

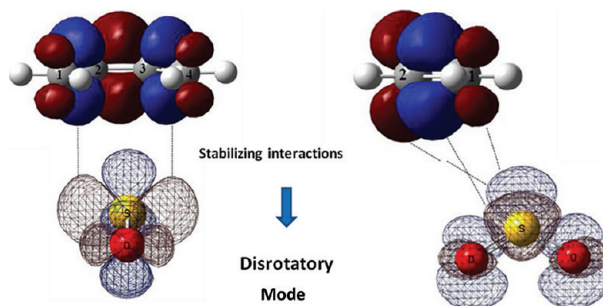
# The Woodward–Hoffmann Rules Reinterpreted by Conceptual Density Functional Theory

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## CONSPECTUS



In an attempt to master the overwhelming amount of data on the properties of substances and their reactions, chemists scrutinize them for underlying common patterns. In modern times quantum mechanics (QM) has played a leading role in the understanding of chemical reactivity. In the late 1960s, Woodward and Hoffmann (WH) proposed one of the most successful and elegant approaches to interpret the outcome of an important type of reaction: they could predict the allowed or forbidden character of pericyclic reactions through inspection of the phase and symmetry of the orbitals of the reactants obtained by simple extended Hückel theory. Today much more powerful computational techniques, such as density functional theory (DFT), are available that yield highly accurate results even for large systems. By focusing on the electron density,  $\rho(r)$ , a fundamental carrier of information compared with the much more complicated wave function in conventional QM, DFT became the computational workhorse for systems of ever increasing complexity. However, the need for the interpretation of computational (and obviously experimental) results remains, and “conceptual DFT” has provided the answer to this challenge within the context of DFT. This branch of DFT has given precision to chemical concepts such as electronegativity, hardness, and softness and has embedded them in a perturbational approach to chemical reactivity. Previously, researchers have successfully applied conceptual DFT to generalized acid–base and, more recently, to radical and redox reactions. In this Account, we present a conceptual DFT ansatz for pericyclic reactions, a stringent test for this density-only approach, because the density has trivial symmetry and no phase.

A density response function is the key quantity in a first approach: the dual descriptor  $f^{(2)}(r)$ , the second derivative of the electron density with respect to the number of electrons. Overlapping regions of the dual descriptor of the reactant(s) with different or the same sign yield pictorial representations similar to the orbital phase and symmetry-based pictures in the WH formulation. In a second approach, a key quantity is the evolution of the chemical hardness at the onset of the reaction. This quantity makes contact with Zimmerman's alternative approach to the WH rules based on the aromaticity of the transition state. Using the dual descriptor and the initial hardness response, we reinterpret the WH results for the four types of pericyclic reactions (cycloadditions, electrocyclicizations, and sigmatropic and chelotropic reactions), both thermodynamically and photochemically. We demonstrate that these two approaches, which require only simple quantum chemical procedures (overlapping densities and HOMO–LUMO gap type calculations along a few points of a model reaction coordinate), are intimately related through a relation that converts the local (i.e., position-dependent) dual descriptor into the global (i.e., position-independent) (initial) hardness response. Our results show that with a density-only based approach the WH rules can be reinterpreted, pointing to the fundamental importance of the electron density as carrier of information as highlighted in the basic theorems of DFT.

## I. Introduction

Chemists face a bewildering amount and diversity of data in their quest to discover the physical and chemical properties of substances. According to recent statistics from CAS, there are more than 50 million known organic and inorganic compounds.<sup>1</sup> The number of potential reactions between these compounds is stupefying and grows daily as the size of this chemical catalogue burgeons. Encyclopedic knowledge of this catalogue is beyond human capacity, so chemists cope by finding underlying patterns.<sup>2</sup> The greatest success along these lines was also the first: the periodic table. It is worth remembering that Mendeleev's table was constructed on the basis of experimental data about the chemical and physical properties of the elements.<sup>3</sup>

In modern times, most principles for understanding chemistry rest on quantum mechanics. Already in the 1930s, due to the pioneering work by Hartree, Slater, etc., the basic structure of the periodic table was recovered through quantum mechanics,<sup>4</sup> thereby giving theoretical and definitive support to Mendeleev's brilliant synthesis. Later on, it led to more sophisticated mathematical frameworks for understanding chemistry. All of these frameworks relied on the concept of an orbital, a wave function describing a hypothetical one-electron state. The primacy of the orbital arose because the electronic Schrödinger equation was not analytically solvable for systems with two or more electrons. Instead, inspired by the exactly solvable hydrogenic atoms, many-electron wave functions were systematically built up from one-electron wave functions, orbitals. This orbital concept, as extended to molecules by Hund, Mulliken, and others, has withstood the test of time.<sup>5</sup>

Most computational approaches to molecular electronic structure theory, or quantum chemistry, are still orbital-based, an exception being quantum Monte Carlo calculations,<sup>6</sup> but even before orbitals were computationally useful, the orbital framework was employed by chemists to interpret the chemical properties of molecules, starting in the 1930s with Hückel's enlightening work on the electronic structure of unsaturated systems and its link to aromaticity<sup>7</sup> and Mulliken's work on chemical bonding.<sup>8</sup> A general framework for chemical reactivity, now termed frontier molecular-orbital theory, was developed by Fukui and others in the 1950s, enabling the practicing chemist to not only interpret but sometimes even predict the outcome of certain types of reactions from the properties of the reactants.<sup>9</sup>

This marriage of experimental chemistry and quantum mechanics was highly successful, and so in the mid 1960s,

the increasing availability of computers meant that theorists could routinely assist experimentalists by rationalizing the outcome of their reactions and experimentalists could provide theorists with new data by which to test their methods. Nevertheless, accurate methods were computationally feasible only for molecules with a handful of atoms.

Three major developments that are directly relevant to this Account characterized the middle and late 1960s.

- 1 The development of computational algorithms and software for *ab initio* quantum chemistry by Pople, Davidson, and others.<sup>10,11</sup> With general-purpose software,<sup>12</sup> one could systematically improve the level of computation by increasing the size of the (orbital) basis set and increasing the number of Slater determinants (of orbitals) included in the wave function. As computers became more powerful, molecules with more atoms became accessible, and higher accuracy became achievable.
- 2 The presentation by Woodward and Hoffmann<sup>13,14</sup> of a wave function/orbital-based rationalization for pericyclic reactions. Using only the phase and symmetry of the orbitals from a simple extended Hückel approach not only permitted the interpretation of existing data but soon turned out to be of high predictive value. The WH rules are among the most beautiful and convincing example of how theoretical chemistry, and specifically orbital-based quantum chemistry, can guide the experimentalist. The simplicity and elegance of the Woodward–Hoffmann argument introduced, and popularized, molecular orbital theory to experimentalists.
- 3 The formulation of the Hohenberg–Kohn theorems,<sup>15</sup> laying the foundation for density-functional theory (DFT). This discovery hinted that wave functions (ergo orbitals), albeit undeniably convenient, might not be strictly necessary for computing and interpreting chemical processes. Specifically, the electron density can be used as the key variable in atomic, molecular, and solid-state quantum theory. The difference in complexity between the electronic density function,  $\rho(\underline{r})$ , and the electronic wave function is amazing: replacing  $\Psi$  with  $\rho$  as the fundamental carrier of information reduces the numbers of variables to 3 from  $4N$ , where  $N$  is the number of electrons, each with three spatial coordinates and one spin coordinate.

