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# Nucleophilicity and Site Selectivity of Commonly Used Arenes and Heteroarenes

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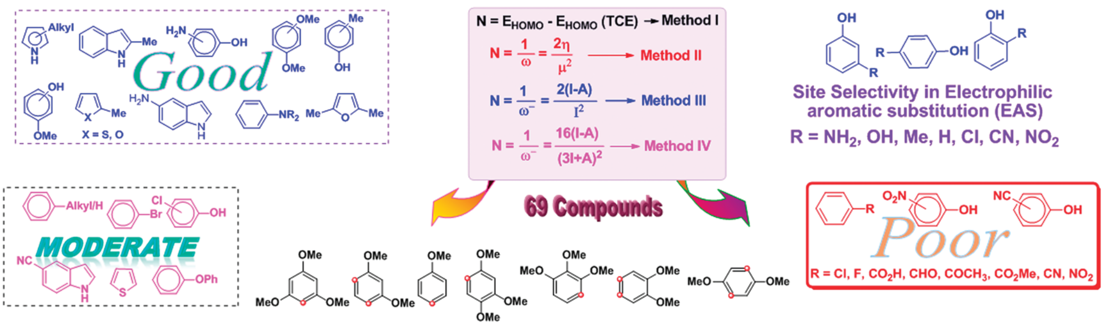

By using the inverse concept of electrophilicity and nucleophilicity and with four different available equations from literature for electrophilicity and electrodonating power, the nucleophilicity values of 69 commonly used arenes and heteroarenes have been calculated at the B3LYP/6-311+G(d,p) level of theory. The linearity between the nucleophilicity and Hammett $\sigma$ and $\sigma_p$ values has been chosen as a test to judge the goodness of the methods used. Finally four different arene and heteroarene series (substituted indoles, phenols, pyrroles, and anisoles) have been subjected to local nucleophilicity analysis in order to predict the site selectivity in electrophilic aromatic substitution reactions (EAS). In each case we have obtained excellent correlation with the experimental result.

## Introduction

Depending on the electronegativity of the fragments in a heteronuclear bond, the electron pairs attach closer to one fragment making it electron rich, while the other fragment becomes electron deficient. Electron density at the fragments decides whether it is an electrophilic (electron loving) or a nucleophile (nucleus loving). Thus, a nucleophile is a reagent that forms a chemical bond to its reaction partner (electrophile) by donating an electron pair. Electrophilicity and nucleophilicity are two useful chemical concepts which help us to rationalize the electronic aspects of reactivity, selectivity, and substituent effects in a reaction.[1] The electrophilic attack involving carbocations or related electrophiles and arene, heteroarene, and nonaromatic $\pi$-systems represents the key step in many synthetically important reactions. Friedel−Crafts alkylations and acylations, Mannich aminoalkylations, and Tsuji−Trost allylations are just a few examples.[2] In all these reactions, an aromatic or a nonaromatic $\pi$-system is regarded as a dominant or a weak nucleophilic partner depending on the electron density, which inter alia controls the overall reactivity in an electrophilic substitution reaction. Additionally the local nucleophilicity also governs the site of attack by an electrophile. It is therefore imperative that an emergent task would be to classify atoms

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and molecules within empirical scales of electrophilicity and nucleophilicity.[2–6] We became attracted to these scales in view of our recent interest in Friedel–Crafts and related reactions involving arenes and heteroarenes by using mono- as well as bimetallic late transition metal Lewis acid catalysts.[7]

