Variational Principles for Describing Chemical Reactions. Reactivity Indices Based on the External Potential

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Abstract: In a recent paper [*J. Am. Chem. Soc.* **2000**, *122,* 2010], the authors explored variational principles that help one understand chemical reactivity on the basis of the changes in electron density associated with a chemical reaction. Here, similar methods are used to explore the effect changing the external potential has on chemical reactivity. Four new indices are defined: (1) a potential energy surface that results from the second-order truncation of the Taylor series in the external potential about some reference, $\Upsilon(\boldsymbol{R}_1,\boldsymbol{R}_2,...,\boldsymbol{R}_M)$; (2) the stabilization energy for the equilibrium nuclear geometry (relative to some reference), Ξ; (3) the flexibility, or "lability", of the molecule at equilibrium, Λ; and (4) the proton hardness, Π, which performs a role in the theory of Brönsted−Lowry acids and bases that is similar to the role of the chemical hardness in the theory of Lewis acids and bases. Applications considered include the orientation of a molecule in an external electric field, molecular association reactions, and reactions between Brönsted−Lowry acids and bases.

I. Introduction

The abundance of chemical knowledge underscores the need for incisive and inclusive tools for systematizing chemical data. In recent years, much attention has been paid to the insights density functional theory[1,2] (DFT) can give into chemical reactivity.[3−7] DFT reactivity indices such as the chemical potential,[1,8] chemical hardness,[9−11] and Fukui function[12,13] are useful for elucidating the principles that guide chemical reactions.

In a recent paper,[14] the authors introduced a "perturbative perspective" on chemical reactivity. The interactions between molecules and, more specifically, problems associated with charge transfer were explored using functional Taylor series truncated at second order and DFT's fundamental variational principles. For a given configuration of the atomic nuclei (fixed external potential), a constrained minimization was performed, wherein the total energy is minimized with respect to all densities that have the appropriate number of electrons (or chemical potential). This yields variational approaches to quantities of computational and conceptual significance, notably the hardness, softness, Fukui function, and local softness.[15] These indices aid the understanding of the electronic rearrangements that occur during the course of chemical reactions. The hardness and its reciprocal, the softness, are global reactivity indicators: the inherent reactivity of a chemical species is well-described through Pearson's hard/soft acid/base[16−18] and maximum hardness[19−29] principles. On the other hand, the Fukui function and the local softness are local reactivity indices that measure the reactivity of a molecular site.[13−15,30]

Such tools are most appropriate when the chemical reaction under consideration can be described as a change in the electronic structure of the molecule; reactions between Lewis acids and Lewis bases are prototypical examples. And while, in principle, every chemical reaction can be completely described through changes in the electron density, $\rho(\boldsymbol{r})$,[31] it is sometimes more useful to change, through a Legendre transformation, the fundamental variables of the problem to the external potential, $v_0(\boldsymbol{r})$, and either the number of electrons, N, or the electronic chemical potential, μ.[32−34] The electronic

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chemical potential is the negative of the Mulliken electronegativity, and it represents the escaping tendency of electrons from a molecular system.[1,8,35] The external potential is the part of the potential felt by electrons that is not due to other electrons in the system. For an isolated molecule the external potential is just the potential due to the atomic nuclei,

$$v_0(\boldsymbol{r}) = \sum_{\alpha=1}^{M} -\frac{Z_\alpha}{|\boldsymbol{r} - \boldsymbol{R}_\alpha|} \tag{1}$$

but the external potential may also include contributions from external electric fields or neighboring molecules.

When the fundamental process driving a reaction is not a change in electronic structure, but a change in the number, location, or kinds of atomic nuclei, it is appropriate to describe this change directly through changes in the external potential, rather than indirectly through the proxy variable of the electron density. Consider, for example, the transfer of a proton from a Brönsted−Lowry acid to a Brönsted−Lowry base:

$$\mathrm{A{-}H} + \mathrm{:B} \rightarrow \mathrm{A:} + \mathrm{H{-}B} \tag{2}$$

While reaction 2 can be described through the resulting changes in the appropriate molecular electron densities, the process is most directly described as a change in external potential. The most transparent conceptual tools for understanding such reactions can be found by developing a theory of chemical reactivity in which the external potential, not the electron density, is the fundamental variable. That is, the most transparent conceptual tools for understanding such reactions will be associated with the electron-following, rather than the electron-preceding, perspective on chemical reactivity.[36] This strict coupling between changes in nuclear positions and electron density is most naturally presented within the adiabatic (e.g., Born−Oppenheimer) approximation; this approximation is implicit throughout the remainder of the paper.

Using methods similar to those described in ref 14, the present paper proposes several "external potential-based" indices for describing chemical reactivity. In analogy to the previous paper, we perform a constrained search: for a fixed number of electrons or electronic chemical potential, we minimize the total energy with respect to all external potentials associated with suitable positions of the atomic nuclei (in particular, we do not allow changes in the charges of the atomic nuclei). However, unlike in ref 14, the results of which were clearly within the exclusive purview of density functional theory, the problem of finding the best way to place atomic centers in a molecule is solved by finding the global minimum on a potential energy surface, and hence is not a problem unique to density functional theory. Accordingly, the theoretical insights of this paper are introduced through consideration of exact potential energy surfaces (section II). Motivated by a desire to find qualitative information about chemical reactivity without computing substantial portions of the potential energy surface, we discuss how to approach key reactivity indices from density functional theory (section III). After extending these results to the grand canonical ensemble (section IV), we give an overview of the description of chemical reactivity provided by the results of ref 14 and the present paper (section V).

II. Potential Energy Surfaces for Molecular Systems

A. Definition. This work centers upon the interpretation of potential energy surfaces, so we start by describing the exact potential energy surface for an M-atom, N-electron molecule. Denoting the set of nuclear charges by $\{Z_\alpha\}_{\alpha=1}^{M}$ and the set of nuclear coordinates by $\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M}$, the *potential energy surface* for an isolated molecule is given by

$$\mathrm{U}(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M}) \equiv E(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M}) + V_{\mathrm{rep}}(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M}) \tag{3}$$

where V_{rep} is the nuclear−nuclear repulsion energy,

$$V_{\mathrm{rep}}(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M}) \equiv \sum_{\alpha=1}^{M} \sum_{\beta>\alpha}^{M} \frac{Z_\alpha Z_\beta}{|\boldsymbol{R}_\alpha - \boldsymbol{R}_\beta|} \tag{4}$$

and E is the electronic energy,

$$E(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M}) \equiv \min_{\Psi}[\langle\Psi|\hat{H}(N,v_0(\boldsymbol{r}))|\Psi\rangle] \tag{5}$$

In eq 5, $\hat{H}(N,v_0(\boldsymbol{r}))$ represents the electronic Hamiltonian operator for the system in question:

$$\hat{H}(N,v_0(\boldsymbol{r})) \equiv \sum_{i=1}^{N}\left[-\frac{\nabla_i^2}{2} + v_0(\boldsymbol{r}_i) + \sum_{j>i}^{N}\frac{1}{r_{ij}}\right] \tag{6}$$

For molecules that are subject to additional electric fields, as imposed by either some apparatus or nearby molecules, the external potential is no longer given by eq 1, and the nuclear−nuclear repulsion energy is no longer given by eq 4. The forces that affect electrons are largely electrostatic, and hence can be expressed as forces exerted upon electrons by an effective "external" charge distribution, $\rho_n(\boldsymbol{r})$. The generalized nuclear−nuclear repulsion energy is then given by

$$V_{rep}[\rho_n] \equiv \frac{1}{2}\underbrace{\iint}_{\boldsymbol{r}\neq\boldsymbol{r}'} \frac{\rho_n(\boldsymbol{r})\rho_n(\boldsymbol{r}')}{|\boldsymbol{r}-\boldsymbol{r}'|}d\boldsymbol{r}d\boldsymbol{r}' \tag{7}$$

which, upon application of Poisson's equation, can be written as

$$V_{rep}[v_0] \equiv \frac{1}{32\pi^2}\underbrace{\iint}_{\boldsymbol{r}\neq\boldsymbol{r}'} \frac{(\nabla_{\boldsymbol{r}}^2 v_0(\boldsymbol{r}))(\nabla_{\boldsymbol{r}'}^2 v_0(\boldsymbol{r}'))}{|\boldsymbol{r}-\boldsymbol{r}'|}d\boldsymbol{r}d\boldsymbol{r}' \tag{8}$$

In eqs 7 and 8, points where $\boldsymbol{r} \neq \boldsymbol{r}'$ are excluded from the domain of the integration, thereby avoiding self-repulsion contributions from the atomic nuclei; eq 8 simplifies to eq 4 for isolated molecules. From eqs 5 and 8, the potential energy surface for a molecule is seen to be a function of the external potential and the number of electrons, $\mathrm{U}[N,v_0(\boldsymbol{r})]$.

Because the zero of energy is arbitrary, one may shift the potential energy surface by a constant without affecting the underlying physics. In particular, it is often helpful set the energy of an appropriate reference state equal to zero, thereby defining a *shifted potential energy surface:*

$$U[N,v_0(\boldsymbol{r})] \equiv \mathrm{U}[N,v_0(\boldsymbol{r})] - \mathrm{U}[N,v_0^{\mathrm{ref}}(\boldsymbol{r})] \tag{9}$$

Many molecular properties may be obtained from a molecule's shifted potential energy surface, $U[N,v_0(\boldsymbol{r})]$. For instance,

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the optimal nuclear configuration is obtained by finding the global minimum of $U[N,v_0(\boldsymbol{r})]$ over the set of all external potentials that may be obtained through rearrangement of the atomic nuclei from the reference external potential, $v_0^{\mathrm{ref}}(\boldsymbol{r})$. The restriction on the external potentials that are to be considered is key, for otherwise no minimum value of $U[N,v_0(\boldsymbol{r})]$ exists.[37] Since the variations of the external potential are restricted to those that may be parametrized through the nuclear coordinates, $\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M}$, we may consider the potential energy surface to be a function of the nuclear coordinates, $U(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M})$.

B. "Reduced" Potential Energy Surfaces. For large polyatomic molecules, the molecular potential energy surface, $U(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M})$, becomes inconveniently complex. However, for many molecular processes, one may, by choosing appropriate nuclear coordinates, approximate a chemical process of interest by considering some (frequently small) number of nuclear coordinates, $\{X_\alpha\}$. That is, we can reduce the amount of information contained in $U(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M})$ by holding certain linear combinations of the $\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M}$ constant, thereby obtaining a *reduced potential energy surface*, $U(X_1,X_2,...)$, that depends only on the coordinates most relevant to a given molecular process. Viewed from a different perspective, while the full $3M$-dimensional potential energy surface, $U(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M})$, is found by restricting the domain of the molecular potential functional, $U[N,v_0(\boldsymbol{r})]$, to just those external potentials that are associated with some rearrangement of the nuclei from the reference external potential, $U(X_1,X_2,...) \equiv U[N,v_0(\boldsymbol{r})]$ represents the restriction of the domain of the molecular potential functional to those external potentials that are associated with certain specific rearrangements of the nuclei from the reference external potential, namely, those rearrangements parametrized through the coordinates X_1, X_2, ...