The first Hohenberg–Kohn theorem is an existence theorem, telling us that the energy, and other molecular properties, can be obtained from the electron density alone. (In mathematical terms:  $E$  is a functional of  $\rho$ ,  $E = E[\rho]$ .)

However it gives no recipe for how to do this. In the second theorem, a variational principle is established. The functional being varied, however, is not known in a simple closed form and must be approximated. To make further progress, Kohn and Sham reintroduced orbitals.<sup>16</sup> Kohn–Sham DFT is really a reformulation of the Hartree model on which so much chemical intuition is based, but now corrected for the effects of exchange and correlation. The unknown quantity is now the exchange–correlation energy, whose functional derivative enters into the Kohn–Sham equations.

With the development of improved exchange–correlation functionals in the late 1980s and early 1990s (among others Becke's exact exchange functional<sup>17</sup>) and the implementation of DFT in popular quantum chemistry codes like Gaussian,<sup>12</sup> Kohn–Sham DFT became the workhorse in many areas of computational chemistry.<sup>18</sup> Development continues, and improved functionals, refined algorithms, and faster computers make DFT applicable to increasingly complex systems (e.g., molecules in solvent, heterogeneous catalysis, reactions in enzymes, potential energy surfaces for complex reaction networks). It seems that, gradually, “everything becomes computable.” Myriad trustworthy computational results are and will be available to the practicing chemists. This at first sounds exciting (and it is), but are we not back to the original problem: chemists facing huge amounts of (now both experimental and computational) data? Is finding some framework for rationalizing and organizing these results not needed? This point stresses that, as the ease of obtaining accurate numbers with quantum chemistry methods increases and quantum chemistry even becomes predictive, the need for interpretative tools that help chemists learn what the data means also increases. As Coulson wrote,<sup>19</sup> “Give me insight, not numbers.” But chemists now (and even then) demand both. The goal of this Account is to show that electron density-based tools provide alternatives to the conventional wave function based routes to chemical insight.

## II. Conceptual Density Functional Theory

Because DFT is so preponderant in computational quantum chemistry and because the electron density can play the fundamental role, it seems natural to employ density-based interpretative tools. This program of research was initiated by Bader<sup>20</sup> (primarily concerned with molecular structure and chemical bonding) and Parr (primarily concerned with chemical reactivity) in the 1970s.<sup>21</sup> The seminal paper in molecular reactivity was published by Parr et al. in 1978.<sup>22</sup> They recognized that the Lagrangian multiplier that is

introduced when minimizing  $E[\rho]$  with respect to the electron density for a fixed total number of electrons,  $N$ , is just the derivative of the energy of the system with respect to the number of electrons, at constant external potential (i.e., molecular geometry).

$$\mu = \left( \frac{\partial E}{\partial N} \right)_v \quad (1)$$

The same quantity had been proposed by Iczkowski and Margrave as (minus one times) the electronegativity.<sup>23</sup> In this way, one of the central, but nebulously defined, traditional chemical concepts (electronegativity) was given a firm theoretical grounding and a precise definition using DFT.

When a reagent approaches a molecule, the molecule is perturbed by electron transfer (changes in the number of electrons) or external potential (representing the interaction of the electrons in the molecule to the nuclei and electrons in the approaching reagent). The change in energy can be expressed as a total differential,

$$dE = \left( \frac{\partial E}{\partial N} \right)_v dN + \int \left( \frac{\delta E}{\delta v(\underline{r})} \right)_N \delta v(\underline{r}) d\underline{r} \quad (2)$$

The functional derivative in the second term,  $(\delta E/\delta v(\underline{r}))_N$  represents the change in energy when the external potential is increased by an infinitesimal amount at the point  $\underline{r}$ . It can be shown that

$$\left( \frac{\delta E}{\delta v(\underline{r})} \right)_N = \rho(\underline{r}) \quad (3)$$

so that, besides  $\mu$ , the other basic quantity of DFT, the electron density itself, appears. Higher order derivatives can of course be written down, the most popular ones being  $(\partial^2 E/\partial N^2)_v$ , identified as the chemical hardness ( $\eta$ ) by Parr and Pearson,<sup>24</sup> and the mixed second-order derivative

$$\left( \frac{\partial \rho(\underline{r})}{\partial N} \right)_v = \left( \frac{\partial^2 E}{\delta v(\underline{r}) \partial N} \right) = f(\underline{r}) \quad (4)$$

termed the Fukui function. The latter quantity indicates how the electron density at given point  $\underline{r}$  changes when the total number of electrons of the system,  $N$ , varies. Since in a MO picture electrons are added to the lowest unoccupied molecular orbital (LUMO) and removed from the highest occupied molecular orbital (HOMO), the Fukui function is the DFT-based extension of Fukui's frontier orbital theory.<sup>25</sup> All of the aforementioned quantities are response functions, quantifying the response of a

system's energy to perturbations in  $N$  and  $v(r)$ . Together with their higher order analogues (Box 1), they can be used as reactivity descriptors. An avalanche of papers investigating and exploiting their capacity as such has appeared, starting in the 1980s (for reviews, see ref 26). Note that these quantities do have advantages to their (molecular) orbital counterparts: (1) they are (at least in principle) experimentally accessible (since they are defined as an energy response), and (2) they can be used irrespective of the level of accuracy of the computation. Note, for example, the chemical interpretation of a wave function becomes increasingly difficult when passing from the single to the multideterminantal case whether it be the full CI limit or a valence bond function with an exploding number of resonance structures. Conceptual DFT can be employed for wave functions that go beyond the orbital model (e.g., quantum Monte Carlo calculations)<sup>6</sup> and even when the Schrödinger equation does not apply at all (as in relativistic calculations using the Dirac equation).<sup>27</sup>

**BOX 1.** Response Functions as Reactivity Indicators

$$\begin{aligned}
 E = E[N, v] &= E^0 + \left( \frac{\partial E}{\partial N} \right)_v \Delta N + \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} \right)_v \Delta N^2 \\
 &+ \int \left( \frac{\delta E}{\delta v(r)} \right)_N \delta v(r) dr + \int \left( \frac{\delta^2 E}{\delta N \delta v(r)} \right) \delta v(r) dr \Delta N \\
 &+ \iint \left( \frac{\delta^2 E}{\delta v(r) \delta v(r')} \right) \delta v(r) \delta v(r') dr dr' \\
 &= E^0 + \underbrace{\mu \Delta N}_{\substack{\text{Electronic} \\ \text{Chemical} \\ \text{Potential}}} + \underbrace{\frac{1}{2} \eta \Delta N^2}_{\substack{\text{Chemical} \\ \text{Hardness}}} + \underbrace{\int \rho(r) \delta v(r) dr + \dots}_{\substack{\text{Electron} \\ \text{Density}}} \\
 &+ \underbrace{\int f(r) \delta v(r) dr}_{\substack{\text{Fukui} \\ \text{function}}} + \underbrace{\iint \chi(r, r') \delta v(r) \delta v(r') dr dr'}_{\substack{\text{Linear response function}}}
 \end{aligned}$$

In the past decades, applications of these descriptors centered on reactions that could be classified as “acid–base” in its broadest sense (i.e., including not only classic inorganic acid/base chemistry but also complexation reactions and classical organic reactions of electrophiles/nucleophiles).<sup>26</sup> Often generalizing principles such as Sanderson's electronegativity equalization principle,<sup>28</sup> Pearson's HSAB principle,<sup>29</sup> and the principle of maximum hardness<sup>29</sup> have served as a guide to

interpret the results. Until recently, oxidation/reduction and pericyclic reactions were not considered. The former series is now documented:<sup>30</sup> by dividing the sometimes complicated overall stoichiometric equation into “elementary” steps, DFT-based reactivity indicators can be used to expose the factors favoring or disfavoring a redox reaction. But what about pericyclic reactions?