The accessible quantitative scales of electrophilicity/nucleophilicity provide useful tools for the rationalization of chemical reactivity. One of the recent illustrations on the benefits of these scales is by Mayr et al. They have successfully evolved an experimentally derived nucleophilicity scale for a large variety of $\pi$-nucleophiles (e.g., alkenes, arenes, enol ethers, ketene acetals, enamines, allyl compounds, transition metal complexes, diazoalkanes, and delocalized carbanions), *N*-nucleophiles (e.g., amines, alcohols, alkoxides, phosphanes, inorganic anions, and pyridines), and $\sigma$-nucleophiles (e.g., hydrides) using benzhydrylium ions and quinone methides as the reference electrophiles. In their approximation, the rate constants have been correlated by using the equation $\log k = s(N + E)$, in which electrophiles are characterized by one parameter ($E$) and nucleophiles are characterized by two parameters ($N$, $s$).[3] Indeed this approach proved to be applicable for a wide variety of electrophile–nucleophile combinations.[4] Alongside these experimental scales of electrophilicity and nucleophilicity, theoretical scales are highly desirable as they can be used to vindicate the electronic aspects of reactivity, selectivity, and their variations induced by field effects arising out of chemical substitution or due to conformational changes. For this reason in the last two decades, several theoretical efforts have been devoted to obtain qualitative and quantitative understanding of these central concepts. Many global and local reactivity descriptors, based on density functional theory (DFT), have been anticipated. Well-known among these are *global hardness and softness*,[5] *local hardness*,[6] *local softness*[8] and *Fukui function*,[9] and the corresponding *condensed forms*,[9] *relative electrophilicity*[10] and *relative nucleophilicity*,[11] *global electrophilicity*,[12a] and most recently the *net electrophilicity*.[12b] The global reactivity descriptors are believed to provide intermolecular reactivity trends whereas local counterpart presents the intramolecular reactivity sequence or site selectivity in an individual chemical system. Though less trivial, different definitions for a nucleophilicity index have been proposed. On the basis of the assumption that electrophilicity and nucleophilicity are inversely related to each other, Chattaraj et al.[13] suggested that nucleophilicity ($N$) can be considered as the multiplicative inverse of the electrophilicity index ($\omega$).[14] By using this concept and using four different equations (Scheme 1, methods I to IV) stated by others,[12a,15,16] we attempted to order the nucleophilicity of 69 commonly used arenes and heteroarenes.

**SCHEME 1.** **Four Equation Used in This Work As Methods I to IV**

$$N = E_{HOMO} - E_{HOMO(TCE)}\ \text{ev} \qquad \rightarrow \textit{Method I}$$

$$N = \frac{1}{\omega} \text{ where } \omega = \frac{\mu^2}{2\eta} \qquad \rightarrow \textit{Method II}$$

$$N = \frac{1}{\omega^-} \text{ where } \omega^- = \frac{I^2}{2(I-A)} \qquad \rightarrow \textit{Method III}$$

$$N = \frac{1}{\omega^-} \text{ where } \omega^- = \frac{(3I+A)^2}{16(I-A)} \qquad \rightarrow \textit{Method IV}$$

$$\eta = (I - A) \approx E_{HOMO} - E_{LUMO}, \mu = \frac{(I + A)}{2} \approx \frac{(E_{HOMO} + E_{LUMO})}{2}$$

## Theoretical Background

Global reactivity descriptors are defined for the system as a whole. Recently electrophilicity has been defined by Parr et al.[12] as the energy of stabilization of a chemical species when it acquires an additional fraction of electronic charge from the environment. The global electrophilicity index $\omega$ is defined as $\omega = \mu^2/2\eta$ where $\mu$ is the electronic chemical potential[17] and $\eta$ is the chemical hardness.[5] These two quantities are calculated by using the vertical ionization energy $I$ and electron affinity $A$.[18] The inverse of $\omega$ is used to represent nucleophilicity (as in method II, Scheme 1).[14] In an important contribution, Gazquez et al.[16] have defined *electrodonating power* ($\omega^-$) as

$$\omega^- = \frac{I^2}{2(I-A)} \quad \text{and} \quad \omega^- = \frac{(3I+A)^2}{16(I-A)}$$

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(14) It may be noted that while the inverse relationship between electrophilicity and nucleophilicity have been successfully utilized in this set of molecules, providing good correlation between experimental and computed results, that does not mean that a weak electrophile automatically becomes a strong nucleophile and vice versa. Indeed in many studies involving organic compounds this inverse relationship did not work. For recent demonstration of such a view please see: (a) Domingo, L. R.; Aurell, M. J.; Perez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417–4423. (b) Domingo, L. R.; Arno, M.; Contreras, R.; Perez, P. *J. Phys. Chem. A* **2002**, *106*, 952–961. We thank one of the reviewers for raising this important issue.

