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Information Conservation Principle Determines Electrophilicity, Nucleophilicity, and Regioselectivity

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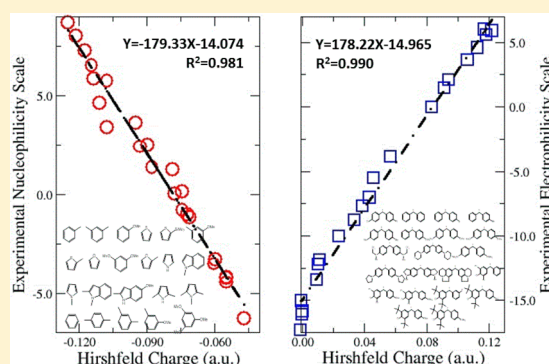
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S Supporting Information

ABSTRACT: Electrophilic and nucleophilic reactions are important chemical transformations involving charge acceptance and donation, so chemical intuition suggests that atomic charges should be a reliable descriptor to determine electrophilicity, nucleophilicity, and regioselectivity. Nevertheless, no such theoretical framework has been established as of yet. Herein, we report that the Hirshfeld charge can be used for such purposes. We justify this usage by showing that it results from the *Information Conservation Principle*. This principle not only decides where electrophilic and nucleophilic attacks will preferably occur but also dictates the amount of the Hirshfeld charge distribution, which, as we will show here, remarkably strongly correlates with experimental scales of both electrophilicity and nucleophilicity.



I. INTRODUCTION

Electrophilicity (nucleophilicity) measures the ability of an electrophile (nucleophile) to accept (donate) electrons.¹ Related to these reactivity properties is the concept of regioselectivity.^{1–4} Much has been devoted to quantifying electrophilicity and nucleophilicity and understanding their regioselectivity from both experimental and theoretical viewpoints. For example, a unified effort toward a general scale of nucleophilicity and electrophilicity using experimental rate constants has been introduced by Mayr and co-workers.^{5–8} In the theoretical front, with the Fukui function from density functional theory,^{9,10} one can predict the reactive site of electrophilic and nucleophilic attacks. There were numerous attempts to formulate electrophilicity and nucleophilicity in the literature.^{11–14} Nevertheless, any effort to provide a unified theoretical framework to quantify electrophilicity and nucleophilicity and determine their regioselectivity has been unsuccessful as of yet.

In principle, electrophilicity and nucleophilicity should be an intrinsic property of molecules, closely related to the lack and excess of electrons on atoms in molecules. Therefore, conventional chemical wisdom would expect that the atomic charge distribution in molecules should suffice in quantifying these quantities. Unfortunately, there is no physical observable corresponding to the atomic charge, so it cannot be uniquely determined. Plus, there have been many different approaches in calculating atomic charges. To the best knowledge of the present authors, no prior report in the literature has been found

to correlate and quantify these quantities with the atomic charge distribution. In this contribution, based on the *Information Conservation Principle* proposed in this work, we show that the Hirshfeld charge¹⁵ can be employed to determine the regioselectivity and simultaneously quantify electrophilicity and nucleophilicity.

II. THEORETICAL FRAMEWORK

The Hirshfeld charge is defined as the following,¹⁵

$$\rho_A = \frac{\rho_A^0}{\sum_A \rho_A^0} \rho \quad (1)$$

where ρ_A is the electron density on atom (or group) A in a molecule, whose total electron density is ρ and the total number of electrons is N and ρ_A^0 is the counterpart of atom (or group) A in the reference state, which can be a neutral atom, ion, or group, etc. According to Nalewajski and Parr,¹⁶ minimizing the information gain (also called Kullback–Leibler divergence, relative entropy, or information divergence)^{17–22} of a molecular system due to its formation from composing ingredients,

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$$I_G = \sum_A \int \rho_A \ln \frac{\rho_A}{\rho_A^0} dr \quad (2)$$

leads to the “stockholder partition” of the electron density proposed by Hirshfeld,¹⁵ eq 1.