This highly specific reduction of the domain of the molecular potential functional to just those external potentials that are most relevant to a given process is best understood through specific examples. In preparation for the examples, we divide the nuclear coordinates into three subsets: a set of three coordinates, denoted $\boldsymbol{R}$, that specify the position of the molecule; a set of two coordinates, denoted (θ,ϕ), that specify the orientation of the molecule; and a set of $3N - 6$ coordinates, $(\{\boldsymbol{R}_{ij}\})$, that specify the relative positions of the molecular nuclei.[38]

C. Examples. ***Example 1.*** **Finding the Optimum Molecular Geometry.** Suppose we want to find the optimum nuclear configuration for a molecule in an isotropic and homogeneous environment. In this instance, then, the energy is independent of the position of the molecule, represented by $\boldsymbol{R}$, and the orientation of the molecule, represented by the angular coordinates (θ,ϕ); that is, the energy depends only upon the relative nuclear positions. This suggests that we consider the "reduced potential energy surface", $U_{\mathrm{geometry}}(\{\boldsymbol{R}_{ij}\})$, which measures the "stabilization energy" of the geometry $(\{\boldsymbol{R}_{ij}\})$ relative to the reference geometry, $(\{\boldsymbol{R}_{ij}^{\mathrm{ref}}\})$. The best placement for the atomic nuclei is found by minimizing U_{geometry} with respect to the relative placement of the nuclei. From an alternative perspective, we find the external potential associated with the ground-state nuclear configuration by minimizing $U[N,v_0(\boldsymbol{r})]$ with respect to the space of external potentials parametrized by the coordinates $(\{\boldsymbol{R}_{ij}\})$.

Example 2. **Finding the Orientation of a Molecule in an Anisotropic Electric Field.** In this instance, the molecular energy is independent of the position of the molecule, $\boldsymbol{R}$, but not of its orientation, (θ,ϕ). The presence of an electric field often changes the relative positions of the atomic nuclei, $(\{\boldsymbol{R}_{ij}\})$, which seems to suggest that we must consider a reduced potential surface that depends on $3(M - 1)$ variables. However, for sufficiently weak fields, the relative nuclear positions in the molecule often change little, and the dominant effect is the reorientation of the molecule in the presence of the field.[39] As an approximation, then, we ignore the changes in the relative nuclear positions and consider the reduced potential energy surface, $U_{\mathrm{anisotropic}}(\theta,\phi)$, which measures the relative energies of various molecular orientations. The best way to orient the molecule in the electromagnetic field is found by minimizing $U_{\mathrm{anisotropic}}(\theta,\phi)$ with respect to the orientation of the molecule, or, equivalently, by minimizing $U[N,v_0(\boldsymbol{r})]$ with respect to the changes in the reference external potential parametrized by (θ,ϕ).

Example 3. **Finding the Position of a Molecule in an Anisotropic, Inhomogeneous Electric Field (Such as, for Example, a Solvent "Cage").** As the field is inhomogeneous, the position of the molecule, $\boldsymbol{R}$, is important; that is, the potential energy surface $U(\{\boldsymbol{R}_\alpha\}_{\alpha=1}^{M})$ no longer possesses translational invariance. If, as in Example 2, we assume that the field causes only minimal changes in the relative positions of the atomic nuclei, we may consider the reduced potential energy surface, $U_{\mathrm{inhomogeneous}}(\boldsymbol{R},\theta,\phi)$. The best position and orientation for the molecule is found by minimizing $U_{\mathrm{inhomogeneous}}(\boldsymbol{R},\theta,\phi)$ with respect to rotations and translations of the molecule, or, equivalently, by minimizing $U[N,v_0(\boldsymbol{r})]$ with respect to changes in the reference external potential that can be achieved through variation of the parameters $(\boldsymbol{R},\theta,\phi)$.

Example 4. **Molecular Association Reactions.** Consider a molecular association reaction

$$\mathrm{A} + \mathrm{B} \rightarrow \mathrm{A{-}B} \tag{10}$$

We wish to predict the relative orientation of molecule A relative to that of molecule B in A−B. In general, finding the geometry of an M-atom product molecule requires consideration of a $(3M - 6)$-dimensional potential energy surface. However, when the relative nuclear positions in A−B strongly resemble those in the isolated fragments A and B, it is plausible to consider a reduced potential energy surface parametrized by the relative positions of fragment A and fragment B, $U_{\mathrm{AB}}(\boldsymbol{R},\theta,\phi)$. That is, we "clamp" fragment B at the origin, $\boldsymbol{R} = 0$, in some orientation (θ_0,ϕ_0) and consider the molecular energy, $U_{\mathrm{AB}}(\boldsymbol{R},\theta,\phi)$, when fragment A is at the point $\boldsymbol{R}$ with orientation (θ,ϕ). The best way to combine A and B is found by minimizing $U_{\mathrm{AB}}(\boldsymbol{R},\theta,\phi)$. If we choose as reference states for A and B the isolated molecular fragments, then $U_{\mathrm{AB}}(\boldsymbol{R}_{\min},\theta_{\min},\phi_{\min})$ represents the molecular interaction energy and approximates the binding energy for A−B.

This procedure requires computing the reduced potential energy surface for the entire molecule, A−B. However, note the similarity between the reduced potential energy surface in

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(37) Consider what happens if one tries to minimize the energy of a one-electron diatomic molecule without imposing a constraint on the external potential. As the nuclear charge at one atomic center increases without bound, the energy $(E \leq -Z_1^2/2 + Z_1Z_2/|(\boldsymbol{R}_1 - \boldsymbol{R}_2)|)$ decreases without bound.

(38) For example, the position of the molecule can be represented by that of the first atom (so $\boldsymbol{R}_1 = \boldsymbol{R}$), the $\theta = 0$ direction can be the direction of the second atom from the first atom (so $\boldsymbol{R}_2 = (R_2, \theta = 0, \phi = 0)$), and the $\phi = 0$ direction can be the direction of a third, noncollinear, atom (so $\boldsymbol{R}_3 = (R_3, \theta_3, \phi = 0)$). This leaves $3N - 6$ "internuclear" coordinates, $(R_2,R_3,\theta_3,\boldsymbol{R}_4,\boldsymbol{R}_5,...,\boldsymbol{R}_M)$, each of which may be measured relative to the position and orientation of the first three atoms.

(39) When the "clamped nuclei" approximation is qualitatively incorrect, one must make recourse to the full potential energy surface. However, if the clamped nuclei approximation yields results that are qualitatively acceptable but not quantitatively satisfactory, one might use the suggested reduced potential energy surfaces for conceptual ease and then refine the quantitative results through geometry optimization (Example 1).

this example and Example 3, wherein a molecule is positioned inside an inhomogeneous, anisotropic electric field. This suggests that we restate the problem posed in reaction 10 as follows: What is the best way to position fragment A in the inhomogeneous, anisotropic electric field generated by fragment B?

Proceeding in this way, we regard the electrons in fragment A as interacting with some “effective external potential”, $v_{\mathrm{B}}^{\mathrm{eff}}(\mathbf{r})$, due to the cumulative effects of the electrons and nuclei associated with fragment B. Likewise, we regard the electrons of fragment B as interacting with some “effective external potential”, $v_{\mathrm{A}}^{\mathrm{eff}}(\mathbf{r})$, due to the electrons and nuclei associated with fragment A. This leads to the following question: What is the effective external potential an electron in fragment A feels due to the electrons and nuclei of fragment B? If the interaction were only electrostatic, then the effective external potential due to fragment B would be

$$v_{\mathrm{B}}^{\mathrm{electrostatic}}(\mathbf{r}) \equiv v_{0,\mathrm{B}}(\mathbf{r}) + \int \frac{\rho_{\mathrm{B}}(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\,\mathrm{d}\mathbf{r}' \tag{11}$$

where $v_{0,\mathrm{B}}(r)$ is the external potential due to the nuclei in fragment B (as given by eq 1) and $\rho_{\mathrm{B}}(\mathbf{r})$ is the electron density of fragment B. While the interaction between the electrons in fragment A and the nuclei in fragment B is strictly electrostatic, the electrons in fragments A and B are identical particles, and hence are subject to the exclusion principle. Moreover, the electrons in fragments A and B are correlated. Accordingly, the suitability of the electrostatic description of the effective external potential is uncertain. A more satisfactory description may be obtained through examining the Kohn−Sham potential-based charge density:

$$q_{\mathrm{B}}^{\mathrm{eff}}(\mathbf{r}) \equiv \frac{-1}{4\pi}\nabla^2 v_{\mathrm{B}}^{\mathrm{K-S}}(\mathbf{r}) \tag{12}$$

where $v_{\mathrm{B}}^{\mathrm{K-S}}(\mathbf{r})$ is the Kohn−Sham effective potential of fragment *B*,[40]

$$v_{\mathrm{B}}^{\mathrm{K-S}}(\mathbf{r}) \equiv v_{0,\mathrm{B}}(\mathbf{r}) + \int \frac{\rho_{\mathrm{B}}(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\,\mathrm{d}\mathbf{r}' + v_{\mathrm{xc,B}}(\mathbf{r}) \tag{13}$$

Since the first term in $q_{\mathrm{B}}^{\mathrm{eff}}(\mathbf{r})$ is due to $v_{0,\mathrm{B}}(\mathbf{r})$, eliminating this term yields the purely electronic charge,

$$q_{\mathrm{B}}^{\mathrm{electronic}}(\mathbf{r}) \equiv \rho_{\mathrm{B}}(\mathbf{r}) + q_{\mathrm{B}}^{\mathrm{xc}}(\mathbf{r}) \tag{14}$$

where $q_{\mathrm{B}}^{\mathrm{xc}}(\mathbf{r})$ is the exchange correlation charge of Görling and Liu, Ayers, and Parr.[41,42] Because[41−43]

$$\int q_{\mathrm{B}}^{\mathrm{electronic}}(\mathbf{r})\,\mathrm{d}r = N_{\mathrm{B}} - 1 \tag{15}$$

an electron in a Kohn−Sham system can be considered to interact *strictly electrostatically* (i.e., there are no correlation or exchange effects) with the nuclei of the system and $N - 1$ “pseudoelectrons” with total electron density $q^{\mathrm{electronic}}(\mathbf{r})$. We might expect, then, that an electron outside fragment B interacts strictly electrostatically with N_{B} pseudoelectrons with electron density $[N_{\mathrm{B}}/(N_{\mathrm{B}} - 1)]q_{\mathrm{B}}^{\mathrm{electronic}}(\mathbf{r})$. In this approximation, the effective external potential due to fragment B is defined by

$$v_{\mathrm{B}}^{\mathrm{eff}}(\mathbf{r}) \equiv v_{0,\mathrm{B}}(\mathbf{r}) + \frac{N_{\mathrm{B}}}{N_{\mathrm{B}}-1}\left[\int \frac{\rho_{\mathrm{B}}(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\,\mathrm{d}\mathbf{r}' + v_{\mathrm{xc,B}}(\mathbf{r})\right] \tag{16}$$

To obtain a different construction, recall that each electron in fragment A is interacting electrostatically with N_{B} pseudoelectrons in fragment B. This suggests that one should use the Kohn−Sham effective potential for the anion, $v_{\mathrm{B^-}}^{\mathrm{K-S}}(\mathbf{r})$, as the effective external potential for fragment B. Both this approximation and the approximation of eq 16 would include the effects of “interfragment” electron exchange and correlation, albeit in an approximate manner.