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(18) Please see the Supporting Information for details.

Note that according to this definition, a low value of $\omega^-$ signifies a better electron donor. To equate with the general notion that "*more is better*", in the present work nucleophilicity is defined as the inverse of electrodonating power ($\omega^-$) while using the above equations for calculation (as in methods III and IV, Scheme 1). We also looked into the simplest approach relating nucleophilicity with the negative value of the gas-phase (intrinsic) ionization potential ($N = -\mathrm{IP}$).[19] and utilized the same for calculation (as in method I, Scheme 1). To calculate $N$ by using method I, the energy of the highest occupied molecular orbital (HOMO) have been calculated and referenced against that of tetracyanoethylene (TCE).

$$N_{\mathrm{Nu}} = E_{\mathrm{HOMO}} - E_{\mathrm{HOMO(TCE)}}\ \mathrm{eV}$$

The HOMO energy is calculated within the Kohn–Sham scheme.[20] TCE is used as the reference since it presents the lowest HOMO energy in a large series of molecules. This choice gives one the convenience of handling a nucleophilicity scale of positive values.

The local reactivities (or site selectivities) of a chemical species are represented by local reactivity descriptors. One such descriptor is Fukui function indices (it is named so because of its conceptual similarity with Fukui's frontier molecular orbital theory).[21] To describe the nucleophilic character of a reactive site within a molecule, a local nucleophilicity index $N^-(r)$ can be obtained by using the relationship

$$N^-(r) = N^* f^-(r)$$

where, $f^-(r)$ is the Fukui function for electrophilic attack at the specific site.[22] For the computation of $f^-(r)$ the Finite Differences Approximation (FDA) has been used (please see the Supporting Information, S-I/1). The Fukui function can be condensed to atoms, using electronic population analyses. In this paper, atomic populations were obtained via the Natural Population Analysis (NPA) method.[23] The corresponding condensed-to-atom forms of the nucleophilicity index for atom $k$ can then be written as:

$$N_k^- = N^* f_k^-$$

Note that the nucleophilicity index leads to an absolute scale, which solely depends on the electronic characteristics of the nucleophile; hence it is independent of the electrophilic partner.

## Results and Discussion

For 69 commonly used arenes and heteroarenes, the global and local nucleophilicity descriptors as described in the preceding sections were calculated at the B3LYP/6-311+G(d,p) level of theory, using methods I to IV, leading to the corresponding nucleophilicity charts. At a qualitative level, the theoretical ordering for the compounds may be correlated with the generally known experimental order of nucleophilic reactivity. The order may be described in terms of categories such as good, moderate, and poor. For example, it is well-known that substituted indole, pyrrole, furan, aniline, N-substituted anilines, phenols, thiophenes, anisoles, etc., are good nucleophiles. In the same vein, toluene, xylene, and benzene may be regarded as moderately active in electrophilic aromatic substitution, while arenes containing an electron-withdrawing substituent (halogen, acid, aldehyde, ester, cyano, nitro, etc.) are known to be poor nucleophiles. While such qualitative attributes are at times useful, we sought to validate the nucleophilicity scales obtained via methods I to IV by judging the goodness of a linear fit between nucleophilicity ($N$) versus Hammett constant ($\sigma$) value. The nucleophilicity values evaluated by using method III and IV show a good linear relationship with the Hammett substituent constant $\sigma$ as well as the Hammett $\sigma_p$ value. Moreover, the trend in the nucleophilicity of the 69 compounds agreed well with the experimental results. It is observed that electron releasing nitrogen and oxygen containing arene and heteroarenes, viz. substituted aniline, pyrrole, indole, and furan derivatives, are good nucleophiles in EAS whereas thiophene and alkyl-substituted arene are moderate nucleophiles but haloarenes and arene and heteroarenes containing electron-withdrawing groups are poor nucleophile (Figure 3). We have also calculated the global nucleophilicity ($N$) and local nucleophilicity indices at the reactive sites ($N_k^-$) of di- and trisubstituted arene and heteroarene. Good correlations have been obtained between calculated and experimental results of reactivity order and site-selectivity.