If the reference state is the neutral atom, ρ_A^0 forms the isoelectronic promolecule, and the difference, $\sum_A (\rho_A - \rho_A^0)$, is the so-called deformation density distribution. These densities should satisfy the following normalization condition,

$$\sum_A \int \rho_A dr = \sum_A \int \rho_A^0 dr = N \quad (3)$$

That is to say, if one employs the Hirshfeld scheme to partition atoms in a molecule, the information gain due to the formation of the molecule from the composing pieces will be minimal. In other words, atoms in molecules partitioned in this manner will preserve their identity (e.g., electrophilic and nucleophilic properties, etc.) of the reference state as much as possible. We call this tendency the *Minimum Information Gain Principle*.

Since atoms in molecules keep their identity of their reference state as much as possible, it is anticipated that ρ_A and ρ_A^0 should be similar. We can define a new variable, $x = (\rho_A - \rho_A^0)/\rho_A$ so the information gain in eq 2 becomes

$$I_G = \sum_A \int \rho_A \ln \frac{1}{1-x} dr \quad (4)$$

Since x is expected to be small, using $\ln 1/(1-x) \approx x$ as the first-order approximation, we have

$$I_G \approx \sum_A \int (\rho_A - \rho_A^0) dr = -\sum_A q_A \quad (5)$$

where q_A is the Hirshfeld charge on atom (or group) A. This result shows that under the first-order approximation, the information gain simply gives rise to the Hirshfeld charge distribution.

At the meanwhile, since ρ_A and ρ_A^0 satisfy the same normalization condition, eq 3, the total information gain in eq 5 must vanish,

$$I_G \approx -\sum_A q_A \equiv 0 \quad (6)$$

suggesting that under the first-order approximation, *the information before and after a system is formed should be conserved*. We call this result the *Information Conservation Principle*. This principle, stemmed from the above first-order approximation, is a special case of the *Minimum Information Gain Principle*, eq 2, with no information gained at all. The actual value of information gain in eq 2 should come from the second and other higher order terms in the Taylor expansion in eq 4, with $\ln 1/(1-x) \approx x + x^2/2 + x^3/3 + \dots$.

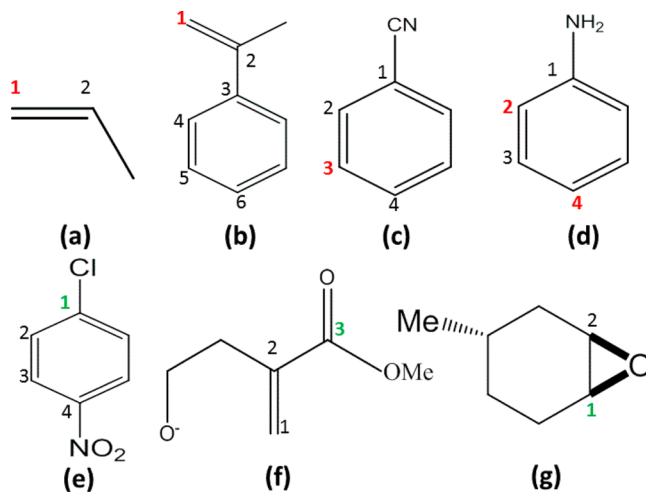
As the main result of this work, eq 6 provides a unique physicochemical insight for the Hirshfeld charge, which will enable us to quantify and predict the chemical reactivity properties for molecular species. According to this principle, when a new molecular system is formed from its components, the identity of its ingredients will be preserved, at least to the first-order approximation. That is to say, if a component is electrophilic or nucleophilic in nature, it will still be so in the newly formed system as well. Moreover, to preserve the identity of the components in the new system, they will have to adjust themselves in such a manner that each of the components becomes charged according to its stockholder contribution in

the electron density, as shown in eq 1. Put together, the new understanding from the *Information Conservation Principle* proposed in this work will provide a novel approach in quantifying reactivity properties, such as electrophilicity, nucleophilicity, and regioselectivity, as will be illustrated by a number of different molecular systems in the following sections.