### III. Pericyclic Reactions: A Test for a Density-Only Approach to Reactivity

To interpret a pericyclic reaction, Woodward and Hoffmann scrutinized how the nature of the wave function evolved as the molecule changes from the reactant to the product structure. The key element of their argument was the correlation diagram between electronic states, which they showed how to construct, qualitatively, using only the overall symmetry of the frontier orbitals. Their key insight is that the symmetry of the orbital should be conserved throughout the reaction. If the symmetries of the occupied and unoccupied orbitals of the reagents and the products match, then they can easily be transformed into one another and the reaction is said to be (orbital) symmetry-allowed. Otherwise the reaction is unfavorable, and there is a high activation barrier associated with the need to promote electrons from an occupied to an unoccupied orbital; in such cases the reaction is said to be (orbital) symmetry-forbidden. An even simpler approach can be distilled into simple reactivity rules based on the symmetry and phase of the frontier orbitals.

All these concepts vanish in a density-only description. The electron density and its derivatives are all real-valued functions (they have no phase). Moreover, for nondegenerate ground states, they transform according to the totally symmetric representation of the molecular symmetry group. Pericyclic reactions are thus a stringent test of the conceptual DFT formalism.

This Account presents two successful density-based approaches for reinterpreting the WH rules for all four types of pericyclic reactions: cycloadditions, electrocyclizations, and sigmatropic and chelotropic reactions. For reasons of brevity, not all cases will be discussed in detail. Relevant examples are given; the reader is referred to the original papers for a more detailed case by case analysis.

The density-based route to the Woodward–Hoffmann approach relies on quantities that are (1) at least in principle experimentally accessible, because they correspond to quantum mechanical observables in view of their energy-derivative character, (2) universal, that is, not dependent on the type of

calculation, and (3) rigorous, fitting in a well-defined and, in principle, exact mathematical framework.<sup>31</sup> These precepts demand an orbital-free approach. This Account demonstrates that an orbital-free reinterpretation of the Woodward–Hoffmann rules can be attained. This demonstrates the chemical relevance of the Hohenberg–Kohn theorems: the electron density contains all information, a message we consider important for a broad chemical community. The actual calculations are mostly reducible to the hardness (say the HOMO–LUMO gap) evaluation along a model reaction coordinate or to the inspection of overlap of density-difference plots obtainable from any standard quantum chemical program package (or, in most cases, even from simple Hückel-type calculations). Our aim is not to replace the two aforementioned routes to the Woodward–Hoffmann rules but, through an independent third route, to further elucidate the origin of these rules and to offer extended use, for example, in the case of diminished or absent symmetry.

#### IV. The Dual Descriptor Approach: Regaining the Woodward–Hoffmann Rules through a Density Response Function

The first approach seeks to retain the spirit of the Woodward–Hoffmann rules as closely as possible, by reinterpreting pericyclic reactivity using a pictorial representation of a density response function instead of orbitals. Considering the unperturbed, isolated molecular electron densities of the reactant(s) does not work: for the type of systems considered, apolar (conjugated) carbon skeletons at most decorated with some polar substituents, the electron density in the reactive regions is very nearly the sum of the densities of the isolated atoms. The molecular electron densities of ethylene and butadiene, therefore, do not differ enough to explain the preferability of the [4 + 2] cycloaddition over [2 + 2] and [4 + 4] cycloadditions. A more “refined” and “differentiating” density-related descriptor, introducing more “structure” (including sign differences), is needed.

Because electrons migrate to and from the partner molecules during the reaction, looking at the response of the electron density to electron transfer seems promising. Expanding the density of reagent A,  $\rho_A(r)$ , in terms of the perturbation,  $\Delta N_A$  (the electron transfer between the two systems), we write (see Box 2)

$$\rho_A(r) = \rho_A^0(r) + \left( \frac{\partial \rho_A(r)}{\partial \Delta N_A} \right)_0 \Delta N_A + \frac{1}{2} \left( \frac{\partial^2 \rho_A(r)}{\partial \Delta N_A^2} \right) \Delta N_A^2 + \dots \quad (5)$$

The second and third terms now contain response functions of the type mentioned above: the Fukui function  $f_A(r)$  and its  $N$  derivative, the dual descriptor  $f_A^{(2)}(r)$ ,<sup>32</sup>

$$f^{(2)}(r) = \left( \frac{\partial^2 \rho(r)}{\partial N^2} \right)_v = \left( \frac{\partial f(r)}{\partial N} \right)_v \quad (6)$$

Higher order derivatives are expected to be small,<sup>26d</sup> and the polarization of the electron density by the change in external potential may be neglected because the highly “unsaturated hydrocarbon” character of the reactants yields a “flat” electrostatic potential.

**BOX 2.** Electron/Electron Interaction Energy between Two (Sub)Systems A and B as Affected by Electron Transfer and Neglecting Polarization Effects

$$\Delta E_{A,B} = \int \frac{\rho_A(r_1) \rho_B(r_2)}{r_{1,2}} dr_1 dr_2$$

$$\rho_A(r) = \rho_A^0(r) + f_A(r) \Delta N_A + \frac{1}{2} f_A^{(2)}(r) \Delta N_A^2 \quad \text{with } \Delta N_A = -\Delta N_B = \Delta N$$

$\downarrow$                        $\downarrow$   
 Fukui function    Dual descriptor

$\hookrightarrow$  “diagonal” terms

$$\Delta E_{A,B}^{0,0} = + \int \frac{\rho_A^0(r_1) \rho_B^0(r_2)}{r_{1,2}} dr_1 dr_2 \quad \text{electrostatic repulsion of unperturbed electron clouds}$$

$$\Delta E_{A,B}^{1,1} = - \int \frac{f_A(r_1) f_B(r_2)}{r_{1,2}} dr_1 dr_2 \Delta N^2 \quad \text{regioselectivity of generalized acid-base reactions}$$

$$\Delta E_{A,B}^{2,2} = + \int \frac{f_A^{(2)}(r_1) f_B^{(2)}(r_2)}{r_{1,2}} dr_1 dr_2 \Delta N^4 \quad \text{selection rules for pericyclic reactions}$$