**Correlation of $\sigma$ versus $N$, and Nucleophilicity Scale.** A reactivity scale should be able to answer fundamental questions about reaction feasibility, various selectivities, and other important aspects of reactivity. To check the validity of the observed nucleophilicity data from four different methods described in the preceding section, substituted arenes were chosen as the test series, and the corresponding calculated $N$ values were plotted against the Hammett substituent constant ($\sigma$ and $\sigma_p$),[24,25] where $\sigma$ is the summation of field effect ($\sigma_I$) and resonance effect ($\sigma_R$). In each case we have obtained good linear correlation between $N$ versus $\sigma$ values (Figures 1 and 2). When judged in terms of correlation coefficient ($R^2$ value) methods III, and IV are found to be superior to methods I and II. Note that the linear plots result in a negative slope. In other words one may conclude that arenes bearing electron-releasing substituent (negative $\sigma$ value) show high nucleophilicity value.

Next we have calculated the nucleophilicity values ($N$) of 69 arenes and heteroarenes in the Kohn–Sham approach using methods I to IV described earlier. When collated in increasing order, the $N$ values obtained via method III were found to correlate well with the experimental observations (Figure 3, for additional plots please see the Supporting Information, S-I).[26]

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[26] It may be noted that while the Hammett correlation coefficients are nearly similar for both methods III and IV, we have found that method III correctly predicts the higher nucleophilicity of thiophenol than ethylbenzene, whereas method IV wrongly predicts the opposite. Thus the method III derived classification of moderate nucleophiles at the boundary of alkylbenzene correlates well with experiment.