III. COMPUTATIONAL DETAILS

As numerical verifications to the above theoretical framework, a total of 50 molecular systems will be investigated in this work, as illustrated in Schemes 1–3. Scheme 1 shows the seven

Scheme 1. Seven Molecular Systems Studied in This Work to Demonstrate Regioselectivity in Their Electrophilic or Nucleophilic Reactions



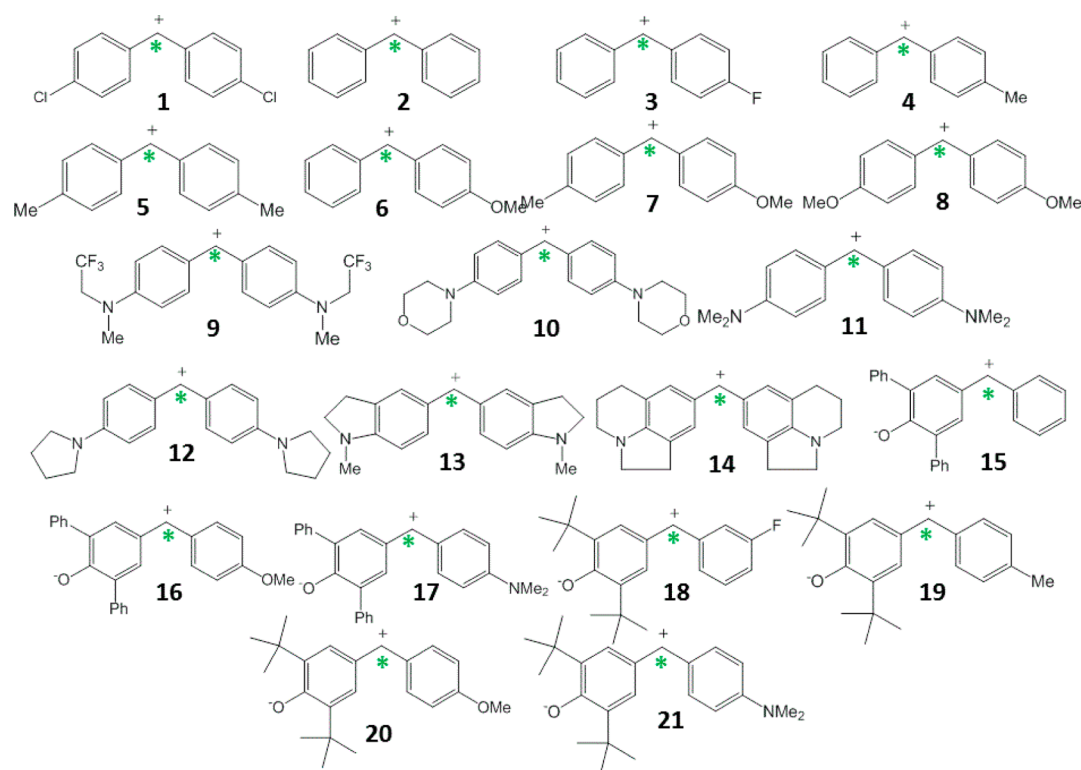
systems to demonstrate the ability of the Hirshfeld charge in determining regioselectivity, whereas Schemes 2 and 3 including more than 21 and 22 species, respectively, showcase the capability of the Hirshfeld charge in quantifying electrophilicity and nucleophilicity. Their optimized Cartesian coordinates are available in the Supporting Information. The experimental scales of electrophilicity and nucleophilicity of these species are from the literature.^{5–8}

All structures were fully optimized at the M062X/6-311+G(d) level of theory^{23,24} using the Gaussian 09²⁵ package (version D01) with tight SCF convergence and ultrafine integration grids. The solvent effect was taken into account by using the implicit solvent model (CPCM the conductor polarizable continuum model)²⁶ in the CH_2Cl_2 solvent. The Multiwfn 3.2 program²⁷ developed by one of the present coauthors was used to calculate the information gain and Hirshfeld charge using the checkpoint file from the above Gaussian calculations as the input file. To obtain the electron density for the isolated state, we employed the spherically averaged electron density of the neutral atom at the ROM062X/6-311+G(d) level of theory.