If we use the expansion in eq 5 to expand the interaction energy between the fragments in powers of  $\Delta N$  (where  $\Delta N = \Delta N_A = -\Delta N_B$ ) and neglect the terms that involve the unperturbed electron densities (recall that these terms are indecisive for reactivity), the leading order contribution to the energy is

$$\Delta E_{AB}^{1,1} = \int f_A(r_1) \frac{1}{r_{12}} f_B(r_2) dr_1 dr_2 \Delta N^2 \quad (7)$$

This type of term, involving the Fukui functions of the interacting partners, is known to describe the regioselectivity in generalized acid–base reactions.<sup>33,34</sup> On the basis of eq 7, favorable interactions are associated with strong Coulombic interactions between the Fukui functions of the fragments. For unsaturated hydrocarbons, the Fukui functions will resemble the frontier  $\pi$ -electron densities (vide infra). This means that the Fukui functions give a relatively uniform pattern, with no qualitative differences (e.g., leading to (mis)matching of signs between a  $4n$  and a  $4n + 2$  electron system). Ignoring the terms in the interaction energy expression that involve the Fukui function,

the reactivity preferences, then, seem likely to be described by the next term in the interaction energy expression,

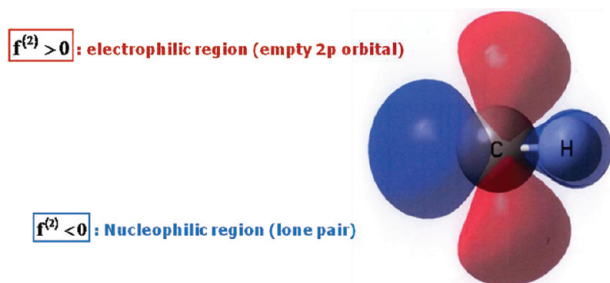
$$\Delta E_{AB}^{2,2} = \int f_A^{(2)}(r_1) \frac{1}{r_{12}} f_B^{(2)}(r_2) dr_1 dr_2 \Delta N^4 \quad (8)$$

which involves the dual descriptors of both partners.

To gain intuition about the Fukui function and the dual descriptor, consider the electron density in the frontier molecular orbital approximation. Denoting the  $N$ -electron density as  $\rho_N(r)$ , the  $N - 1$  and  $N + 1$  electron densities may be approximated in terms of the frontier molecular orbital densities as

$$\rho_{N-1}(r) = \rho_N(r) - |\phi_{\text{HOMO}}(r)|^2 \quad (9a)$$

$$\rho_{N+1}(r) = \rho_N(r) + |\phi_{\text{LUMO}}(r)|^2 \quad (9b)$$



**FIGURE 1.** The dual descriptor for carbene ( $\pm 0.01$  au surface plot): a one shot picture of both electrophilic and nucleophilic regions in space (see also ref 35).

By approximating the derivatives using finite differences, one obtains approximations for the Fukui function,

$$f^+(r) = |\phi_{\text{LUMO}}(r)|^2 \text{ for a reaction with a nucleophile} \quad (10a)$$

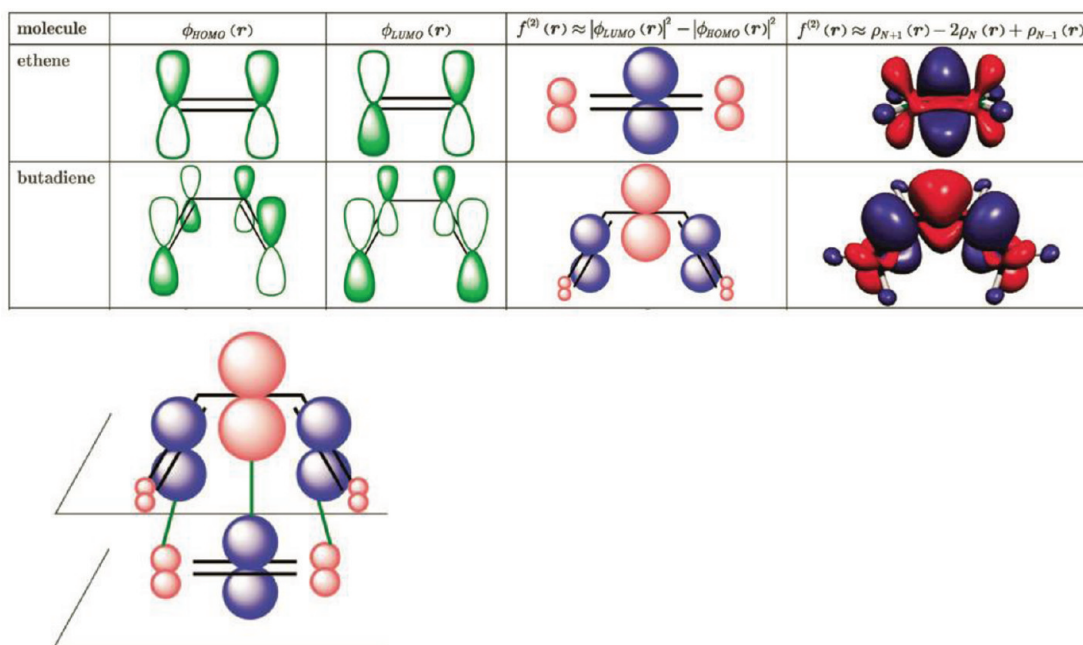
and

$$f^-(r) = |\phi_{\text{HOMO}}(r)|^2 \text{ for a reaction with an electrophile} \quad (10b)$$

The dual descriptor then can be written as

$$f^{(2)}(r) = \left( \frac{\partial f(r)}{\partial N} \right)_v \approx |\phi_{\text{LUMO}}(r)|^2 - |\phi_{\text{HOMO}}(r)|^2 \quad (11)$$

Notice that the essential ingredient of the frontier MOs, their phase and the relative sign of the contribution of the different atoms to the MO, disappears in the density-based reactivity indicators. However, unlike the Fukui function (which is everywhere positive in the frontier MO approximation), the dual descriptor has positive and negative regions in space, just like orbitals. Moreover, it is clear from eq 11 that  $f^{(2)}(r)$  will be positive in regions that are better at accepting electrons than they are at donating electrons.  $f^{(2)}(r)$  will be negative when the reverse is true.<sup>32</sup> A plot of  $f^{(2)}(r)$  gives a “single shot” picture of the “dual” electron-accepting and electron-donating capabilities of a molecule, as shown in Figure 1 for the case of carbene.



**FIGURE 2.** The dual descriptor approach for the suprafacial/suprafacial [4 + 2] cycloaddition between butadiene and ethene. The molecules align so that the favorable interactions (green lines) between their dual descriptors are maximized. Reprinted with permission from ref 36. Copyright 2007 John Wiley and Sons.

Equation 9 is the mathematical statement of the intuitively obvious reactivity rule: favorable interactions between molecules result when the nucleophilic regions of one molecule ( $f_A^{(2)r} < 0$ ; blue regions in plots) are aligned with the electrophilic regions of another molecule ( $f_B^{(2)r} > 0$ ; red regions in plots), and vice versa. This very simple rule suffices to distinguish between the two alternatives for a reaction as is typical in the WH rules: “allowed” and “forbidden”.