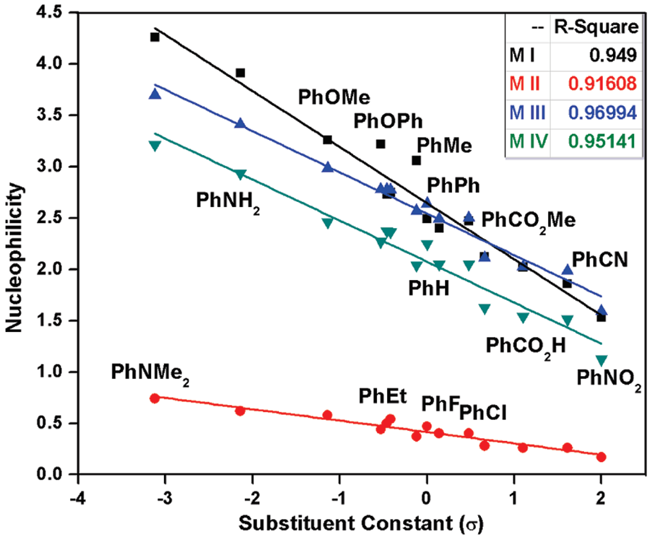

**FIGURE 1.** Plot of substituent constant (from ref 24) versus calculated nucleophilicity in all four methods.

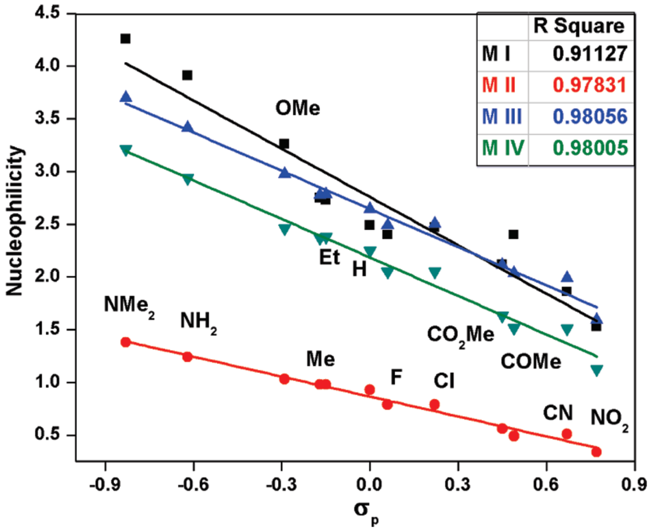

**FIGURE 2.** Plot of Hammett substituent constant ($\sigma_p$) versus calculated nucleophilicity in all four method.

As shown in Figure 3, we have classified the arenes and heteroarenes into three classes, namely good, moderate, and poor nucleophiles in accordance with $N$ values from high to low. The classification correlates well with the generally observed experimental order of reactivity in electrophilic aromatic substitution reactions (EAS). Thus, the good nucleophiles include amino-, hydroxy-, and methoxy-benzenes, thiophenols, phenols, and N/O-heterocycles such as pyrroles, indoles, and furans. The moderate nucleophiles include a few homologues of benzene, chlorophenols, chloroindoles, and bromobenzene. The weak nucleophiles in our list are the arenes having an electron-withdrawing group.

We also calculated the nucleophilicity of 69 compounds in methods II, III, and IV using computed vertical ionization energy ($I$) and electron affinity ($A$). But the nucleophilicity values obtained via this approach did not correlate well with experimental result. For example, thiophenol and phenol showed higher nucleophilicity than 2-methylfuran and pyrrole. Similarly, pyrrole derivatives showed higher nucleophilicity over indole derivatives (for details please see the Supporting Information, S-I/17−22).

**Comparison of Global and Local Nucleophilicity Trend in a Select Group of Arenes and Heteroarenes.** The often explored parameters in an electrophilic aromatic substitution (EAS) reaction are the following: (a) the comparative reactivity of two compounds belonging to a series toward an electrophile and (b) the comparative local reactivity (site selectivity) of the plausible sites of electrophilic attack in a nucleophile. Both parameters play an immense role in the design of a retrosynthetic plan that an organic chemist recourses to. Due to these importances there have been numerous studies to understand the intermolecular and intramolecular reactivities in EAS.[27] We therefore considered it appropriate to analyze the global and local nucleophilcity trends in a selected group of arenes and heteroarenes. These include indoles, pyrroles, phenols, and anisoles. As noted in the introductory remarks, Mayr et al. have significantly contributed toward the experimental determination of global nucleophilicity scales. Presented below are our studies on both global and local nucleophilicity trends based on $N$ and $N_k^-$ values for select groups of arenes and heteroarenes. It may be noted that we have relied on the global nucleophilicity indices to compare intermolecular reactivity, while local nucleophilicity indices derived using the Fukui function were used in judging the intramolecular reactivity (site selectivity).[28]

**Substituted Indoles.** Substituted indoles are important biologically active compounds. The Friedel−Crafts alkylation and acylation of indole and substituted indoles is an important reaction to generate useful building blocks which are utilized for further synthetic manipulation. As a result the reactivity and site selectivity issues become important in indoles and we calculated both global and local nucleophilicity values. Gratifyingly, the $N$ values obtained by us showed excellent correlation with experimental results (Figure 4).[29a] Also, the local nucleophilicity indices clearly point out that electrophilic attack at the 3-position will be preferred over that at the 2-position. Interestingly, in 5-amino, 5-methoxy, and 2-methyl indoles we could also observe an enhanced local nucleophilicity (ranging from 0.42 to 0.48) at the 4-position.

**Substituted Phenols.** The monosubstituted phenols are yet another important group of compounds in EAS and were taken up by us for analysis. The substituents ($-NH_2$, $-OMe$, $-Me$, $-OH$, $-Cl$, $-CN$, and $-NO_2$) were chosen so as to

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(28) The reader may note that the local nucleophilicity indices do not conform well in predicting intermolecular reactivity order in a group of arenes and heteroarenes containing an electron-withdrawing group. Geerling et a.l has also observed that Fukui function works less well for arenes having deactivating functional groups. Please see: (a) Langenaeker, W.; De Proft, F.; Geerlings, P. *J. Phys. Chem.* **1995**, *99*, 6424–6431. (b) Langenaeker, W.; De Proft, F.; Geerlings *THEOCHEM* **1996**, *362*, 175–179. We thank one of the reviewers for pointing this out to us.