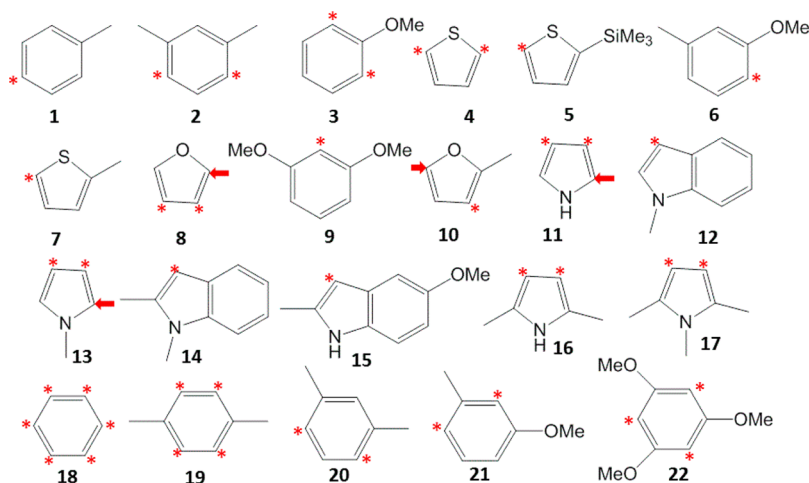
IV. RESULTS AND DISCUSSION

To demonstrate the reliability of the first-order approximation, shown in Figure 1 is the comparison of local behaviors between information gain in eq 2 and the deformation density in eq 5 for nitrobenzene. This figure clearly demonstrates that the differences between these two quantities are indistinguishable. Also, shown in Figure S1 of the Supporting Information) is the

Scheme 2. Twenty-One Structures Studied in This Work to Compare the Information Gain and Hirshfeld Charge with the Experimental Electrophilicity Scale by Mayr et al.



Scheme 3. Twenty-Three Structures Studied in This Work to Compare the Information Gain and Hirshfeld Charge with Experimental Nucleophilicity Scale by Mayr et al.



linear relationship between information gain and Hirshfeld charge from the preferred attack sites of all the systems studied in the work, with the correlation coefficient equal to 0.998. From these Figures, it becomes unambiguously apparent that the two quantities strongly correlate with each other, confirming that eq 5 should be a reliable approximation for the information gain in eq 2.

To illustrate that the Hirshfeld charge can determine regioselectivity, seven examples are illustrated in Scheme 1, where the preferred sites of reactions are marked in red for electrophilic attacks (a–d) and green for nucleophilic attacks (e–g). Values of the information gain and Hirshfeld charge for a few possible attack sites are shown in Table S1 of the

Supporting Information. Electrophiles prefer to attack sites with more negative charges and thus larger information gains (a–d), whereas nucleophiles attack sites with more positive charges and thus smaller information gains (e–g). In every case, our computational result agrees well with the experimental evidence. The reactions studied here include (a) the addition of protic acids to alkenes and (b) halohydrin formation reaction of 2-propenylbenzene, where proton prefers to attach to the carbon with fewer alkyl substituents (Markovnikov's rule).² Also shown in Scheme 1–3 are examples of electrophilic aromatic substitutions, where the phenomenon of (c) meta directors and (d) ortho/para directors is observed. Ortho/para directors are groups with unshared electron pairs, such as the