Given a satisfactory form for the “effective external potentials” for fragments A and B, one then solves the Kohn−Sham equations for the fragments:

$$\left\{\left[-\frac{\nabla^2}{2} + v_{0,\mathrm{A}}(\mathbf{r}) + \int \frac{\rho_{\mathrm{A}}(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\,\mathrm{d}\mathbf{r}' + v_{\mathrm{xc}}[\rho_{\mathrm{A}};\mathbf{r}] + v_{\mathrm{B}}^{\mathrm{eff}}[\rho_{\mathrm{B}};\mathbf{r}]\right]\psi_{i,\mathrm{A}}(\mathbf{r}) = \epsilon_{i,\mathrm{A}}\psi_{i,\mathrm{A}}(\mathbf{r})\right\}_{i=1}^{\infty}$$

$$\left\{\left[-\frac{\nabla^2}{2} + v_{0,\mathrm{B}}(\mathbf{r}) + \int \frac{\rho_{\mathrm{B}}(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\,\mathrm{d}\mathbf{r}' + v_{\mathrm{xc}}[\rho_{\mathrm{B}};\mathbf{r}] + v_{\mathrm{A}}^{\mathrm{eff}}[\rho_{\mathrm{A}};\mathbf{r}]\right]\psi_{i,\mathrm{B}}(\mathbf{r}) = \epsilon_{i,\mathrm{B}}\psi_{i,\mathrm{B}}(\mathbf{r})\right\}_{i=1}^{\infty} \tag{17}$$

These equations are coupled, and hence must be solved self-consistently. From them one gets the fragment densities, $\rho_{\mathrm{A}}(\mathbf{r})$ and $\rho_{\mathrm{B}}(\mathbf{r})$, and hence the molecular density,

$$\rho_{\mathrm{AB}}(\mathbf{r}) \equiv \rho_{\mathrm{A}}(\mathbf{r}) + \rho_{\mathrm{B}}(\mathbf{r}) \tag{18}$$

Moreover, one can compute the electronic energies of the fragments:

$$\begin{aligned} E_{\mathrm{A}} \equiv{}& T_{\mathrm{s}}[\rho_{\mathrm{A}}] + \int \rho_{\mathrm{A}}(\mathbf{r})v_{0,\mathrm{A}}(\mathbf{r})\,\mathrm{d}\mathbf{r} \\ &+ \frac{1}{2}\int\int \frac{\rho_{\mathrm{A}}(\mathbf{r})\rho_{\mathrm{A}}(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' + E_{\mathrm{xc}}[\rho_{\mathrm{A}}] \\ E_{\mathrm{B}} \equiv{}& T_{\mathrm{s}}[\rho_{\mathrm{B}}] + \int \rho_{\mathrm{B}}(\mathbf{r})v_{0,\mathrm{B}}(\mathbf{r})\,\mathrm{d}\mathbf{r} \\ &+ \frac{1}{2}\int\int \frac{\rho_{\mathrm{B}}(\mathbf{r})\rho_{\mathrm{B}}(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' + E_{\mathrm{xc}}[\rho_{\mathrm{B}}] \end{aligned} \tag{19}$$

The total electronic molecular energy will be

$$E_{\mathrm{AB}} = E_{\mathrm{A}} + E_{\mathrm{B}} + I_{\mathrm{AB}} \tag{20}$$

where I_{AB} is the molecular interaction energy, which can be defined as[44]

$$\begin{aligned} I_{\mathrm{AB}} \equiv{}& T_{\mathrm{s}}[\rho_{\mathrm{A}} + \rho_{\mathrm{B}}] \\ &+ \int (\rho_{\mathrm{A}}(\mathbf{r}) + \rho_{\mathrm{B}}(\mathbf{r}))(v_{0,\mathrm{A}}(\mathbf{r}) + v_{0,\mathrm{B}}(\mathbf{r}))\,\mathrm{d}\mathbf{r} \\ &+ \frac{1}{2}\int\int \frac{(\rho_{\mathrm{A}}(\mathbf{r}) + \rho_{\mathrm{B}}(\mathbf{r}))(\rho_{\mathrm{A}}(\mathbf{r}') + \rho_{\mathrm{B}}(\mathbf{r}'))}{|\mathbf{r}-\mathbf{r}'|}\,\mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' \\ &+ E_{\mathrm{xc}}[\rho_{\mathrm{A}} + \rho_{\mathrm{B}}] - E_{\mathrm{A}} - E_{\mathrm{B}} \end{aligned} \tag{21}$$

Given an approximate exchange-correlation energy density functional, the only term in eq 21 that remains unknown is

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$T_s[\rho_A + \rho_B]$, which could be computed, for example, by the procedure of Zhao, Morrison, and Parr.[45−47] However, the procedure of Zhao, Morrison, and Parr is more computationally demanding than a Kohn−Sham calculation performed on the entire molecule, A−B, and so one desires alternative procedures. As a first approximation, we might assume

$$T_s[\rho_A] + T_s[\rho_B] \approx T_s[\rho_A + \rho_B] \tag{22}$$

thereby attaining

$$\begin{aligned} E_{AB} \equiv\ & T_s[\rho_A] + T_s[\rho_B] \\ & + \int (\rho_A(\boldsymbol{r}) + \rho_B(\boldsymbol{r}))(v_{0,A}(\boldsymbol{r}) + v_{0,B}(\boldsymbol{r}))\, d\boldsymbol{r} \\ & + \frac{1}{2}\int\int \frac{(\rho_A(\boldsymbol{r}) + \rho_B(\boldsymbol{r}))(\rho_A(\boldsymbol{r}') + \rho_B(\boldsymbol{r}'))}{|\boldsymbol{r} - \boldsymbol{r}'|}\, d\boldsymbol{r}\, d\boldsymbol{r}' \\ & + E_{xc}[\rho_A + \rho_B] \end{aligned} \tag{23}$$

We expect eq 22 to be a satisfactory approximation only when the fragments are well-separated, so that the Kohn−Sham orbitals of the two fragments are almost orthogonal (otherwise, eq 22 violates the Pauli exclusion principle)[48] (Alternatively, solving eqs 17 subject to the constraint that the Kohn−Sham orbitals from the two fragments are orthogonal ensures that the molecular description provided by eq 23 is consistent with the Pauli exclusion principle.)

Finally, we discuss how to construct the reduced potential energy surface, $U_{AB}(\boldsymbol{R},\theta,\phi)$. As before, we fix fragment B at the origin in some orientation, (θ_0,ϕ_0). We then solve eqs 17 for various positions and orientations of fragment A and compute $E_{AB}(\boldsymbol{R},\theta,\phi)$. The reduced potential energy surface $U_{AB}(\boldsymbol{R},\theta,\phi)$, is obtained from $E_{AB}(\boldsymbol{R},\theta,\phi)$ by adding the nuclear−nuclear repulsion energy and subtracting the total energy of the reference state, which we assume to be the isolated molecular fragments.

***Example 5.* Brönsted−Lowry Acids and Bases.** From the defining reaction (eq 2), it is clear that a Brönsted−Lowry base, B, is a proton acceptor, while a Brönsted−Lowry acid, A−H, is a proton donor. Therefore, to assess the basicity of B, we address the optimum way to add a proton to B. In many cases (e.g., the ammonia molecule), the geometry of molecule B changes little upon protonation. This suggests that we may consider the reduced potential energy surface for H−B that is parametrized by the position of the proton, $\boldsymbol{R}$; that is, fixing molecule B at the origin ($\boldsymbol{R} = 0$) in some reference orientation (θ_0,ϕ_0), we consider the change in energy when a proton is placed at the point $\boldsymbol{R}$, $U_{BL-base}(\boldsymbol{R})$. The place where B is protonated corresponds to the point, $\boldsymbol{R}_{min}$, that minimizes $U_{BL-base}(\boldsymbol{R})$. Moreover, by choosing the reference state to be the system with the proton infinitely far from *B*, we ensure that $-U_{BL-base}(\boldsymbol{R}_{min})$ represents the proton affinity. Accordingly, the magnitude of $U_{BL-base}(\boldsymbol{R}_{min})$ reflects the basicity of B in the gas phase. Proton affinities may also be used to provide qualitative explanations for solution phase acid/base chemistry.[49−51]

To find a reduced potential energy surface appropriate to Brönsted−Lowry acids, we consider the effect of deprotonating A−H. We may cancel the external potential due to a proton by adding a unit negative point charge to the molecule at the location of a proton, $\boldsymbol{R}_H$. Ignoring the rearrangement of A that occurs after this change in the external potential, we consider the value of the reduced potential energy surface $U_{BL-acid}(\boldsymbol{R}_H)$ at positions corresponding to the placement of each hydrogen in the Brönsted−Lowry acid, A−H. The place where $U_{BL-acid}(\boldsymbol{R}_H)$ is minimum, $\boldsymbol{R}_H^{min}$, predicts which proton most readily dissociates from A, and the value of $U_{BL-acid}(\boldsymbol{R}_H^{min})$ represents this proton's dissociation energy. Moreover, gas-phase proton transfer from A to B (reaction 2) is energetically favorable only when the proton affinity of B is greater than the proton dissociation energy for A−H, so that

$$U^A_{BL-acid}(\boldsymbol{R}_H^{min}) + U^B_{BL-base}(\boldsymbol{R}_{min}) < 0 \tag{24}$$

The reactivity indices $U_{BL-base}(\boldsymbol{R})$ and $U_{BL-acid}(\boldsymbol{R})$ are key quantities and have applicability to systems other than Brönsted−Lowry acids and bases. Consider that $U_{BL-base}(\boldsymbol{R})$ represents the change in molecular energy from placing a positive "test charge" of unit magnitude at the point $\boldsymbol{R}$, while $U_{BL-acid}(\boldsymbol{R})$ represents the energy change from placing a negative "test charge" at the point $\boldsymbol{R}$. If the test charge had infinitesimal magnitude, $U_{BL-base}(\boldsymbol{R})$ and $-U_{BL-acid}(\boldsymbol{R})$ would both reflect the electrostatic potential due to the electron density and nuclear charges of the molecule.[52−54] However, when the test charge has the magnitude of the charge on the electron, the polarization of the density induced by the point charge is important, and hence $U_{BL-base}(\boldsymbol{R})$ and $-U_{BL-acid}(\boldsymbol{R})$ are no longer equal. Because chemical reactions may be characterized through interactions between "atomic" or "partial" charges whose magnitude is on the order of the charge on the electron, we expect that the energy changes due to adding a unit positive charge, $U_{BL-base}(\boldsymbol{R})$, and adding a unit negative charge, $U_{BL-acid}(\boldsymbol{R})$, at the point $\boldsymbol{R}$ are appropriate tools for qualitative descriptions of chemical reactivity.