In Figure 2, we explore the situation for the case of a [4 + 2] cycloaddition between butadiene and ethylene.<sup>36</sup> The qualitative features of the dual descriptor are clear for ethene already at the Hückel level and confirmed at DFT level: the electron-donating capability of ethene is associated with the double bond and the electron-accepting ability is associated with the ever-so-slightly acidic hydrogen atoms. Similar features are present in butadiene and hexatriene. In Figure 2, representing the [4 + 2] suprafacial/suprafacial addition of butadiene to ethene, the reagents are appropriately matched: if the ethene molecule approaches from below the plane of the butadiene molecule, regions with opposite signs for the dual descriptor align, leading to the WH “allowed” character of the reaction. The [2 + 2] addition (Figure 3) reaction between two ethene molecules clearly shows “repulsive” interactions (blue/blue and red/red interactions). In order to create favorable interactions (indicated in green), the molecules must be strongly distorted, so that their double bonds become perpendicular, which cannot be achieved in a small unsaturated system like ethene. This chain of reasoning retrieves the s/s forbidden and a/s allowed WH rules from this (perturbed) density-only approach. In the [6 + 2] case (not shown), one observes that the best alignment of the dual descriptor plots occurs when molecules orient themselves so that a [4 + 2] addition can occur. The s/s [6 + 2] is thereby forbidden in the ground state. The fundamental role of the sign of the dual descriptor and its relevance in the energy expression in Box 2 is at the root of its success.

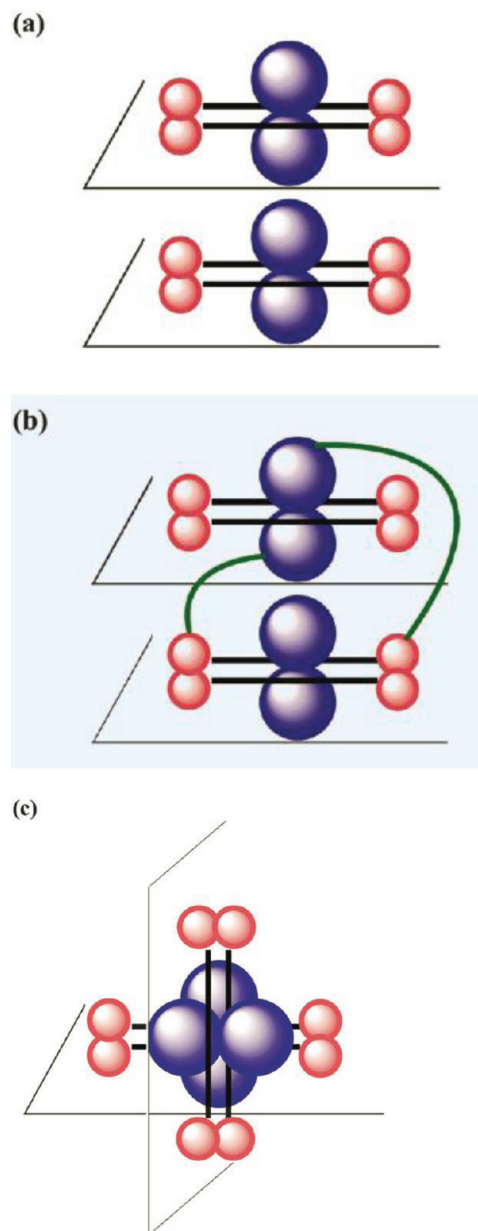
A remarkable property of the dual descriptor approach is that it directly predicts the inversion of the selection rules when passing to excited-state reactivity. In a finite difference, frozen core approximation, the electron density for the excited state  $\rho_{N,es}$  can be written as (see eq 9)

$$\rho_{N,es}(\mathbf{r}) = \rho_N(\mathbf{r}) + |\phi_{\text{LUMO}}(\mathbf{r})|^2 - |\phi_{\text{HOMO}}(\mathbf{r})|^2 \quad (12)$$

whence it is easily seen via eq 11 that

$$f_{es}^{(2)}(\mathbf{r}) \sim |\phi_{\text{HOMO}}(\mathbf{r})|^2 - |\phi_{\text{LUMO}}(\mathbf{r})|^2 \sim -f_{gs}^{(2)}(\mathbf{r}) \quad (13)$$

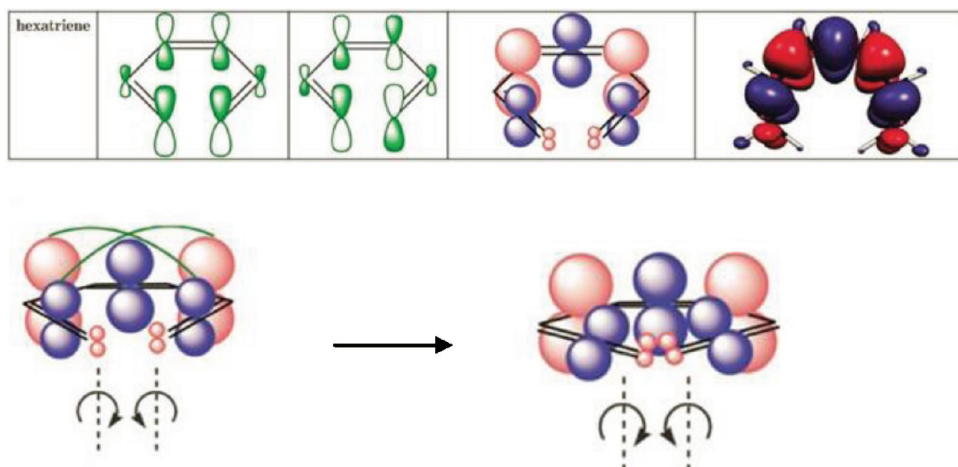
that is, the dual descriptor for the excited state,  $f_{es}^{(2)}$ , is the negative of the dual descriptor for the ground state  $f_{gs}^{(2)}$ .



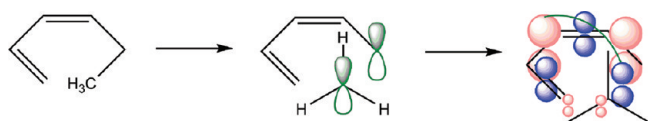
**FIGURE 3.** The dual descriptor approach for the suprafacial/antarafacial [2 + 2] cycloaddition between two ethene molecules (a). The attractive interactions (green ribbons) (b) can be exploited, if the ethene molecules rotate so that their double bonds are perpendicular (c). Reprinted with permission from ref 36. Copyright 2007 John Wiley and Sons.

In view of this, the blue and red colored regions for  $f_{gs}^{(2)}$  simply invert when passing to the excited state case. Therefore the “allowed” or “forbidden” character of the thermal reactions is inverted when passing to the excited state, retrieving a general characteristic of the WH rules.<sup>37</sup>

The dual descriptor is also the key reactivity indicator for interpreting the other types of pericyclic reactions. The electrocycloaddition of 1,3,5-hexatriene can be considered as a “generalized” Diels–Alder reaction in which the



**FIGURE 4.** The dual descriptor approach for the 1,3,5-hexatriene  $\rightarrow$  1,3-cyclohexadiene electrocyclic reaction: favorable interactions in the dual descriptor tend to make the ring buckle inward in a disrotatory fashion. Reprinted with permission from ref 36. Copyright 2007 John Wiley and Sons.