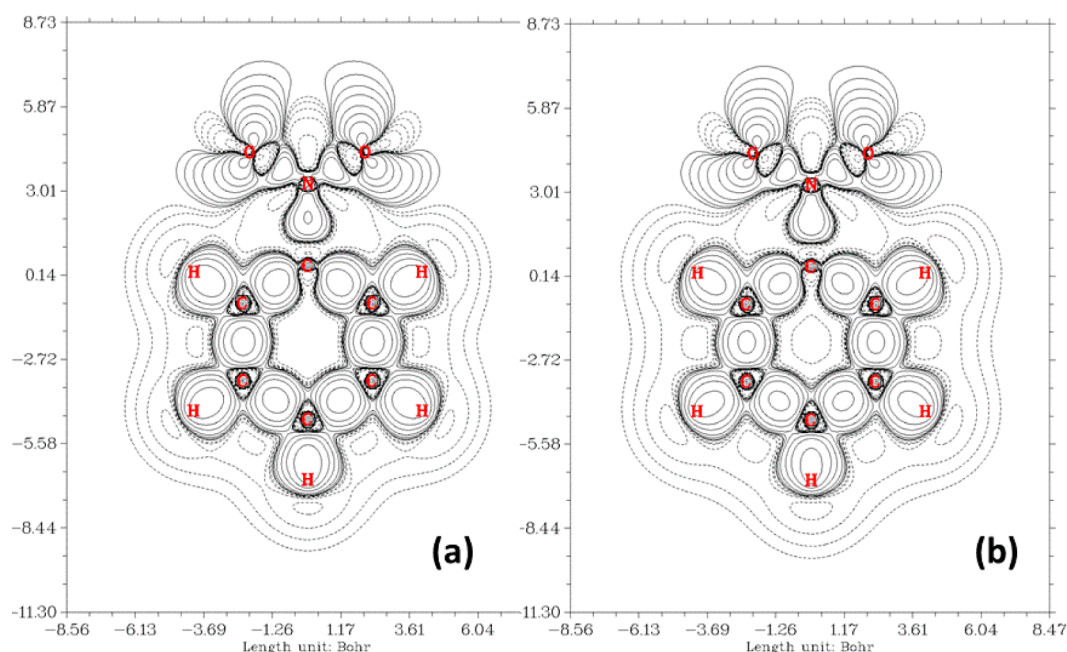


Figure 1. Comparison of local behaviors between (a) information gain in eq 2 and (b) deformation density in eq 5 for the nitrobenzene molecule.

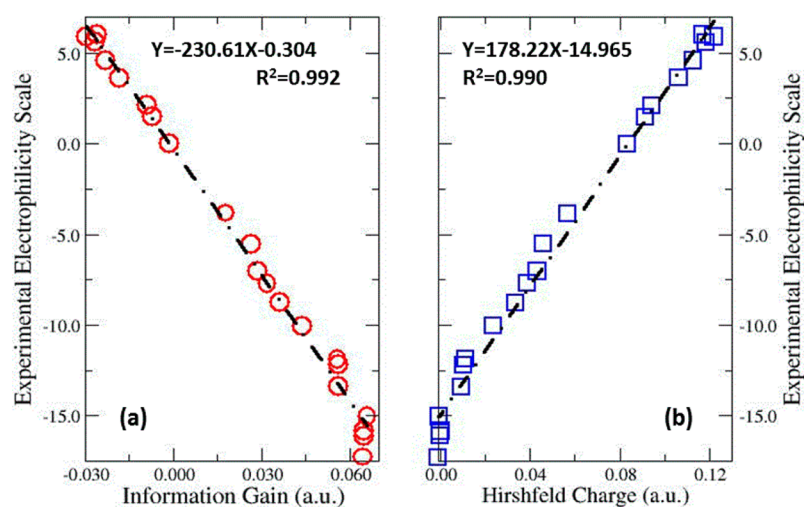


Figure 2. Comparison of the experimental electrophilicity scale of Mayr et al. with (a) information gain and (b) Hirshfeld charge for 21 systems listed in Scheme 2.

amino group of (d) aniline, and meta directors are electron-withdrawing groups such as $-\text{CN}$ in (c). Shown in (e) is the nucleophilic aromatic substitution of *p*-chloro-nitrobenzene, where replacement of the Cl element (nucleophilic attack at the C1 position) is predicted, which agrees well with the experimental evidence. Shown in (f) is the nucleophilic regioselectivity in the ring closure reaction for alicyclic compounds (Baldwin rule),³ where the C3 site is preferred through 5-exo-trig. In (g), the addition of nucleophiles to the epoxide is preferred at the C1 position, as governed by the Fürst–Plattner rule (also known as the trans-diaxial effect).⁴

These results show that the regioselectivity rule using information gain and Hirshfeld charge is the following. For electrophilic attacks, the site with the largest information gain and thus the most negative charge is preferred, and for nucleophilic attacks, the site with the smallest information gain and thus the most positive charge is selected. Given the atomic charge nature in eq 5, this regioselectivity rule is consistent with

the chemical intuition. Nevertheless, we should caution that this rule can only be applied to the rate-determining step of reactions that is kinetically controlled. This is because our approach only predicts the likelihood of the attack on different possible sites. It cannot determine stability differences among different products, which are thermodynamically controlled.

Electrophilicity (nucleophilicity) is the ability of an atom or group to accept (donate) electrons. Mayr and Patz⁵ have defined the scale for electrophilicity and nucleophilicity using reaction rate constants. In the Mayr–Patz equation,⁵

$$\log(k) = s_N(N + E) \quad (7)$$

where k is the second-order reaction rate constant at 20 °C between a nucleophile with the nucleophilicity scale of N and an electrophile with the scale E , and s_N is a nucleophile-dependent slope parameter, which is defined as 1.0 with 2-methyl-1-pentene as the nucleophile. These scales have been found to be independent of the reaction partners. Mayr and co-