D. Reactivity Indices Derived from Reduced Potential Energy Surfaces. It is apparent from the foregoing examples that the reduced potential energy surfaces, $U(\boldsymbol{X})$, contain much information about the reactivity preferences for a system. Hence, it is useful to develop quantities that summarize important features of $U(\boldsymbol{X})$. Of particular interest is the behavior of $U(\boldsymbol{X})$ at and near its global minimum, $\boldsymbol{X}_{min}$. For instance, the value of $U(\boldsymbol{X})$ at its global minimum represents the stabilization energy of the optimal geometry relative to the reference geometry. $U(\boldsymbol{X}_{min})$, however, is typically negative, and hence small values of $U(\boldsymbol{X}_{min})$ correspond to high stability. Accordingly, we define the *stability* through[55]

$$\begin{aligned} X &\equiv -U(\boldsymbol{X}_{min}) \\ &= \mathrm{U}[N,v_0(\boldsymbol{X}^{ref};\boldsymbol{r})] - \mathrm{U}[N,v_0(\boldsymbol{X}_{min};r)] \end{aligned} \tag{25}$$

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[45] Zhao, Q.; Parr, R. G. *Phys. Rev. A* **1992**, *46*, 237.

[46] Zhao, Q.; Parr, R. G. *J. Chem. Phys.* **1993**, *98*, 543.

[47] Zhao, Q.; Morrison, R. C.; Parr, R. G. *Phys. Rev. A* **1994**, *50*, 2138.

[48] Both the coupled Kohn−Sham equations (eqs 17) and the non-additivity of fragment kinetic energies (eq 22) are explored in the following: Nalewajski, R. F. *Int. J. Quantum Chem.* **2000**, *76*, 252.

[49] Ritchie, C. D. *Physical Organic Chemistry: The Fundamental Concepts*, 2nd ed.; Marcel Dekker: New York, 1990.

[50] Douglas, B. E.; McDaniel, D. H. *Concepts and Models of Inorganic Chemistry*; Blaisdell, Waltham, MA, 1965.

[51] Huheey, J. E.; Keiter, E. A.; Keiter, R. L. *Inorganic Chemistry: Principles of Structure and Reactivity*, 4th ed.; Harper Collins: New York, 1993.

[52] Politzer, P. *J. Chem. Phys.* **1980**, *72*, 3027.

[53] Politzer, P. *J. Chem. Phys.* **1980**, *73*, 3264.

[54] Murray, J. S., Sen, K., Eds. *Molecular Electrostatic Potentials: Concepts and Applications*; Theoretical and Computational Chemistry, Vol. 3; Elsevier: Amsterdam, 1996.

[55] As a mnemonic device, one may note that X represents the "excitation" energy required to change from the optimal nuclear configuration to the reference configuration.

Applying eq 25 to Examples 1−5, we find that (with natural choices for the reference states):[56]

1. X_{geometry} models the atomization energy of a molecule.

2,3. $X_{\text{isotropic}}$ and $X_{\text{inhomogeneous}}$ model the energy stabilization from repositioning a molecule in an electric field.

4. X_{AB} models the bond dissociation energy for A−B.

5. $X_{BL-\text{base}}$ models the proton affinity of a Brönsted−Lowry base, and $X_{BL-\text{acid}}$ models the proton dissociation energy for a Brönsted−Lowry acid.[57] The physical significance of these quantities indicates that X is a key index for describing chemical reactivity.

In addition to X, which reflects the stability of a system relative to a reference configuration, we may wish to consider the lability or “floppiness” of the molecule; that is, how “flat” is the reduced potential energy surface near $\mathbf{X}_{\min}$? Is the system rigidly constrained to near-optimal geometries, or do fairly small stimuli cause large conformational changes? These questions may be answered by studying the Hessian matrix,

$$\begin{aligned} F_{ij} &\equiv \left.\frac{\partial^2 U(\mathbf{X})}{\partial X_i\,\partial X_j}\right]_{\mathbf{X}=\mathbf{X}_{\min}} \\ &= [\nabla\nabla U(\mathbf{X})]_{\mathbf{X}=\mathbf{X}_{\min}} \end{aligned} \tag{26}$$

The eigenvalues of the Hessian matrix are the force constants for displacements about the optimal orientation, and hence when the trace of the Hessian matrix is small, the molecule is very labile. This suggests a definition for the *lability*:

$$L \equiv \frac{\dim(\mathbf{X})}{\mathrm{Tr}\{F_{ij}\}} \tag{27}$$

Here, the number of parameters in $\mathbf{X}$ ($\dim(\mathbf{X})$) is a normalizing factor, so that the lability is the reciprocal of an average force constant for the system.[58] Accordingly, when $\dim(\mathbf{X}) = 1$ (as for a diatomic molecule), L is simply the reciprocal of the force constant in the direction X. More generally, the lability is related to the number of different molecular configurations that are accessible at low temperatures.

III. Perturbation Expansions for the Potential Energy Surface

A. Functional Taylor Series in the External Potential. Insofar as the potential energy surface measures the potential energy relative to an appropriate reference state, perturbative expansions about this reference state are appropriate for exploring molecular potential energy surfaces. Since we wish to probe how the molecular energy changes as the external potential changes, we consider the functional Taylor series:

$$\begin{aligned} \mathrm{U}[N,v_0(\mathbf{r})] = {} & \mathrm{U}[N,v_0^{\text{ref}}(\mathbf{r})] \\ & + \int \left.\frac{\delta \mathrm{U}}{\delta v_0(\mathbf{r})}\right]_{v_0=v_0^{\text{ref}}} (v_0(\mathbf{r}) - v_0^{\text{ref}}(\mathbf{r}))\, d\mathbf{r} \\ & + \frac{1}{2}\int\int (v_0(\mathbf{r}') - v_0^{\text{ref}}(\mathbf{r}')) \left.\frac{\delta^2 \mathrm{U}}{\delta v_0(\mathbf{r}')\,\delta v_0(\mathbf{r})}\right]_{v_0=v_0^{\text{ref}}} \\ & \times (v_0(\mathbf{r}) - v_0^{\text{ref}}(\mathbf{r}))\, d\mathbf{r}\, d\mathbf{r}' + ... \end{aligned} \tag{28}$$

Shifting the zero of the potential energy surface has no effect on the general form of the perturbation expansion; consequently, we prefer the expression

$$\begin{aligned} U[N,v_0(\mathbf{r})] = {} & \int \left.\frac{\delta U}{\delta v_0(\mathbf{r})}\right]_{v_0^{\text{ref}}} (v_0(\mathbf{r}) - v_0^{\text{ref}}(\mathbf{r}))\, d\mathbf{r} \\ & + \frac{1}{2}\int\int (v_0(\mathbf{r}') - v_0^{\text{ref}}(\mathbf{r}')) \left.\frac{\delta^2 U}{\delta v_0(\mathbf{r}')\,\delta v_0(\mathbf{r})}\right]_{v_0^{\text{ref}}} \\ & \times (v_0(\mathbf{r}) - v_0^{\text{ref}}(\mathbf{r}))\, d\mathbf{r}\, d\mathbf{r}' + ... \end{aligned} \tag{29}$$

If the external potential of the state of interest resembles that of the reference state sufficiently closely, low-order truncations of these functional Taylor series will be accurate.

B. Truncation of the Perturbation Expansion. To explore the properties of this Taylor series, note that, since $V_{\text{rep}}[v_0(\mathbf{r})]$ (eq 8) is a quadratic functional of $v_0(\mathbf{r})$, functional Taylor series expansions of $V_{\text{rep}}[v_0(\mathbf{r})]$ truncate after the second-order term. Hence, truncating the Taylor series at second order and separating the nuclear−nuclear repulsion terms from the electronic energy terms yields

$$\begin{aligned} \Upsilon[N,v_0(\mathbf{r})] \equiv {} & \Delta V_{\text{rep}}[v_0] \\ & + \int \left.\left(\frac{\delta E}{\delta v_0(\mathbf{r})}\right)_N\right]_{v_0^{\text{ref}}} (v_0(\mathbf{r}) - v_0^{\text{ref}}(\mathbf{r}))\, d\mathbf{r} \\ & + \frac{1}{2}\int\int (v_0(\mathbf{r}') - v_0^{\text{ref}}(\mathbf{r}')) \left.\left(\frac{\delta^2 E}{\delta v_0(\mathbf{r}')\,\delta v_0(\mathbf{r})}\right)_N\right]_{v_0^{\text{ref}}} \\ & \times (v_0(\mathbf{r}) - v_0^{\text{ref}}(\mathbf{r}))\, d\mathbf{r}\, d\mathbf{r}' \end{aligned} \tag{30}$$

where $\Delta V_{\text{rep}}[v_0] \equiv V_{\text{rep}}[v_0] - V_{\text{rep}}[v_0^{\text{ref}}]$. (In eq 30 and through the remainder of the paper, second-order truncation of the Taylor series is accompanied by changing the symbol for a variable to a capital Greek letter (so $U \rightarrow \Upsilon$, $X \rightarrow \Xi$, and $L \rightarrow \Lambda$).)

