a and b, it is apparent that the sign convention in eqs 73–76 implies that  $\epsilon_{(i)}$ ,  $\epsilon_{(ii)}$ ,  $\epsilon_{(iii)}$ , and  $\epsilon_{(iv)}$  are usually positive constants. We will now characterize the size of these constants.

When eqs 73 and 74 are examined, it seems clear that the size of the error should be related to the magnitude of  $\Phi_{\text{nucleophile}}(r)$  in the region where the electrophile is attacking. Similarly, in eqs 75 and 76, the error incurred by the point charge approximation should be small when  $v_{\text{nucleophile}}^{f-}(r)$  is small in the region where the electrophile is attacking. On the other hand, if  $v_{\text{nucleophile}}^{f-}(r)$  is large at the reactive site, this suggests that  $f_{\text{nucleophile}}^{f-}(r)$  is also large near the reactive site, which suggests that the point charge approximation to the integrals in eq 75 will be poor.

Hence, (c) the error in the left-hand sides of eqs 73 and 74 is roughly proportional to the magnitude of the electrostatic potential at the position where the electrophile attacks,  $\Phi_{\text{nucleophile}}(r_p)$ .

(d) The error in the left-hand sides of eqs 75 and 76 is roughly proportional to the magnitude of the Fukui potential at the position where the electrophile attacks,  $v_{\text{nucleophile}}^{f-}(r_p)$ .

By including an appropriate dependence on  $\Phi_{\text{nucleophile}}(r_p)$  or  $v_{\text{nucleophile}}^{f-}(r_p)$  in the right-hand side of the defining eqs 73–76, we ensure that  $\epsilon_{(i)} - \epsilon_{(iv)}$  depend only weakly on the relative magnitude of the electrostatic and Fukui potentials at the reactive sites. Our choice of definition, then, ensures that  $\epsilon_{(i)} - \epsilon_{(iv)}$  measure the *intrinsic error* in the point charge approximations.

In the discussion surrounding eq 78, we pointed out that the primary error in the single reactive site approximation was associated with the interaction between the tails of electronic distributions centered on the electrophile and the nucleophile. This error is expected to be most severe in eq 76, because the Fukui functions (1) have slow asymptotic decays and (2) are concentrated on the “frontiers” of the reagents.

(e) We expect  $\epsilon_{(iv)}$  to be relatively large. The error due to the point charge approximation can be rather large in this case because the interaction between the asymptotic tails of the Fukui functions might be significantly underestimated by the result from the point charge representation.

By contrast, the error in eq 73 might be relatively small, because the electron density is concentrated near the atomic nuclei.

(f) We expect  $\epsilon_{(i)}$  to be relatively small, because the interaction between the asymptotic tails of the electron

densities should be only a small part of the total interaction between the electronic distributions.

The errors in eqs 74 and 75 should be intermediate.

(g) We expect  $\epsilon_{(ii)}$  and  $\epsilon_{(iii)}$  to be relatively large compared to  $\epsilon_{(i)}$  because the Fukui function in these integrals is concentrated on the frontiers of the molecule. However, we expect  $\epsilon_{(ii)}$  and  $\epsilon_{(iii)}$  to be smaller than  $\epsilon_{(iv)}$ , because point charge approximation is the least accurate in eq 76, where both of the Fukui functions are involved.

Using results from a, b, e, f, and g, we have the following ordering of relative errors.

$$0 < \epsilon_{(i)} < \epsilon_{(ii)} \approx \epsilon_{(iii)} < \epsilon_{(iv)} \quad (80)$$

It should be stressed that the preceding analysis is strictly qualitative. Exceptions to the ordering in eq 80 will occur. Henceforth, we will never rely upon the details of this analysis; the approximate ordering of errors in eq 80 is sufficient to establish our results.

As discussed in sections III.A and III.B, the key parameters in the reactivity model are the number of electrons donated by the nucleophile to the electrophile,  $\Delta N \leq 0$ , and the quantity

$$\tilde{\kappa} = q_{\text{electrophile}}^{(0)} + \Delta N f_{\text{electrophile}}^{(+)} \quad (81)$$

Inserting the expression for  $\tilde{\kappa}$  into eq 27 gave the oversimplified regioselectivity indicator in eq 30.