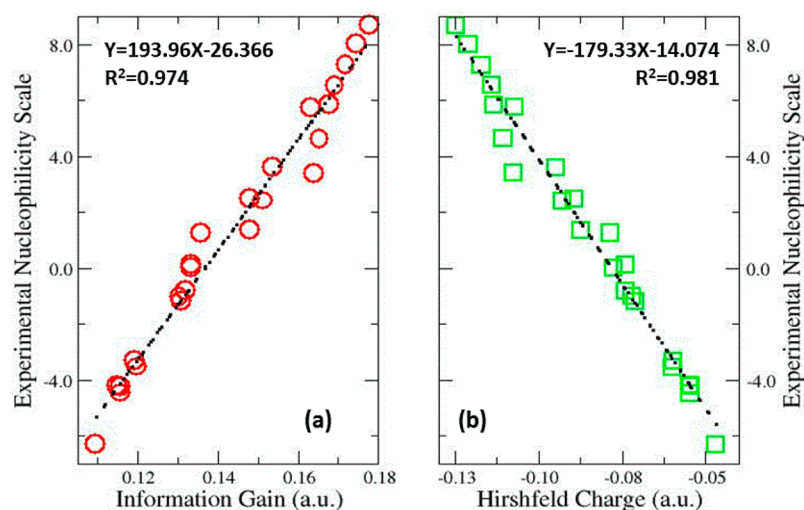


Figure 3. Comparison of the experimental nucleophilicity scale by Mayr et al. with (a) information gain and (b) Hirshfeld charge for 22 systems listed in Scheme 3.

workers have extended these scales over many orders of magnitude, and the validity of these scales has been experimentally validated and well-documented in the literature.^{6–8}

While the rate constant of a chemical reaction is understandably governed by many factors, one of the key factors dictating electrophilic and nucleophilic reactions should be the nature and amount of the atomic charge distributed on the regioselective site available for either donation or acceptance. Since the Hirshfeld charge is stemmed from the *Information Conservation Principle*, which requires that the atomic identity should be retained as much as possible in molecules, this charge must reflect the electronegativity or electropositivity nature of atoms. On the basis of this argument, we anticipate that the Hirshfeld charge should be a good measure of the capability for atoms to donate or accept electrons. To verify this point, shown in Figures 2 and 3 (data in Tables S2 and S3 in the Supporting Information) are the strong linear correlation of experimental electrophilicity (Figure 2) and nucleophilicity (Figure 3) scales with (a) the information gain and (b) Hirshfeld charge for two series of molecular systems shown in Schemes 2 and 3 (Cartesian coordinates included in the Supporting Information), respectively. Also exhibited in the two Schemes are the preferred reaction sites marked by stars for electrophiles (in green) and nucleophiles (in red). As can be seen from the Figures, there exist remarkably strong linear correlations between our theoretical results and experimental scales by Mayr et al.^{5–8} In Figure 2b, we find that the electrophilicity scale is positively proportional to the amount of the Hirshfeld charge on the preferred site. In Figure 3b, the nucleophilicity scale is negatively proportional to the amount of Hirshfeld charge. The larger the amount of the negative (positive) charge [i.e., the better electron-donating (electron-accepting) capability, on the preferred site], the larger the nucleophilicity (electrophilicity) scale. These observations agree well with the conventional chemical wisdom about electrophilic and nucleophilic reactions. As one of the major results of this work, different from any previous effort in the literature,^{11,12} these results show that we can not only use these quantities to concurrently and quantitatively determine both electrophilicity and nucleophilicity but also simultaneously ascertain the

preferred reaction site and thus resolve the issue of predicting regioselectivity.

The predicted reaction sites are in general in good agreement with experimental evidence, except for a few cases (marked by red arrows in Scheme 3), which, as will be shown below, are believed to be thermodynamically controlled. For furan and pyrrole and some of their derivatives, the experimental regioselective site is the 2-position (next to the heteronuclear atom), instead of the 3-position predicted by our calculations. Our results show that for some systems, the 2-position is actually positively charged, and thus it can never be a suitable site for an electrophilic attack. For example, for furan, the Hirshfeld charge on the 2- and 3-positions is +0.013 and −0.083 au, respectively. For pyrrole, even though both 2- and 3-positions are both negatively charged, with the total Hirshfeld equal to −0.032 au and −0.096 au, respectively, the 3-position is much more negatively charged than the 2-position. These results unambiguously show that the 3-position of these 5-member ring compounds is favored in the initial electrophilic attack. On the other hand, the result of the energy difference between two products after a proton is attached to either the 2- or 3- position shows that the one with the proton attached to the 2-position is more stable. For instance, the energy difference of these products for furan and pyrrole is 11.2 and 4.8 kcal/mol, respectively, indicating that the 2-position product is more stable than the 3-position counterpart. These results, thus, confirm that the process could be thermodynamically controlled. This is what we understand the exceptions of regioselectivity to be in Scheme 3: the 3-position is preferred at the initial electrophilic attack, but there is equilibrium between the products of 2- and 3-positions, with the 2-position product thermodynamically more favorable. It is possible that there exists a fast isomerization process after a proton is attached to the 3-position after the initial electrophilic attack on the 3-position and eventually give the 2-position protonation as the end product.