**FIGURE 5.** The dual descriptor approach for the [1,5]-methyl sigmatropic shift considered as a generalized [2 + 4] cycloaddition. After rehybridization on the way to the TS, attractive interactions within the dual descriptor (green ribbons) pull the molecule in an energetically favorable alignment. Reprinted with permission from ref 36. Copyright 2007 John Wiley and Sons.

two fragments are tethered together at their ends. Thus the electrocyclic reaction of hexatriene is related to the [4 + 2] cycloaddition discussed above, and it will be favorable for the ethene and butadiene fragments to twist toward each other. In Figure 4, favorable blue/red overlaps occur when an inward buckling of the six-membered ring being formed is performed. This corresponds to a disrotatory motion of the terminal  $\text{CH}_2$  groups, in agreement with the WH rules. Again the [2 + 2] case and the photochemical reaction give exactly the opposite behavior.<sup>36</sup>

As an example of a sigmatropic reaction,<sup>36</sup> the 1,5-methyl shift is shown in Figure 5. To characterize the migration of a methyl group, the TS is modeled by rehybridization of the methyl group to  $\text{sp}^2$ , after which the molecule resembles an ethene-type fragment (consisting of the migrating methyl group and the neighboring carbon atom) and a remnant. A favorable blue–red interaction of the dual descriptor causes the ring to buckle inward, just as in the case of the disrotatory electrocyclic reaction of cyclohexatriene. This corresponds to a suprafacial sigmatropic shift, again in agreement with the WH rules. If the remnant has two carbons (1,3-sigmatropic shift), the reaction resembles the electrocyclic reaction of butadiene, and the favored antarafacial

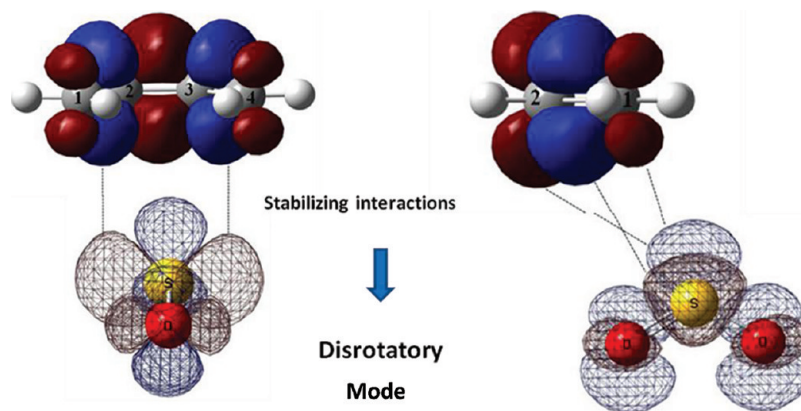
sigmatropic shift can be identified with a conrotatory mode in the electrocyclic reaction.

As an example of a chelotropic reaction, Figure 6 shows the chelotropic addition of  $\text{SO}_2$  to butadiene. For a linear approach<sup>14,37</sup> (with the  $\text{SO}_2$  plane perpendicular to the plane of butadiene and bisecting the central CC bond), there are stabilizing interactions between the central  $\text{C}_2\text{C}_3$  region and the lone pair of  $\text{SO}_2$  and, more importantly, between the  $\text{C}_1\text{C}_2$  and  $\text{C}_3\text{C}_4$  regions of the diene and the empty p-orbital region of  $\text{SO}_2$ . These interactions are enhanced and the destabilizing blue/blue interactions are diminished upon a disrotatory, outward movement of the two  $\text{CH}_2$  groups. Switching from a  $4n$  to a  $4n + 2$  system inverts the situation.<sup>38</sup> The nonlinear case (with the  $\text{SO}_2$  molecule approaching the diene or triene in a plane parallel to the central CC bond) again inverts all previous results, in agreement with the orbital-based WH rules.<sup>14,37</sup> Note that although the mathematical framework in Boxes 1 and 2 looks complicated, the successful reinterpretation of the Woodward–Hoffmann rules has been achieved without evaluation of all terms or equations in the boxes. For the practicing chemist, a few relatively simple electron density calculations and visual inspection of their overlap is sufficient to judge on the allowed or forbidden character of the reaction.

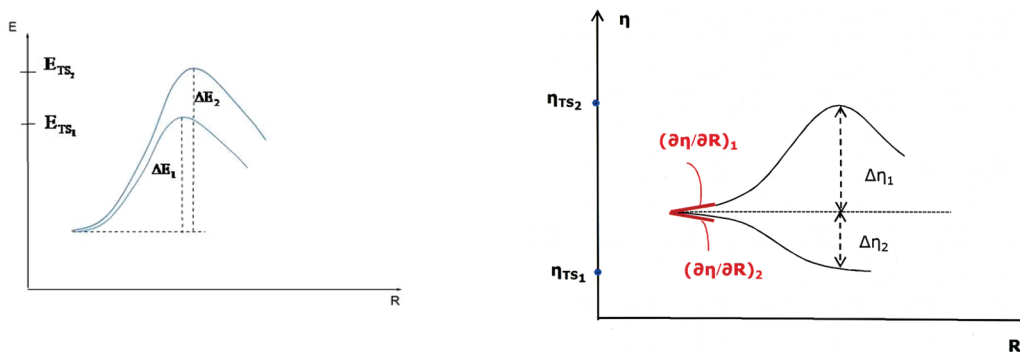
## V. An Alternative Conceptual DFT Approach: The Initial Hardness Response

In cases where electron transfer is small, it is more natural to think of the dual descriptor as a response function not of the electron density but of the chemical hardness. To derive this relationship, interchange the order of the derivatives in the definition of the dual descriptor and use eqs 3 and 10) to





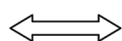
**FIGURE 6.** The dual descriptor approach for the  $4n$  linear chelotropic reaction: 1,3-butadiene +  $\text{SO}_2$ . In the linear approach, stabilizing interactions between the dual descriptor of the reactants are enhanced by a disrotatory movement of the two  $\text{CH}_2$  groups. Reprinted with permission from ref 38. Copyright 2010 NRC Research Press.



$$E_{\text{TS}_1} < E_{\text{TS}_2}$$

$$\Delta E_1 < \Delta E_2$$

Aromaticity  $\text{TS}_1 > \text{Aromaticity TS}_2$



$$\eta_{\text{TS}_1} > \eta_{\text{TS}_2}$$

$$\Delta \eta_1 > \Delta \eta_2$$

$$\left( \frac{\partial \eta}{\partial R} \right)_1 > \left( \frac{\partial \eta}{\partial R} \right)_2$$