To continue further, we must evaluate the functional derivatives of the energy. A detailed discussion of functional derivatives and functional Taylor series is included both in ref 14 and in Appendix A of ref 1, and will not be repeated here. Here it suffices to know that $(\delta E/\delta v_0(\mathbf{r}))_N]_{v_0^{\text{ref}}}$ may be interpreted as the relative change in energy induced by a small increase[59] in $v_0(\mathbf{r})$ at the point $\mathbf{r}$ and that $\int\{(\delta E/\delta v_0(\mathbf{r}))_N]_{v_0^{\text{ref}}}(v_0(\mathbf{r}) - v_0^{\text{ref}}(\mathbf{r}'))\}\, d\mathbf{r}$ represents the first-order change in the energy due to changing the external potential from $v_0^{\text{ref}}(\mathbf{r})$ to $v_0(\mathbf{r})$.

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[56] Tables of accurate atomization energies, proton affinities, and other relevant properties have been compiled by Pople and co-workers, see: Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys* **1991**, *94*, 7221. Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Pople, J. A. *J. Chem. Phys.* **1997**, *106*, 1063. Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Pople, J. A. *J. Chem. Phys.* **2000**, *112*, 7374.

[57] Lohr, L. L. *J. Phys. Chem.* **1984**, *88*, 3607.

[58] This definition of the lability is not unique. One could argue that the lability of a molecule is characterized by its flexibility in the direction in which it is most easily deformed, leading to the definition

$$L \equiv \frac{1}{\min\{\phi_i\}}$$

where $\{\phi_i\}_{i=1}^{\dim(\mathbf{X})}$ are the eigenvalues of the Hessian matrix. Equation 27 reflects the “average” lability; by this definition, a molecule whose potential energy surface has a “long, narrow valley” is not very labile since many “near-optimal” nuclear configurations are energetically inaccessible. That is, the definition of lability adopted in the text quantifies the “floppiness” of the molecule, while the alternative given in this footnote quantifies the “stretchiness” of the molecule when a force is applied in the direction of the normal coordinate corresponding to the lowest fundamental frequency.

[59] In particular, the perturbation may be considered to be

$$\lim_{\epsilon \to 0^+} \epsilon\delta(\mathbf{r}' - \mathbf{r})$$

Functional derivatives may evaluated by perturbation theory. For instance, consider the perturbed Hamiltonians,

$$\hat{H}_\epsilon[N,v_0(\boldsymbol{r})] \equiv \hat{H}[N,v_0^{\text{ref}}(\boldsymbol{r})] + \sum_{i=1}^{N}\epsilon(v_0(\boldsymbol{r}_i) - v_0^{\text{ref}}(\boldsymbol{r}_i)) \tag{31}$$

$\hat{H}_{\epsilon=0}[N,v_0(\boldsymbol{r})]$ corresponds to Hamiltonian of the reference system, while $\hat{H}_{\epsilon=1}[N,v_0(\boldsymbol{r})]$ is the Hamiltonian for the "target" of the perturbation expansion. Expanding the energy as a Taylor series in ϵ,

$$E(1) = E(0) + \left.\frac{\partial E}{\partial \epsilon}\right]_{\epsilon=0} + \frac{1}{2}\left.\frac{\partial^2 E}{\partial \epsilon^2}\right]_{\epsilon=0} + ... \tag{32}$$

it follows that

$$\int \left.\left(\frac{\partial E}{\delta v_0(\boldsymbol{r})}\right)_N\right]_{v_0^{\text{ref}}}(v_0(\boldsymbol{r}) - v_0^{\text{ref}}(\boldsymbol{r}))\,\mathrm{d}\boldsymbol{r} = \left.\frac{\partial E}{\partial \epsilon}\right]_{\epsilon=0} \tag{33}$$

For nondegenerate states, the Hellmann−Feynman theorem indicates that

$$\left.\frac{\partial E}{\partial \epsilon}\right]_{\epsilon=0} \equiv \int \rho_k^{\text{ref}}(\boldsymbol{r})(v_0(\boldsymbol{r}) - v_0^{\text{ref}}(\boldsymbol{r}))\,\mathrm{d}\boldsymbol{r} \tag{34}$$

where $\rho_k^{\text{ref}}(\boldsymbol{r})$ is the density for the reference state. Hence,[1]

$$\left.\left(\frac{\delta E}{\delta v_0(\boldsymbol{r})}\right)_N\right]_{v_0^{\text{ref}}} \equiv \rho_k^{\text{ref}}(\boldsymbol{r}) \tag{35}$$

The second functional derivative is defined to be the functional derivative of the first functional derivative; hence[1]

$$\left.\left(\frac{\delta^2 E}{\delta v_0(\boldsymbol{r}')\,\delta v_0(\boldsymbol{r})}\right)_N\right]_{v_0^{\text{ref}}} = \left(\frac{\delta \rho_k^{\text{ref}}(\boldsymbol{r})}{\delta v_0(\boldsymbol{r}')}\right)_N \tag{36}$$

From the perturbation theory of nondegenerate states, we have

$$\begin{aligned}\left.\frac{\partial^2 E}{\partial \epsilon^2}\right]_{\epsilon=0} &= \int\int (v_0(\boldsymbol{r}_2) - v_0^{\text{ref}}(\boldsymbol{r}_2)) \\ &\times [2N^2\sum_{j\neq k}\{[\int\cdots\int \Psi_j^*(x_1,...,x_N)\Psi_k(x_1,...,x_N)\,\mathrm{d}s_2\,\mathrm{d}x_1\,\mathrm{d}x_3\,...\,\mathrm{d}x_N] \\ &\times [\int\cdots\int \Psi_k^*(x_1,...,x_N)\Psi_j(x_1,...,x_N)\,\mathrm{d}s_1\,\mathrm{d}x_2\,...\,\mathrm{d}x_N]\}/ \\ &(E_k - E_j)](v_0(\boldsymbol{r}_1) - v_0^{\text{ref}}(\boldsymbol{r}_1))\,\mathrm{d}\boldsymbol{r}_1\,\mathrm{d}\boldsymbol{r}_2\end{aligned} \tag{37}$$

where $\{\Psi_k(x_1,...,x_N)\}_{k=0}^{\infty}$ are the eigenfunctions of the reference system, $\int \mathrm{d}s_i$ denotes summation over the spin coordinate s_i, and x_i denotes both the spatial coordinate, $\boldsymbol{r}_i$, and the spin coordinate, s_i. Equation 37 shows that we may identify $(\delta\rho_k^{\text{ref}}(\boldsymbol{r})/\delta v_0(\boldsymbol{r}'))_N$ with the polarizability kernel of the reference system,[1]

$$\begin{aligned}P_k^{\text{ref}}(\boldsymbol{r}_1,\boldsymbol{r}_2) &\equiv 2N^2\sum_{j\neq k}\{[\int\cdots\int \Psi_j^*(x_1,...,x_N) \\ &\times \Psi_k(x_1,...,x_N)\,\mathrm{d}s_2\,\mathrm{d}x_1\,\mathrm{d}x_3\,...\,\mathrm{d}x_N] \\ &\times [\int\cdots\int \Psi_k^*(x_1,...,x_N)\Psi_j(x_1,...,x_N)\,\mathrm{d}s_1\,\mathrm{d}x_2\,...\,\mathrm{d}x_N]\}/ \\ &(E_k - E_j) \\ &= \left(\frac{\delta \rho_k^{\text{ref}}(\boldsymbol{r}_1)}{\delta v_0(\boldsymbol{r}_2)}\right)_N\end{aligned} \tag{38}$$

When similar manipulations are performed for the higher order functional derivatives, one obtains hyperpolarizability kernels of successive orders. Inserting our explicit expressions for the functional derivatives (eqs 35 and 38) into eq 30 gives a compact expression for the shifted potential energy surface:

$$\begin{aligned}\Upsilon[N,v_0(\boldsymbol{r})] &\equiv \Delta V_{\text{rep}}[v_0] + \int \rho_k^{\text{ref}}(\boldsymbol{r})(v_0(\boldsymbol{r}) - v_0^{\text{ref}}(\boldsymbol{r}))\,\mathrm{d}\boldsymbol{r} \\ &+ \frac{1}{2}\int\int (v_0(\boldsymbol{r}') - v_0^{\text{ref}}(\boldsymbol{r}'))P_k^{\text{ref}}(\boldsymbol{r},\boldsymbol{r}')(v_0(\boldsymbol{r}) - v_0^{\text{ref}}(\boldsymbol{r}))\,\mathrm{d}\boldsymbol{r}\,\mathrm{d}\boldsymbol{r}'\end{aligned} \tag{39}$$

To justify the decision to truncate eq 29 at second order, we examine the physical significance of each term in eq 39. The first two terms in eq 39 represent the change in the electrostatic energy of the system, including both the change in the self-repulsion of the external potential and the change in the interaction between the electrons and the charges contributing to the external potential. For example, addition of a unit positive point charge at the point $\boldsymbol{R}$,

$$\Delta v_0(\boldsymbol{r}) \equiv v_0(\boldsymbol{r}) - v_0^{\text{ref}}(\boldsymbol{r}) \equiv -\frac{1}{|\boldsymbol{r} - \boldsymbol{R}|} \tag{40}$$

and truncation of eq 39 after the first-order term in $\Delta v_0(\boldsymbol{r})$ yields the molecular electrostatic potential, $\phi(\boldsymbol{R})$.