In addition, as a piece of supporting evidence to the above argument, we notice that, in Figure 3, if the Hirshfeld charge or information gain result of the 2-position for furan, pyrrole, and their derivatives is employed for the fitting, a much worse correlation would have been generated. We have to use the

Hirshfeld charge and information gain results from the 3-position to obtain the result shown in Figure 3.

The exceptionally strong correlations between these two theoretical quantities with experimental scales in Figures 2 and 3 confirm that the amount of charge available on the regioselective site should be a reliable descriptor of electrophilicity and nucleophilicity. If one plugs the linear relationship between electrophilicity (nucleophilicity) and Hirshfeld charge (or information gain) obtained in the two Figures back into eq 6, the rate constant of these kinetically controlled reactions could be readily predicted through this simple equation,

$$\log(k) = Aq_N + Bq_E + C \quad (8)$$

where q_N and q_E are Hirshfeld charges on the nucleophilic and electrophilic partners of the reaction, respectively, and A, B, and C are constants independent of the partners. Using this linear-free-energy-like relationship, one can predict the rate constant from computed Hirshfeld charges of reaction partners.

It is well-known that the Hirshfeld charges are often much smaller in magnitude than other charges, as confirmed by the data shown above (Figures and Tables S1–S3 of the Supporting Information). Its close relationship to the *Information Conservation Principles* shown here should have provided an explanation for why it must be small. It requires that when atoms form molecules, their identity is preserved as much as possible. On the other hand, as shown in Figures 2 and 3, a small change in the Hirshfeld charge can result in a huge difference in electrophilic and nucleophilic scales. For example, in Figure 2b, a 0.1 au of difference in the Hirshfeld charge will result in 20 orders of magnitude difference in reaction rates.

V. CONCLUDING REMARKS

In summary, in this work, we present a unified framework to determine electrophilicity, nucleophilicity, and regioselectivity quantitatively and simultaneously. Electrophilicity or nucleophilicity as the capability of atoms in molecules to accept or donate electrons ought to be dictated by the nature and amount of the atomic charge on the regioselective site in a molecule. While the utility of atomic charges for predicting electrophilic/nucleophilic attack is well-known,^{28–34} the perspective presented in this work is certainly new. With the *Information Conservation Principle* proposed in this work, we justified that the Hirshfeld charge can be employed for this purpose, which has been confirmed by our numerical results. This theoretical framework should have laid a solid foundation for using the Hirshfeld charge to unambiguously pinpoint the regioselectivity and concurrently quantify electrophilicity and nucleophilicity. On the basis of this work, a novel and unified theoretical scale of electrophilicity and nucleophilicity using the Hirshfeld charge is possible. Since the rate constants employed by Mayr et al. to experimentally quantify these quantities are kinetic in nature, this new scale could be different from what Mayr and co-workers had proposed. However, the exceedingly strong linear correlations between Hirshfeld charges and the experimental scales shown in Figures 2 and 3 imply that they might be closely correlated in practice. This and other studies related to this topic such as the dependence of choices in the reference state and approximate functionals, as well as their comparison with Fukui functions, etc., are in progress, whose results will be reported elsewhere.

■ ASSOCIATED CONTENT

Supporting Information

Complete list of ref 25, Tables S1–S3, Figure S1, and Cartesian coordinates of 50 structures studied in this work. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

S.B.L. proposed the research topic, performed the calculations, analyzed the results, and wrote the manuscript. C.Y.R. performed the calculations. T.L. implemented the algorithm and coded the program.

Notes

The authors declare no competing financial interest.

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