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A Frontier Molecular Orbital Theory Approach to Understanding the Mayr Equation and to Quantifying Nucleophilicity and Electrophilicity by Using HOMO and LUMO Energies**

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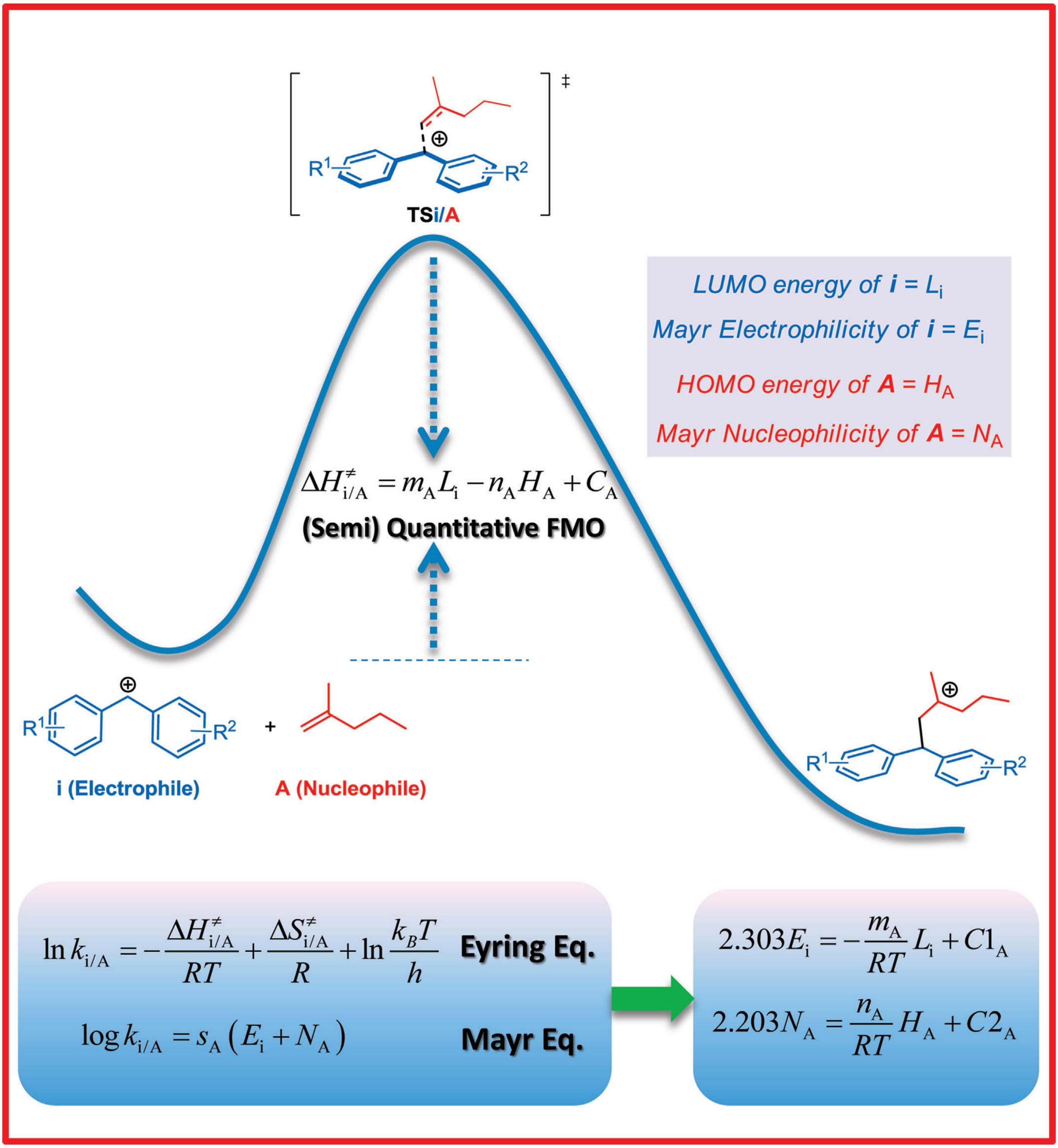