Electrostatic effects are not sufficient for explaining chemical reactivity. As an example, consider the thiocyanate anion, SCN^-, which is a Lewis base. Both resonance effects and inductive effects tend to concentrate electron density near the nitrogen atom, and, as expected, the electrostatic potential is found to be most negative (and hence most attractive to positive species (e.g., a Lewis acids)) near the nitrogen atom. However, with the exception of very hard Lewis acids, SCN^- binds through the sulfur atom.[60] While the electrostatic potential directs the Lewis acid to bind to the nitrogen atom, the electron density of SCN^- is most readily polarized near the sulfur center, and hence the sulfur center is the favored binding site for polarizable reagents (soft Lewis acids). A theory that successfully treats ambidentate ligands such as SCN^-, then, must include both electrostatic effects (in order to successfully predict reactivity with hard acids) and polarization (in order to successfully predict reactivity with softer acids). The third term in eq 39 represents the "linear response" of the density to the change in external potential, consequently including the effects of density polarization. *Accordingly, truncation of the functional Taylor series at second order provides a theory that accounts for both electrostatic effects and the polarization of the density due to the change in external potential.*

It is not easy to calculate hyperpolarizability tensors. While the third-order and higher order terms in the Taylor series are negligible when the reference state strongly resembles the target state, the electric fields due to $\Delta v_0(\boldsymbol{r})$ are typically strong (because of the small distances involved), and so, in general, hyperpolarizability contributions to the energy may not be neglected. However, since the hyperpolarizability terms, like the linear polarizability term, reflect the deformation of the density due to the change in external potential, these terms do not represent effects qualitatively different from those already included in $\Upsilon[N,v_0(\boldsymbol{r})]$; hence, truncation of the functional Taylor series at second order can be useful for qualitative studies of chemical reactivity. We emphasize, however, that the second-

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(60) The proton is the prototypical hard Lewis acid. Consider, then, that both HSCN and HNCS are stable species. Since $K_a^{\text{HSCN}}/K_a^{\text{HNCS}} = 660$, we find that, as expected for a very hard acid, HNCS is more stable that HSCN. However, the fact that HSCN exists at all underscores the chemical importance of electron density polarization effects.

order truncation of the Taylor series will probably not yield quantitative accuracy for geometries that do not resemble the reference geometry, $v_0^{\mathrm{ref}}(\boldsymbol{r})$. One might remedy this situation by truncating the perturbation series (eq 29) at higher order. Alternatively, one could use the functional analogue of Taylor's series with remainder;[61] for instance:[62]

$$\Upsilon[N,v_0(\boldsymbol{r})] \equiv \Delta V_{\mathrm{rep}}[v_0] + \int \rho_k^{\mathrm{ref}}(\boldsymbol{r})\Delta v_0(\boldsymbol{r})\,\mathrm{d}\boldsymbol{r} + \int_0^1 \{(1-\epsilon)\int\int \Delta v_0(\boldsymbol{r}')P_k^{v_0^{\mathrm{ref}}(\boldsymbol{r})+\epsilon\Delta v_0(\boldsymbol{r})}(\boldsymbol{r},\boldsymbol{r}')\Delta v_0(\boldsymbol{r})\,\mathrm{d}\boldsymbol{r}\,\mathrm{d}\boldsymbol{r}'\}\,\mathrm{d}\epsilon \tag{41}$$

Note that evaluating the "path integral" in eq 41 requires computing the polarizability kernel for intermediate geometries: $v_0^{\mathrm{ref}}(\boldsymbol{r}) + \epsilon\Delta v_0(\boldsymbol{r})$ $(0 < \epsilon < 1)$.

C. Descriptors for Chemical Reactivity from the Truncated Taylor Series. Given $\Upsilon[N,v_0(\boldsymbol{r})]$, one may then construct reduced potential energy surfaces by considering only those portions of $\Upsilon[N,v_0(\boldsymbol{r})]$ that may be accessed through changes in the parameters, $\boldsymbol{X}$. We denote the resulting reduced potential energy surface as $\Upsilon(\boldsymbol{X})$. The optimal configuration for the molecule corresponds to the choice of parameters, $\boldsymbol{X}_{\mathrm{min}}$, that minimizes $\Upsilon(\boldsymbol{X})$. One may then compute the stability,

$$\Xi \equiv -\Upsilon(\boldsymbol{X}_{\mathrm{min}}) \tag{42}$$

and the lability,

$$\Lambda \equiv \frac{\dim(\boldsymbol{X})}{\mathrm{Tr}\{\Phi_{ij}\}} \tag{43}$$

where, in analogy to eq 26, the Hessian for the reduced potential energy surface is defined by

$$\Phi_{ij} \equiv \left.\frac{\partial^2\Upsilon(\boldsymbol{X})}{\partial X_i\,\partial X_j}\right]_{\boldsymbol{X}=\boldsymbol{X}_{\mathrm{min}}} = [\nabla\nabla\Upsilon(\boldsymbol{X})]_{\boldsymbol{X}=\boldsymbol{X}_{\mathrm{min}}} \tag{44}$$

Equations 39, 42–44 extend the results from section II to the reduced potential energy surfaces obtained through second-order truncation of the functional Taylor series expansion about the reference state. These quantities, then, can be used to explain chemical reactivity in the way the exact quantities were used in section IIC.

The reduced potential energy surfaces for Brönsted–Lowry acids and bases (Example 5) merit special attention. Recall that $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ represents the change in the molecular energy (to within the error accrued through truncation of the Taylor series) caused by adding a proton at the point $\boldsymbol{R}$. (The requisite change in external potential is given by eq 40.) Accordingly, $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ is exactly the electrostatic potential,[52–54] $\phi(\boldsymbol{R})$, plus a correction that approximates the polarizing effect of the proton on the density. Because it includes polarization effects, $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ represents a more appropriate reactivity index than $\phi(\boldsymbol{R})$ for ambidentate ligands and soft reagents.

The quantity $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ is related to the change in molecular energy induced by placing a negative point charge at the point $\boldsymbol{R}$, and is hence expected to possess utility similar to that of $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$. In particular, we expect $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ to be appropriate to Brönsted–Lowry acids and the reactions of molecules with anionic reagents. Similarly, we expect $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ to be an appropriate index for describing Brönsted–Lowry bases and reactions of molecules with cationic reagents. (Here, a reagent is regarded as anionic if the active site is negatively charged, while a reagent is regarded as cationic if the active site has a positive change.)

Because $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ and $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ are obtained by adding point charges to the system, these indices are most appropriate for describing the reactivity of a molecule with respect to small, unpolarizable reagents. That is, $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ is particularly appropriate to hard, cationic reagents, while $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ is particularly appropriate to hard, anionic reagents. While many cationic reagents are fairly hard, most anionic reagents are quite soft. To describe the reactivity of a molecule with respect to soft reagents, we replace the point charge in the description of $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ and $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ with a "smeared" point charge,

$$n_{\pm}(\boldsymbol{R};\boldsymbol{r}) \equiv \pm\frac{1}{\pi^{3/2}\sigma^3}\,\mathrm{e}^{-(|\boldsymbol{r}-\boldsymbol{R}|/\sigma)^2} \tag{45}$$

where σ approximates the size of the reagent. Analogous to eq 40, which represents the change in the external potential due to a point charge, when using the smeared point charge of eq 45, the change in external potential is given by

$$v_0(\boldsymbol{r}) - v_0^{\mathrm{ref}}(\boldsymbol{r}) \equiv -\int n_{\pm}(\boldsymbol{R};\boldsymbol{r})\frac{1}{|\boldsymbol{r}-\boldsymbol{R}|}\,\mathrm{d}\boldsymbol{r} \tag{46}$$

Substituting eq 46 into eq 39, we obtain a generalization of $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ and $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ that is more appropriate for soft reagents, which we denote $\Upsilon_{\mathrm{BL-base}}^{\mathrm{soft}}(\boldsymbol{R})$ and $\Upsilon_{\mathrm{BL-acid}}^{\mathrm{soft}}(\boldsymbol{R})$. In the limit of infinitely small reagent size ($\sigma \to 0$), $\Upsilon_{\mathrm{BL-base}}^{\mathrm{soft}}(\boldsymbol{R})$ and $\Upsilon_{\mathrm{BL-acid}}^{\mathrm{soft}}(\boldsymbol{R})$ become equal to $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ and $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$.

D. Extension to Degenerate States. Note that eqs 35 and 38 hold not only for ground states, but for any nondegenerate state. Hence, the developments of this section are appropriate not only for reactions on ground-state potential energy surfaces, but also for reactions on excited-state potential energy surfaces.

For degenerate states, different perturbations, $\delta v(\boldsymbol{r}) \equiv v_0(\boldsymbol{r}) - v_0^{\mathrm{ref}}(\boldsymbol{r})$, affect the degeneracy in different ways. This physical observation is reflected in the fact that the functional derivatives, $(\delta E/\delta v_0(\boldsymbol{r}))_N$ and $(\delta^2E/\delta v_0(\boldsymbol{r}')\,\delta v_0(\boldsymbol{r}))_N$, no longer exist. However, making use of the perturbation theory of degenerate states, one may generalize the results from this section. For degenerate states, however, the quantities $(\delta E/\delta v_0(\boldsymbol{r}))_N$ and $(\delta^2E/\delta v_0(\boldsymbol{r}')\,\delta v_0(\boldsymbol{r}))_N$ are supplanted by generalized forms for the functional derivative, $\delta E_N[v_0,\delta v]$ and $\delta^2E_N[v_0,\delta v]$, wherein the differentials depend not only upon the reference state $(N,v_0(\boldsymbol{r}))$, but also upon the particular perturbation, $\delta v(\boldsymbol{r})$, under consideration.[63]

IV. Grand Canonical Ensemble

For multicomponent systems, the indistinguishability of electrons prevents one from assigning particular electrons to an individual component, rendering it difficult to define the number of electrons in a component, N_c. In analogy to classical statistical mechanics, one performs a Legendre transformation,

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[61] van Leeuwen, R.; Baerends, E. J. *Phys. Rev. A* **1995**, *51*, 170.

[62] Equation 41 follows directly from the first-order Taylor Series + remainder form of eq 32 and the chain rule for functional derivatives.

[63] The functional derivatives considered in the text are Fréchet functional derivatives. The somewhat weaker concept of a Gâteaux functional derivative (see eq 3 of ref 14) would be sufficient for the present purposes, but it, like the Fréchet derivative, does not exist for degenerate states. The "generalized functional derivative" considered here is usually referred to as a Gâteaux variation. More information on the various definitions of functional derivatives may be found in the following: Sagan, H. *Introduction to the Calculus of Variations*; Dover: New York, 1992; Chapter 1.

$$\Omega[\mu,v_0(\boldsymbol{r})] \equiv E[N,v_0(\boldsymbol{r})] - \mu N \tag{47}$$

which shifts variables from the electron number to the electronic chemical potential.[32−34] The electronic chemical potential enters eq 47 as a Lagrange multiplier, enforcing the constraint of constant particle number, and hence is given by[8]

$$\mu \equiv \left(\frac{\partial E[N,v_0(\boldsymbol{r})]}{\partial N}\right)_{v_0(\boldsymbol{r})} \tag{48}$$

When the system is in its ground state, μ is constant throughout the system, and hence the chemical potential of a component of the system, $\mu_c \equiv \mu$, is easily defined. Accordingly, the Legendre transformation from the canonical ensemble to the grand canonical ensemble is especially useful for treating systems which consist of multiple, strongly interacting components. The canonical ensemble is most often appropriate for gas-phase processes (where the number of electrons in the reactants and products is equal), while the grand canonical ensemble is often appropriate for solution-phase processes (where, in equilibrium, the electronic chemical potentials of the reactants and products both equal the electronic chemical potential of the solvent).