$\tilde{\kappa}$  measures the relative importance of electrostatic and electron-transfer effects. When  $\tilde{\kappa}$  is significantly positive, the electrophile is highly charged and electron transfer is minimal; such reactions are expected to be electrostatically controlled. When  $\tilde{\kappa}$  is significantly negative, then electron transfer to the electrophilic site is important, but the electrophile is not especially highly charged; such reactions are expected to be electron-transfer-controlled.

As long as  $\tilde{\kappa}$  is very different from zero, it is reasonable to neglect the errors due to the point-charge approximations to the integrals, because they should be small compared to  $\tilde{\kappa}$ . To address the case where  $\tilde{\kappa} \approx 0$ , insert the expressions for  $\epsilon_{(i)}$ ,  $\epsilon_{(ii)}$ ,  $\epsilon_{(iii)}$ , and  $\epsilon_{(iv)}$  into eq 21. This gives an “error-corrected” version of the reactive-site interaction model in eq 30, namely,

$$\tilde{\Xi}_{\Delta N \leq 0}^{\tilde{\kappa}, \epsilon_{(i)-(iv)}}(r_p) \equiv [\tilde{\kappa} + (-\epsilon_{(i)} + \epsilon_{(ii)}\Delta N)] \Phi_{\text{nucleophile}}(r_p) - \Delta N[\tilde{\kappa} + (-\epsilon_{(iii)} + \epsilon_{(iv)}\Delta N)] v_{\text{nucleophile}}^-(r_p) \quad (82)$$

Because  $\epsilon_{(i)} < \epsilon_{(iii)}$ ,  $\epsilon_{(ii)} < \epsilon_{(iv)}$ , and  $\Delta N \leq 0$ ,

$$-\epsilon_{(iii)} + \epsilon_{(iv)}\Delta N < -\epsilon_{(i)} + \epsilon_{(ii)}\Delta N \quad (83)$$

Comparing eqs 31 and 82 allows us to make the identification

$$\epsilon_{\rho} = -\epsilon_{(i)} + \epsilon_{(ii)}\Delta N \quad (84)$$

$$\epsilon_f = -\epsilon_{(iii)} + \epsilon_{(iv)}\Delta N \quad (85)$$

Equation 83 then establishes that  $\epsilon_{\rho} > \epsilon_f$ , as stated in eq 32. The general-purpose reactivity indicator then follows from the analysis in section III.B. In particular, because

$$\tilde{\kappa} - \epsilon_{(i)} + \epsilon_{(ii)}\Delta N > \tilde{\kappa} - \epsilon_{(iii)} + \epsilon_{(iv)}\Delta N \quad (86)$$

the qualitative structure of the interaction energy model in eq 82 is recaptured by the simple expression

$$\Xi_{\Delta N \leq 0}^{\kappa}(r_p) \equiv (\kappa + 1)\Phi_{\text{nucleophile}}(r_p) - \Delta N(\kappa - 1)v_{\text{nucleophile}}^-(r_p) \quad (87)$$

The new parameter,  $\kappa$ , is linearly related to the more fundamental  $\tilde{\kappa}$  via the equation

$$\kappa = 2 \left( \frac{\tilde{\kappa} - \epsilon_{(i)} + \epsilon_{(ii)}\Delta N}{\epsilon_{(iii)} - \epsilon_{(i)} + (\epsilon_{(ii)} - \epsilon_{(iv)})\Delta N} \right) - 1 \quad (88)$$

The approximate proportionality reported in eq 38 is clearly accurate whenever  $\tilde{\kappa}$  is large compared to the error terms. The motivation for this transformation of variables is that it gives a simple appealing qualitative picture, with  $\kappa = +1$  and  $\kappa = -1$  corresponding to pure electrostatic control and pure electron-transfer control, respectively.

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