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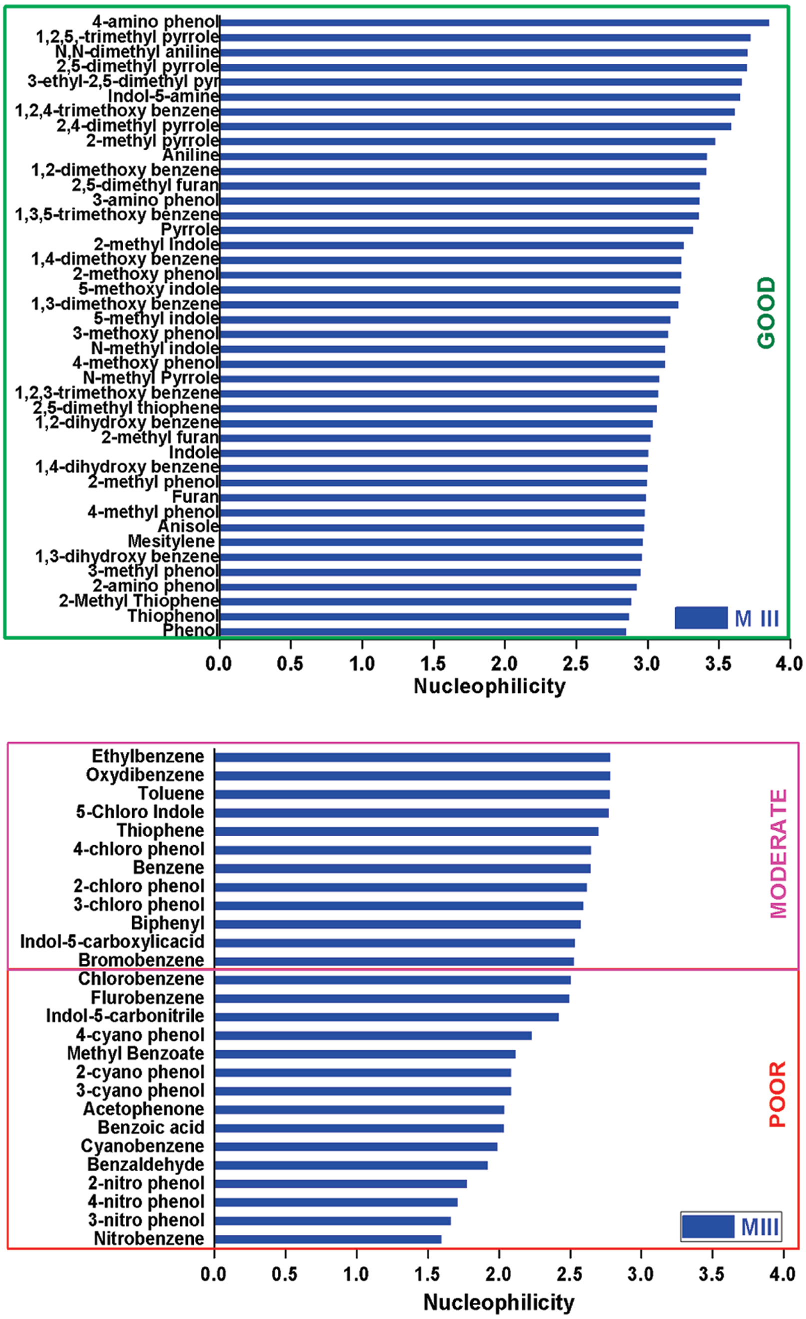

**FIGURE 3.** Classification of 69 molecules according to nucleophilicity evaluated via method III.

represent a broader spectrum in terms of inductive, resonance, and polarizability effects. The trends in $N$ and $N_k^-$ values upon variation of the position of substituent (ortho, meta, and para) in each case are discussed below.

**For Para-Disubstituted Phenol.** The order of calculated global nucleophilicity values are in close agreement with the experimental results.[7d] This trend is the same irrespective of the method of calculation as is methods I−IV (see the Supporting Information). The local nucleophilicity indices clearly reveal the generally observed regioselectivity (Figure 5).