We would like to develop results for the grand canonical ensemble that are analogous to the results from sections II and III. The results in sections II and III were derived subject to the constraint of constant particle number, and hence, by analogy, results for the grand canonical ensemble will be derived subject to the constraint of constant chemical potential. This leaves section II unchanged except for the replacement of the electronic energy, $E[N,v_0(\boldsymbol{r})]$, with $E[N,v_0(\boldsymbol{r})] - \mu N$. When measuring the potential energy relative to some reference state (eq 9), this change results in the additional term

$$-\mu(N - N_{\mathrm{ref}}) \tag{49}$$

where N_{ref} is the number of particles associated with the reference state.

The first substantial change comes in section III, where eq 30 is replaced by the analogous

$$\begin{aligned}\Upsilon_\mu[\mu,v_0(\boldsymbol{r})] = {} & \Delta V_{\mathrm{rep}}[v_0] \\ & + \int \left(\frac{\delta\Omega}{\delta v_0(\boldsymbol{r})}\right)_\mu\Bigg]_{v_0^{\mathrm{ref}}} (v_0(\boldsymbol{r}) - v_0^{\mathrm{ref}}(\boldsymbol{r}))\,\mathrm{d}\boldsymbol{r} \\ & + \frac{1}{2}\int\int (v_0(\boldsymbol{r}') - v_0^{\mathrm{ref}}(\boldsymbol{r}'))\left(\frac{\delta^2\Omega}{\delta v_0(\boldsymbol{r}')\,\delta v_0(\boldsymbol{r})}\right)_\mu\Bigg]_{v_0^{\mathrm{ref}}} \\ & \times (v_0(\boldsymbol{r}) - v_0^{\mathrm{ref}}(\boldsymbol{r}))\,\mathrm{d}\boldsymbol{r}\,\mathrm{d}\boldsymbol{r}'\end{aligned} \tag{50}$$

In eq 50, we denote the truncated functional Taylor series expansion of the reduced potential energy surface by $\Upsilon_\mu[\mu,v_0(\boldsymbol{r})]$, but the subscript may be omitted whenever there is little chance of confusion with the constant N case.

Equations 30 and 50 differ only in the functional derivatives, for while

$$\left(\frac{\delta\Omega}{\delta v_0(\boldsymbol{r})}\right)_\mu\Bigg]_{v_0^{\mathrm{ref}}} = \rho^{\mathrm{ref}}(\boldsymbol{r}) = \left(\frac{\delta E}{\delta v_0(\boldsymbol{r})}\right)_N\Bigg]_{v_0^{\mathrm{ref}}} \tag{51}$$

the softness kernel,

$$s^{\mathrm{ref}}(\boldsymbol{r},\boldsymbol{r}') \equiv -\left(\frac{\delta\rho^{\mathrm{ref}}(\boldsymbol{r})}{\delta v_0(\boldsymbol{r}')}\right)_\mu = -\left(\frac{\delta^2\Omega}{\delta v_0(\boldsymbol{r}')\,\delta v_0(\boldsymbol{r})}\right)_\mu\Bigg]_{v_0^{\mathrm{ref}}} \tag{52}$$

is not always equal to the negative of the polarizability kernel (eq 37), $-P_0^{\mathrm{ref}}(\boldsymbol{r},\boldsymbol{r}')$. (However, $s^{\mathrm{ref}}(\boldsymbol{r},\boldsymbol{r}') = -P_0^{\mathrm{ref}}(\boldsymbol{r},\boldsymbol{r}')$ at zero temperature.[64−66]) Substitution of eqs 51 and 52 into eq 50 yields a compact form for the shifted potential energy surface:

$$\begin{aligned}\Upsilon_\mu[\mu,v_0(\boldsymbol{r})] = {} & \Delta V_{\mathrm{rep}}[v_0] + \int \rho^{\mathrm{ref}}(\boldsymbol{r})(v_0(\boldsymbol{r}) - v_0^{\mathrm{ref}}(\boldsymbol{r}))\,\mathrm{d}\boldsymbol{r} \\ & - \frac{1}{2}\int\int (v_0(\boldsymbol{r}') - v_0^{\mathrm{ref}}(\boldsymbol{r}'))s^{\mathrm{ref}}(\boldsymbol{r},\boldsymbol{r}')(v_0(\boldsymbol{r}) - v_0^{\mathrm{ref}}(\boldsymbol{r}))\,\mathrm{d}\boldsymbol{r}\,\mathrm{d}\boldsymbol{r}'\end{aligned} \tag{53}$$

Equation 53 is analogous to eq 39. The definitions for the stability, Ξ, and the lability, Λ, in grand canonical ansatz are analogous to their definitions in eqs 42 and 43.

Because the functional derivative of $E[N,v_0(\boldsymbol{r})]$ with respect to the external potential and the functional derivative of the grand potential $\Omega[\mu,v_0(\boldsymbol{r})]$ with respect to the external potential both equal the electron density, the first-order truncations of $\Upsilon N(\boldsymbol{X})$ (eq 39) and $\Upsilon_\mu(\boldsymbol{X})$ (eq 53) are identical. Accordingly, in both the canonical and the grand canonical ensembles, the effect of changing the external potential is, to first order, strictly electrostatic. As we may regard $s(\boldsymbol{r},\boldsymbol{r}')$ as a polarizability kernel for a system at constant chemical potential, the second-order terms in eqs 39 and 53 measure similar effects, namely, the change in energy due to the rearrangement of the density that occurs after a change in the external potential.

V. Discussion

A. Links between External Potential-Based and Electron Density-Based Reactivity Descriptors. By considering how the molecular energy changes as the external potential changes, but the electron number (or chemical potential) is held constant, we have derived a number of reactivity indices, chief among them the diverse reduced potential energy surfaces, $\Upsilon(\boldsymbol{X})$, the stability, Ξ, and the lability, Λ. We may refer to these indices as "external potential-based" reactivity indices, in contrast with the usual reactivity indices of density functional theory,[1,14] which we refer to as "electron density-based" indices. As mentioned in the Introduction, external potential-based indices are most appropriate for describing chemical reactions in which the external potential changes but the number of electrons (or chemical potential) changes little, if at all.

Using methods similar to those used here, in ref 14 electron density-based reactivity indices were explored. Just as the best way to change the external potential at constant electron number (or chemical potential) is found by minimizing the molecular energy with respect to the family of external potentials associated with the parametrization $\boldsymbol{X}$, the best way to increase or decrease the number of electrons (or the chemical potential) is found by minimizing the molecular energy with respect to the family of electron densities that possess the appropriate number of electrons (or chemical potential). These two variational constructs yield the external potential-based and electron density-based reactivity indices, respectively.

Starting with the work of Berkowitz and Parr,[67] many researchers have sought relationships between electron density-based descriptors of chemical reactivity and changes in molecular geometry. In particular, many authors have explored the relationships between the potential energy surface for a reaction and the chemical hardness, chemical potential, and polarizability along the reaction path.[68−70] The changes in molecular confor-

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mation due to ionization and electron capture may be predicted using the nuclear Fukui functions.[65,71] Similar results for electronic excited states were derived by Ayers and Parr in the context of the Grochala−Albrecht−Hoffmann rule.[72,73] Subsuming all of these results is the general theory of "mapping relations" between changes in electron density and changes in molecular geometry.[74−78]

Recall that for a system with an integer numbers of particles at zero temperature, derivatives of the energy with respect to particle number do not exist; hence at zero temperature, each electron density-based descriptor is replaced by two descriptors, one in which the derivative is taken from above, and one in which the derivative is taken from below.[79] For instance, corresponding to eq 48, one now has two chemical potentials, one where the derivative is taken from above,

$$\mu^{+} \equiv \left(\frac{\partial E[N,v_0(\boldsymbol{r})]}{\partial N}\right)^{+}_{v_0(\boldsymbol{r})} = -A \tag{54}$$

and one where the derivative is taken from below,

$$\mu^{-} \equiv \left(\frac{\partial E[N,v_0(\boldsymbol{r})]}{\partial N}\right)^{-}_{v_0(\boldsymbol{r})} = -I \tag{55}$$

I and A denote the ionization potential and electron affinity, respectively. Likewise, there are now two Fukui functions,

$$f^{+}(\boldsymbol{r}) \equiv \left(\frac{\partial \rho(\boldsymbol{r})}{\partial N}\right)^{+}_{v_0(\boldsymbol{r})} = \left(\frac{\delta \mu^{+}}{\delta v_0(\boldsymbol{r})}\right)_{N} = \rho_{N+1}(\boldsymbol{r}) - \rho_{N}(\boldsymbol{r}) \tag{56}$$

and

$$f^{-}(\boldsymbol{r}) \equiv \left(\frac{\partial \rho(\boldsymbol{r})}{\partial N}\right)^{-}_{v_0(\boldsymbol{r})} = \left(\frac{\delta \mu^{-}}{\delta v_0(\boldsymbol{r})}\right)_{N} = \rho_{N}(\boldsymbol{r}) - \rho_{N-1}(\boldsymbol{r}) \tag{57}$$

where $\rho_N(\boldsymbol{r})$ denotes the electron density for the N-electron system with external potential $v_0(\boldsymbol{r})$. At zero temperature, the hardness,

$$\eta \equiv \left(\frac{\partial^2 E[N,v_0(\boldsymbol{r})]}{\partial N^2}\right)_{v_0(\boldsymbol{r})} \tag{58}$$

is zero when the derivatives are taken from above or below and infinite when a central difference formula is used. For this reason, it is most useful to define η with the "$\Delta N = 1$" finite difference approximation to eq 58:

$$\eta = \mu^{+} - \mu^{-} = I - A \tag{59}$$

Table 1. Correspondences between External Potential-Based and Electron Density-Based Reactivity Indices

	type of index	
	external potential-based	electron density-based
local reactivity	$\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$	$f^{+}(\boldsymbol{r})$
	$\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$	$f^{-}(\boldsymbol{r})$
global stability	$\Xi_{\mathrm{BL-acid}}$	μ^{+}
	$\Xi_{\mathrm{BL-base}}$	μ^{-}
selectivity	Λ,Π	η

The Fukui function from above, $f^{+}(\boldsymbol{r})$, represents the best way to add an electron to a molecule, M, while the chemical potential from above, μ^{+}, represents the energy gained when that electron is added. Accordingly, we expect that M reacts most readily with Lewis bases (electron donors) where $f^{+}(\boldsymbol{r})$ is large and that the magnitude of μ^{+} measures the propensity of M to accept electrons. Similarly, M reacts most readily with Lewis acids (electron acceptors) where $f^{-}(\boldsymbol{r})$ is large, and a large value for μ^{-} (small negative value) indicates that M readily donates electrons. In general, then, given a reaction between a Lewis acid, A, and a Lewis base, B,

$$\mathrm{A} + \mathrm{B} \rightarrow \mathrm{A{-}B} \tag{60}$$

we observe that A and B bind together, where $f^{+}_{\mathrm{A}}(\boldsymbol{r})$ and $f^{-}_{\mathrm{B}}(\boldsymbol{r})$ are largest. The reaction 60 is energetically favorable when

$$\Delta E \approx \mu^{+}_{\mathrm{A}} - \mu^{-}_{\mathrm{B}} = I_{\mathrm{B}} - A_{\mathrm{A}} < 0 \tag{61}$$

We conclude that strong Lewis acids have small (large negative) μ^{+}_{A}, while strong Lewis bases have large (small negative) μ^{-}_{B}. Summarizing, $f^{+}_{\mathrm{A}}(\boldsymbol{r})$ is large at the reactive sites of Lewis acids and $f^{-}(\boldsymbol{r})$ is large at the reactive sites of Lewis bases. μ^{+} measures how badly a Lewis Acid "wants" additional electrons, while μ^{-} measures how willingly a Lewis base will donate electrons.