**FIGURE 7.** From activation energy ( $\Delta E$ ) to aromaticity of the transition state (TS), activation hardness ( $\Delta \eta$ ) and the initial hardness response ( $\partial \eta / \partial R$ ). For the sake of simplicity, the position of the TS along the reaction path for comparable reactions was taken as identical. In the case shown, reaction 1 shows increasing hardness ( $\Delta \eta > 0$ ), whereas reaction 2 shows a decreasing hardness ( $\Delta \eta$  being defined as  $\eta_{\text{react}} - \eta_{\text{TS}}$ ). Reaction 1 with positive initial hardness response ( $\partial \eta / \partial R > 0$ ) is allowed; reaction 2 with negative initial hardness response ( $\partial \eta / \partial R < 0$ ) is forbidden.

simplify the result, obtaining

$$\begin{aligned} f^{(2)}(\underline{r}) &= \left( \frac{\partial^2}{\partial N^2} \rho(\underline{r}) \right)_v = \frac{\partial^2}{\partial N^2} \left( \frac{\delta E}{\delta v(\underline{r})} \right)_N \\ &= \left[ \frac{\delta}{\delta v(\underline{r})} \left( \frac{\partial^2 E}{\partial N^2} \right)_{v(\underline{r})} \right]_N = \left( \frac{\delta \eta}{\delta v(\underline{r})} \right)_N \end{aligned} \quad (14)$$

The dual descriptor is the functional derivative of the hardness with respect to the external potential.

Suppose the two reagents, A and B, are far apart. If we assume that the atomic charges and relative positions within A and B are fixed, it is only the separation between the fragments along the reaction coordinate,  $R$ , that is changing. The changes in hardness upon changing geometry can be

SCHEME 1. The Initial Hardness Response as a Reactivity Indicator for Pericyclic Reactions<sup>d</sup>

Type of pericyclic reaction		Concrete case	Outcome		Reference
Cycloaddition	4n	ethene/ethene (s/s)	+ (photochemical)		39
	4n+2	ethene/butadiene (s/s)	+ (thermochemical)		39
			<b>Thermochemical</b>	<b>Photochemical</b>	
Electrocyclization	4n	butadiene-cyclobutene	+ (conrotatory)	+ (disrotatory)	43
	4n+2	hexatriene – cyclohexadiene	+ (disrotatory)	+ (conrotatory)	43
Sigmatropic H-shift	4n	propene [1,3] H-shift	+ (antarafacial)		44
		butene cation [1,4] H-shift	+ (antarafacial)		44
	4n+2	pentadiene [1,5] H-shift	+ (suprafacial)	+ (antarafacial)	44
		hexadiene cation [1,6] H-shift	+ (suprafacial)	+ (antarafacial)	44
Chelotropic reaction	4n	butadiene/SO <sub>2</sub> - linear	+ (disrotatory)		38
		-non-linear	+ (conrotatory)		38
	4n+2	hexatriene/SO <sub>2</sub> -linear	+ (conrotatory)		38
		- non-linear	+ (disrotatory)		38

<sup>d</sup>(+) indicates allowedness of the reaction, in the indicated mode/state in agreement with the WH rules. For all cases, except the chelotropic reactions, both thermochemical and photochemical pathways are investigated.

written in terms of the dual descriptor as

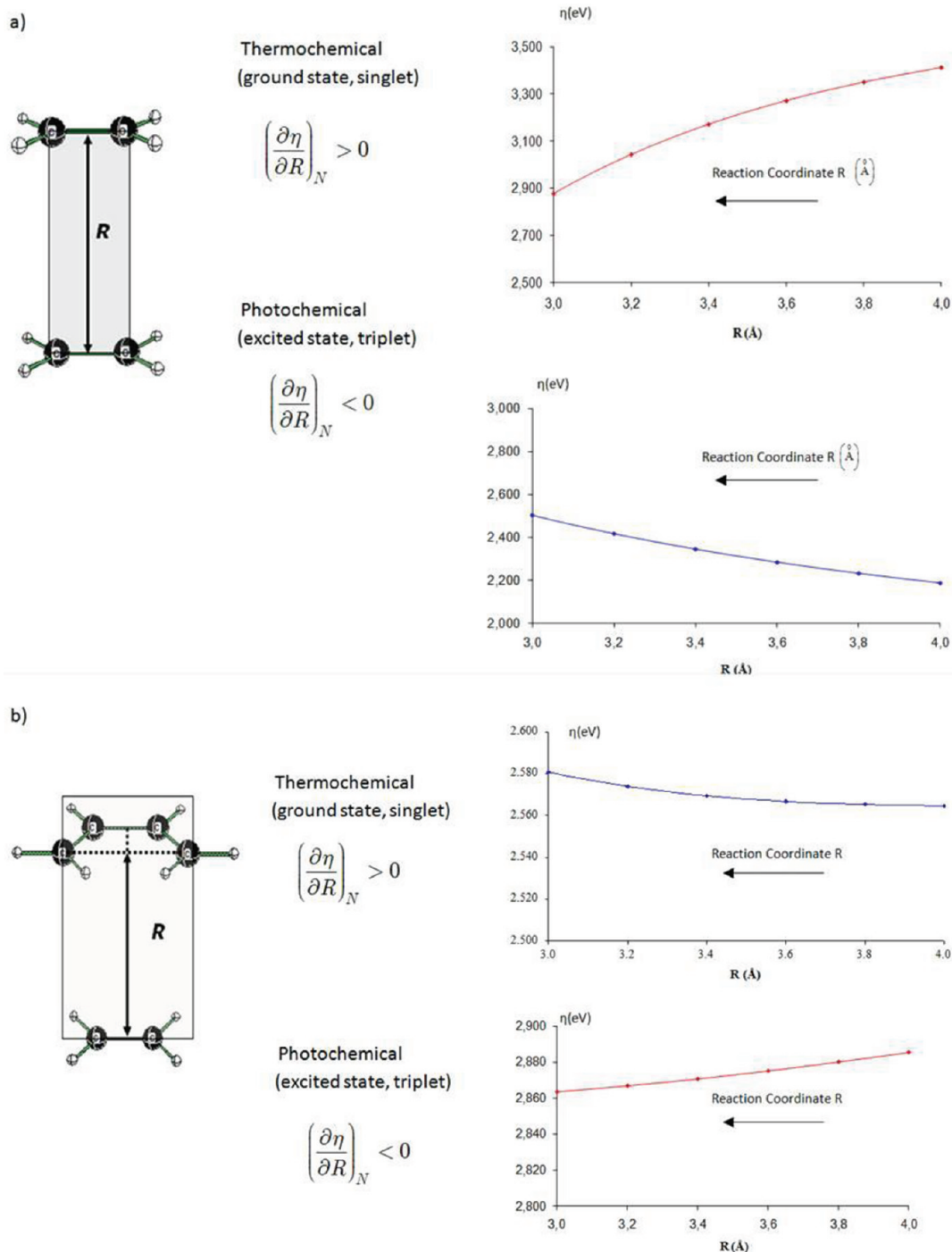
$$\begin{aligned} \left(\frac{\partial\eta}{\partial R}\right)_N &= \int \left(\frac{\delta\eta}{\delta v(r)}\right)_N \left(\frac{\partial v(r)}{\partial R}\right) dr \\ &= \int f^{(2)}(r) \left(\frac{\partial v(r)}{\partial R}\right) dr \end{aligned} \quad (15)$$