**For Meta-Disubstituted Phenol.** While the global nucleophilicity trend confirms the expected order of reactivity, the local nucleophilicity indices suggest preferential substitution at the C-4 position, expect for 3-aminophenol. In this latter case the C-6 position is more nucleophilic that C-4 (Figure 6).

**For Ortho-Disubstituted Phenol.** In this series the global nucleophilicity order is in very good correlation with the +R effect of the substituent (Figure 7). As the +R effect of the substituent decreases in the order $-NH_2 > -OMe > -OH > -Me > -Cl > -CN > -NO_2$ so also does the reactivity order of the corresponding phenol derivatives. Again as in the previous case, as the +R effect of $NH_2$ is greater than that of OH so C-5 is more electron rich than C-4. The same trends were followed in 2-methoxyphenol and 2-methylphenol.

**Alkyl-Substituted Pyrroles.** Pyrrole and its derivatives are important compounds, and constitute important substructure in

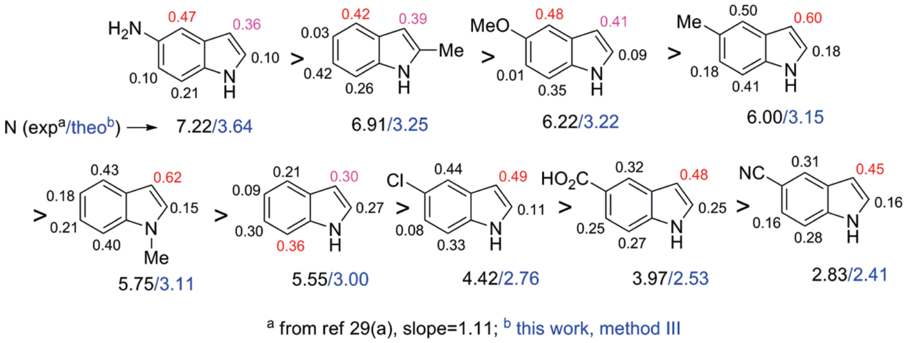

**FIGURE 4.** Global nucleophilicity ($N$) order and local nucleophilicity index ($N_k^-$) values of all positions in substituted indole in method III.

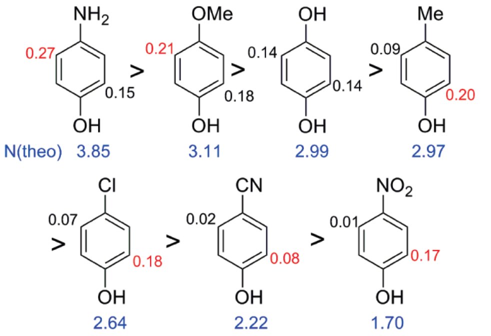

**FIGURE 5.** Global nucleophilicity ($N$) order and local nucleophilicity index ($N_k^-$) values of all positions in para-disubstituted phenols in method III.

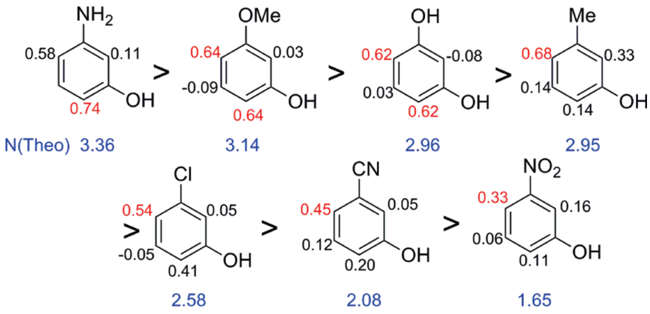

**FIGURE 6.** Global nucleophilicity ($N$) order and local nucleophilicity index ($N_k^-$) values of all positions in meta-disubstituted phenols in method III.

many natural products from chlorophyll to the pyrrole alkaloids. The site selectivity indicated by the local nucleophilicity values conformed well to experimental observation (Figure 8).[29b]

**Substituted Anisoles.** The experimentally observed reactivity and site selectivity of substituted anisoles are at times difficult to comprehend in terms of the (+R)-effect of the methoxy group alone. Steric factors are invoked in such cases. Keeping this in view we subjected the methoxy-series to analysis. In fact the global nucleophilicity trend matched well with the experimental reactivity order except in the case of 1,4-dimethoxybenzene (Figure 9).[7d,30] In contrast, the site selectivity predicted by using local nucleophilicity indices correlates well with the experimental observation.[7d,30]