The finite difference chemical hardness (eq 59), η, represents how "choosey" a molecule is about whether it accepts or donates electrons. Because the ionization potential of a molecule is always greater than its electron affinity, η is always positive. Recall that a molecule is a good Lewis base when I is small, and a good Lewis acid when A is big. Accordingly, a molecule is a good Lewis acid *and* a good Lewis base when η is small. That is, for a given acid strength (value of A), softer Lewis acids are better Lewis bases than harder Lewis acids. If one considers that an electron-transfer reaction between two molecules, A and B, occurs when either $I_{\mathrm{A}} - A_{\mathrm{B}}$ (electron transfer from A to B) or $I_{\mathrm{B}} - A_{\mathrm{A}}$ (electron transfer from B to A) is greater than zero, it becomes apparent that soft acids and bases react with a wider range of compounds than hard acids and bases of similar strength. Ergo the "hardness implies stability" maxim.[19,28]

Recalling that Brönsted−Lowry acid/base theory is a special case of Lewis acid/base theory, we expect that there exist correspondences between the external potential-based indices for Brönsted−Lowry acids and bases and the electron density-based indices for Lewis acids and bases. These correspondences are summarized in Table 1. $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ and $f^{+}_{\mathrm{A}}(\boldsymbol{r})$ are similar indices. Recall that $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ approximates the change in molecular energy due to placing a negative point charge at the point $\boldsymbol{R}$. Since $f^{+}_{\mathrm{A}}(\boldsymbol{r})$ is large in those regions of A that are most conducive to stabilizing electrons, and since electrons are negatively charged, we expect that $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ and $f^{+}_{\mathrm{A}}(\boldsymbol{r})$ are large in similar regions of the molecule. Similarly, corresponding to $f^{-}_{\mathrm{B}}(\boldsymbol{r})$, we have $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$. $f^{-}_{\mathrm{B}}(\boldsymbol{r})$ is large in regions of B where electrons are poorly stabilized by the external potential, and we expect that it is exactly these locations where the addition of a proton most effectively stabilizes the molecule. Accordingly,

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(79) A more detailed derivation of these results is found in the appendix of ref 14.

we expect $f_{\mathrm{B}}^{-}(\boldsymbol{r})$ and $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$ to frequently agree in their predictions of molecular reactivity.

Corresponding to the global reactivity indices, μ^{+} and μ^{-}, are the Brönsted–Lowry stabilities,

$$\begin{aligned}\Xi_{\mathrm{BL-acid}} &\approx X_{\mathrm{BL-acid}} \equiv -\mathrm{PDE}\\ &\equiv E[\mathrm{H{:}A}] - E[\mathrm{A{:}}] \approx \left(\frac{\partial E_{\mathrm{H:A}}}{\partial N_{\mathrm{H}}}\right)^{-}\\ \Xi_{\mathrm{BL-base}} &\approx X_{\mathrm{BL-base}} \equiv \mathrm{PA}\\ &\equiv E[\mathrm{B{:}}] - E[\mathrm{H{:}B}] \approx -\left(\frac{\partial E_{\mathrm{B:}}}{\partial N_{\mathrm{H}}}\right)^{+}\end{aligned} \tag{62}$$

where PDE is the proton dissociation energy and PA is the proton affinity. Note that, like the electron dissociation energy (I) and the electron affinity (A), both the PDE and the PA are nonnegative. Large values for the Brönsted–Lowry stabilities indicate strong acids and bases. By contrast, small values of μ^{+} (large A) are associated with strong Lewis acids, and large values of μ^{-} (small I) are associated with strong Lewis bases.[80] Note that the electron chemical potentials (eqs 54 and 55) and the Brönsted–Lowry stabilities (eq 62) are related to finite difference approximations to the energy derivatives with respect to the number of electrons and protons, respectively. Lohr exploited this similarity to define the protofelicity,

$$\chi_{\mathrm{P}} \equiv \frac{\mathrm{PDE} + \mathrm{PA}}{2} \tag{63}$$

The protofelicity performs a role in the theory of proton-transfer analogous to that of the electronegativity in the theory of electron transfer.[57]

The lability does not correspond to any of these electron density-based indices. The lability represents the local selectivity of the site in a Brönsted–Lowry acid or base and hence measures the "decisiveness" of the local indices, $\Upsilon_{\mathrm{BL-acid}}(\boldsymbol{R})$ and $\Upsilon_{\mathrm{BL-base}}(\boldsymbol{R})$. To draw a connection to electron density-based theory, Λ corresponds to how strongly peaked the Fukui function is in regions of high reactivity.

The "external potential-based" analogue to the chemical hardness is provided by the *proton hardness*:[57]

$$\begin{aligned}\Pi &\equiv -(\Xi_{\mathrm{BL-acid}} + \Xi_{\mathrm{BL-base}})\\ &\approx P \equiv \mathrm{PDE} - \mathrm{PA} \approx \frac{\partial^2 E}{\partial N_{\mathrm{H}}^2}\end{aligned} \tag{64}$$

The proton hardness, like the chemical hardness, is nonnegative. Also like the chemical hardness, for a given acid strength (so that $\Xi_{\mathrm{BL-acid}}$ is fixed), better bases possess smaller values for Π. Similarly, for a given base strength, better acids possess smaller values for Π.[81] Hence, molecules with large Π are "choosey" as to whether they act as acids or bases, while molecules with small Π possess both acidic protons and basic sites. This indicates that molecules with small Π are more reactive than molecules with large Π, and hence the "hardness implies stability" maxim applies not only to the electronic hardness, η, but also the proton hardness, Π.

B. Concluding Remarks. To summarize, the external potential-based description in this paper provides reactivity indices appropriate to processes wherein the external potential changes, but either the number of electrons or the chemical potential remains constant. By contrast, the electron density-based description of ref 14 and elsewhere[1] provides reactivity indices that are most appropriate for reactions, such as electron-transfer reactions, in which the number of electrons or chemical potential changes, while the external potential changes little. *Since any chemical process can be written as a sum of two steps, one in which the electron number (or chemical potential) changes but the external potential does not, and one in which the external potential changes but the number of electrons (or chemical potential) does not, the reactivity indices introduced in this paper, when combined with the already extant reactivity indices explored in the previous paper, provide a complete set of reactivity indices for understanding any ground-state chemical process.*

Throughout ref 14, we considered changes in electron density at constant external potential, $v_0(\boldsymbol{r})$. By contrast, throughout the present paper, we have considered the effect changing the external potential has on the electron density (the polarizability terms in eqs 39 and 53 measure the way the electron density "follows" changes in the external potential). One may reasonably ask, then, about the form of a theory in which the external potential, $\omega(\boldsymbol{r})$, and the density, $\rho(\boldsymbol{r})$, are varied independently. For this purpose, we define the molecular energy functional,

$$E[\rho,w] \equiv F[\rho] + \int \rho(\boldsymbol{r}) w(\boldsymbol{r})\, \mathrm{d}\boldsymbol{r} \tag{65}$$

where $F[\rho]$ is the Hohenberg–Kohn functional. In both ref 14 and sections III and IV herein, the key mathematical result is the second-order Taylor series expansion. Taking the Taylor series expansion of eq 65, substituting in the definitions from Table 1 of ref 14, and simplifying, we obtain

$$\begin{aligned}E[\rho,w] = {}& E[\rho_0,w_0] + \int \rho(\boldsymbol{r})(w(\boldsymbol{r}) - w_0(\boldsymbol{r}))\, \mathrm{d}\boldsymbol{r}\\ &+ \int \{(\mu[\rho] - v[\rho;\boldsymbol{r}]) + w_0(\boldsymbol{r})\}(\rho(\boldsymbol{r}) - \rho_0(\boldsymbol{r}))\, \mathrm{d}\boldsymbol{r}\\ &+ \frac{1}{2}\int\int (\rho(\boldsymbol{r}) - \rho_0(\boldsymbol{r}))\eta[\rho;\boldsymbol{r},\boldsymbol{r}'](\rho(\boldsymbol{r}') - \rho_0(\boldsymbol{r}'))\, \mathrm{d}\boldsymbol{r}\, \mathrm{d}\boldsymbol{r}' + \ldots\end{aligned} \tag{66}$$

In particular, we note that because eq 65 is a linear functional of $w(\boldsymbol{r})$, all functional derivatives of $E[\rho,w]$ which are of greater than first order in $\delta w(\boldsymbol{r})$ vanish. Except for the $\int \rho(\boldsymbol{r})(w(\boldsymbol{r}) - w_0(\boldsymbol{r}))\, \mathrm{d}\boldsymbol{r}$ term, eq 66 is identical to eq 15 in ref 14. (This similarity results from the following identity: $E[\rho,w] - E[\rho_0,w_0] \equiv E_{\omega_0}[\rho] - E_{w_0}[\rho_0] + \int \rho(\boldsymbol{r})(w(\boldsymbol{r}) - w_0(\boldsymbol{r}))\, \mathrm{d}\boldsymbol{r}$.)

Noting that the external potential-based indices of this paper apply to both ground and excited states, it is reasonable to ask whether one can obtain electron density-based indices for excited states. In a series of papers, Chattaraj and Poddar have examined the properties of electron density-based reactivity indices for the lowest state of any given symmetry.[82−84] Extending these results to other excited states requires an alternative formulation of density functional theory and will not be pursued here.[85]

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(80) Table 1 in ref 57 compares electron density-based quantities (I and A) to their external potential based analogues (PDE and PA).

(81) For a table of protofelicities and proton hardnesses, the reader is referred to ref 57.

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