that is, a convolution of the linear response function and the derivative of the external potential with respect to the change in geometry. This leads us to suppose that the response of the hardness to a change in the intermolecular separation between two well-separated fragments might provide the basis of a reinterpretation of the WH rules. If one uses a perturbation theory expansion at the onset of the reaction, this brings us in a natural way to investigate the initial hardness response,<sup>39</sup> which is defined as the variation of the system's hardness with respect to the reaction coordinate at the onset of the reaction. Assuming that the hardness profiles do not cross, then we expect that this response function parallels the activation hardness,<sup>40</sup> defined by Zhou and Parr as the hardness difference between reactants and TS. Because a harder TS is more stable or less unstable, one can expect that the more positive (or less negative) initial hardness response corresponds to the preferred reaction (see Figure 7). Zhou and Parr also noted that hardness is correlated with aromaticity; therefore, harder transition

states (larger activation hardness) are associated with greater aromatic character in the transition state. This makes contact with the Zimmerman's alternative approach to the WH rules, based on the aromaticity of the TS,<sup>41</sup> and elucidates the origins of the maximum hardness principle.<sup>29</sup> Indeed the more aromatic the TS, the more stable it is, the higher its hardness, the more positive (or less negative) the initial hardness response.

This hypothesis was tested, as shown in Scheme 1, on a nearly identical set of pericyclic reactions studied with the dual descriptor. A plus sign in the scheme stands for agreement with the WH rules. In all cases considered (only a few photochemical reactions were left out for technical computational reasons), the results are in agreement with the WH rules. In two cases, the simple model reaction coordinate had to be replaced by the true intrinsic reaction coordinate (IRC)<sup>42</sup> to recover the qualitative trends: these were systems with limited conformational freedom [sigmatropic hydrogen shifts in propene and the butene cation].

As a first example, we revisit the [2 + 2] and [4 + 2] cycloadditions of ethene with ethene and butadiene, respectively, in the case of a supra/supra attack (Figure 8). In the ground state allowed [ $\pi 4_s + \pi 2_s$ ] cycloaddition, the hardness increases upon approach of the reactants ( $(\partial\eta/\partial R)_N > 0$ ), whereas for the photochemical reaction a decrease is noticed ( $(\partial\eta/\partial R)_N < 0$ ). The reverse is seen for the [ $\pi 2_s + \pi 2_s$ ] reaction. The initial hardness response thus retrieves the



**FIGURE 8.** Initial hardness response: comparison of the hardness profile of the [2 + 2] (a) and [4 + 2] (b) supra/supra cycloadditions between ethene/ethene and butadiene/ethene, respectively, in the case of thermochemical (ground state/singlet) and photochemical (excited state/triplet) reactions. Reprinted with permission of ref 39. Copyright 2006 AIP.

WH rules. As a final example, we depict in Scheme 2 a quantitative comparison between a series of energy- and hardness-related characteristics of  $4n$  and  $4n + 2$  cycloadditions, namely, thermochemical con- and disrotatory electrocyclicizations of 2, 4-hexadiene ( $4n$ ), -cyclooctatetraene, and -cycloheptatriene ( $4n + 2$ ). A comparison is made between activation energy,

$E_a$ , activation hardness,  $\eta_a$ , and the initial hardness response ( $\partial \eta / \partial R$ ), where  $R$  is the mass-weighted internal coordinate corresponding to the reactive mode.<sup>43</sup> The results are internally consistent: the (thermally) allowed reactions (underlined in red) in each case have a lower activation energy, have a more negative activation hardness (evolution toward

**SCHEME 2.** Energy and Hardness-Related Characteristics of  $4n$  and  $4n + 2$  Cycloadditions: Activation Energy,  $E_a$ , Activation Hardness,  $\eta_a$ , and Initial Hardness Response  $(\partial\eta/\partial Q)^a$ 

		$E_a$	$\eta_a$	$(\partial\eta/\partial Q)$
2,4-hexadiene	conrotatory (A)	<u>43.8</u>	<u>-0.343</u>	<u>-0.152</u>
	disrotatory (F)	49.0	-0.028	-0.210
cyclooctatetraene	conrotatory (A)	<u>30.0</u>	<u>-1.212</u>	<u>0.095</u>
	disrotatory (F)	67.2	-0.098	-0.158
cycloheptatriene	conrotatory (A)	<u>10.9</u>	<u>-0.715</u>	<u>0.310</u>
	disrotatory (F)	61.7	-0.238	0.008

<sup>a</sup>Value for the thermally allowed (A) reactions underlined in red.

Hückel aromatic TS in the  $6\pi$  system and to a Möbius aromatic TS in the  $4\pi$  system), and are invariably accompanied by the most positive or least negative initial hardness response. Note again that the relevant calculations are quite standard and do not imply the detailed evaluation of equations in Boxes 1 and 2; one only needs to compute the HOMO–LUMO gap (or the ionization potential and electron affinity) at a few points along a model reaction coordinate to draw a conclusion.

## VI. Conclusions

Two alternative approaches to the WH rules were offered, both rooted in conceptual DFT. In this Account, it is shown that in DFT, despite its deep physical roots and mathematical richness, the judicious choice of the relevant terms in the energy perturbation expansion leads to a simple route to study the allowed or forbidden character of pericyclic reactions. In the first approach, the response of the density to changes in electron number is used to obtain a simple picture of allowed and forbidden reactions. The second approach highlights the ability of conceptual DFT to combine quantitative precision with chemical insight and is based on the response of the chemical hardness to the approaching reagents. The density-based dual descriptor, local in nature, yields a pictorial representation resembling the original orbital-based WH approach; the initial hardness response, global in nature, extends the aromatic transition state concept. Both approaches provide orbital-free reinterpretations of the WH rules.

## BIOGRAPHICAL INFORMATION

**Paul Geerlings** (Antwerp, 1949) received his Ph.D. and Habilitation from the Vrije Universiteit Brussel. At this University, he heads since the late 1980s a research group involved in conceptual and computational DFT with applications in organic, inorganic, materials, and biochemistry. He is the author or coauthor of about 390 publications in international journals or as book chapters. He organized several international conferences around DFT, among others DFT 2003 in Brussels.

**Paul W. Ayers** received a B.Sc. in chemistry, physics, and mathematics from Lipscomb University, a Ph.D. in chemistry from the University of North Carolina under the direction of Robert Parr, and postdoctoral training from Weitao Yang at Duke University. He is presently an Associate Professor and Canada Research Chair at McMaster University, where he works on developing new theoretical and computational methods for modeling and gaining insight into chemical and biochemical reactions.

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**Frank De Proft** obtained his Ph D in Chemistry at the Free University of Brussels (VUB) in 1995. In the period 1995–1999, he was a postdoctoral fellow at the Fund for Scientific Research Flanders (Belgium) during which he was a postdoctoral fellow in the group of Professor R. G. Parr at the University of North Carolina in Chapel Hill. He is the author or coauthor of more than 200 research publications, mainly on conceptual DFT. His present work involves the development and interpretative use of DFT-based reactivity descriptors and the modeling and theoretical investigation of organic, inorganic, and biochemical compounds and reactions.

#### FOOTNOTES

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