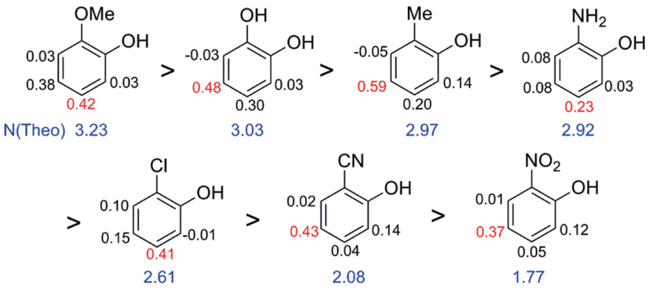

**FIGURE 7.** Global nucleophilicity ($N$) order and local nucleophilicity index ($N_k^-$) values of all positions in ortho-disubstituted phenols in method III.

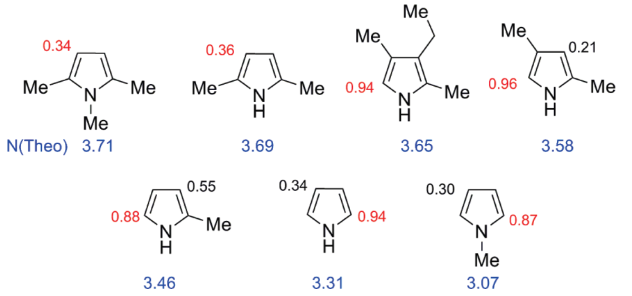

**FIGURE 8.** Global nucleophilicity ($N$) values and local nucleophilicity index ($N_k^-$) values of all positions in substituted pyrroles in method III.

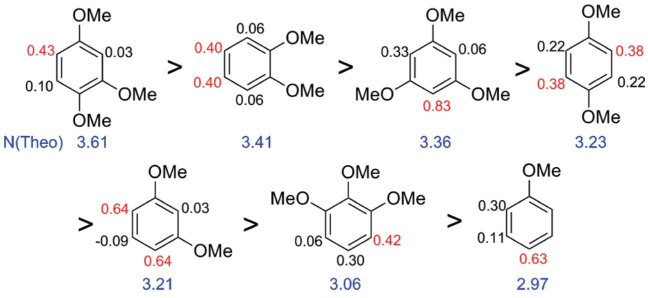

**FIGURE 9.** Global nucleophilicity ($N$) order and local nucleophilicity index ($N_k^-$) values of all positions substituted anisoles in EAS.

## Conclusions

In summary, the global nucleophilicity values ($N$) of 69 commonly used arenes and heteroarenes in organic

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(30) Zhuang-ping, Z.; Jing-liang, Y.; Hui-juan, L.; Yuan-yuan, C.; Rui-feng, Y.; Wen-zhen, Y.; Jun-ping., L. *J. Org. Chem.* **2006**, *71*, 8298.

chemistry has been calculated by using four different methods. The goodness of the methods was tested from the linear fit between $N$ and Hammett $\sigma$ and $\sigma_p$ values. The $N$ values offer an at-a-glance assessment of chemical reactivity in electrophilic aromatic substitution reactions. From the global nucleophilicity values ($N$) we could categorize the compounds in three groups, namely, good, moderate, and poor. In electrophilic aromatic substitution reactions, the other important parameter that assumes importance is the preferential site of attack in a nucleophile. To assess the same, we have utilized the concept of local nucleophilicity index ($N_k^-$). For four different arene and heteroarene series (substituted indoles, substituted phenols, alkyl-substituted pyrroles, and substituted anisoles) the local nucleophilicity parameters for every site in each compound were calculated. The resulting site-selectivity has been found to correlate well with the experimental results.

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**Supporting Information Available:** Computational methodology and all the results in detail (S-I) and optimized structure of all the compounds with coordinates (S-II). This material is available free of charge via the Internet at http://pubs.acs.org.