Abstract: Obtaining the reactivities (such as nucleophilicities and electrophilicities) of molecules is of fundamental importance in chemistry. Mayr and co-workers have developed the Mayr equation, which has been widely used to quantify nucleophilicity and electrophilicity. Herein we propose a theoretical understanding of the Mayr equation based on frontier molecular orbital (FMO) theory and the Eyring equation of the transition state theory, showing that the nucleophilicity of a molecule is related to the energy of this molecule's highest occupied molecular orbital (HOMO), while the electrophilicity is related to the energy of the lowest unoccupied molecular orbital (LUMO) of the electrophile. Consequently, we propose a new approach by combining the FMO theory and the Mayr equation to predict the reactivities of new molecules. Ab initio calculation results support these linear relationships between LUMO energies and the Mayr electrophilicities (E) and the HOMO energies and the Mayr nucleophilicities (N) for sets of electrophiles and nucleophiles, respectively. For each set of nucleophiles or electrophiles, their different reactivities are mainly controlled by the electronic effects of the substituents. If other effects, such as sterics, affect reactivity for a set of electrophiles or nucleophiles, the linear relationships between HOMO levels and N values and LUMO levels and E values cannot be secured. The present approach through combining Mayr equation and the quantitative FMO theory suggests that the Mayr nucleophilicity or electrophilicity of a new molecule, which could be an intermediate of a reaction, unstable reactant, or a hypothetical reactive species, can be obtained through ab initio calculations of the frontier molecular orbital energies, and this will greatly expand the data sets of Mayr nucleophilicities and electrophilicities.

Keywords: density functional calculations · electrophilicity · FMO theory · Mayr equation · nucleophilicity

Introduction

Understanding the reactivity of a chemical species, which could be either a stable or an active species (generated in situ or in a reaction as an active intermediate, or a theoretically designed one), is one of the fundamental questions in chemistry. The development of theories to explain the factors affecting reactivities is highly prized to understand why a reaction happens and how fast a reaction can be. Similarly, obtaining quantitative indexes of reactivities is also crucial in rational design, because these indexes can help chemists calculate and predict the reaction rates of new or designed reactions. For these reasons, many efforts have been made by chemists to develop quantitative descriptors of reactivities.[1]

The development of understanding reactivity can be traced back to the 1930s, when Ingold introduced the concepts of nucleophilicity and electrophilicity to quantify the strength of nucleophiles and electrophiles.[2] Later, several attempts to quantitatively describe molecules according to this general concept have been proposed, for example by Swain and Scott,[3] Edwards,[4] and Ritchie.[5] In the 1990s, Mayr and co-workers developed an equation [$\log k = s(E+N)$] that can be used very broadly to measure nucleophilicities (N) and electrophilicities (E).[6,7] Recently, the Mayr equation, as it is now known, has been successfully applied to a broad range of reactions, thus greatly expanding the knowledge of the reactivities of molecules.[6]

Several theoretical and computational approaches have been devoted to understanding the Mayr equation and to compute Mayr nucleophilicities and electrophilicities.[8] Schindele, Houk, and Mayr conducted DFT calculations on the affinities of benzhydryl cations $(XC_6H_4)_2CH^+$ for the methyl anion, hydroxide, and hydride anion and compared the computed values of rate and equilibrium constants with those obtained experimentally in solution, revealing an excellent linear correlation between the electrophilicity parameters (E) and the calculated methyl anion affinities.[8a] Contreras et al. proposed a series of models based on global reactivity indexes (ω) defined by Parr et al. in terms of the electronic chemical potential and the chemical hardness.[8b–h] Some interesting features of the free-energy relationships were found between N and ω^-, and between E and ω^+. Direct ab initio transition-state calculations were performed by Liu et al. to predict the nucleophilicity parameters (N) for π nucleophiles in CH_2Cl_2.[8i] In their study, the authors also used energies of the highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs) to describe the reactivities, and they found that LUMO and E are linearly correlated but HOMO and N are not. The reasons behind these results have not been well investigated, even though steric factors were used to explain these effects. Despite these computational efforts to rationalize the reactivity parameters, a theoretical foundation and further understanding of the Mayr equation are needed to significantly advance our understanding of reactivities.[6g]

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[**] HOMO = highest occupied molecular orbital, LUMO = lowest unoccupied molecular orbital.

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Frontier molecular orbital (FMO) theory is widely and extensively used to explain reactivities and stereo- and regioselectivities.[9,10] The FMO theory assumes that the reaction rate of a bimolecular reaction is influenced by the energies of HOMO and LUMO orbitals of the reactants. In a substitution reaction, for example, FMO theory indicates that the reaction rate is proportional to the energy gap between the HOMO of the nucleophile and LUMO of the electrophile. The smaller this gap is, the greater the interaction between $\mathrm{HOMO_{nu}}$ and $\mathrm{LUMO_{el}}$ in stabilizing the transition state, and consequently the faster the nucleophilic reaction is. The shape of these frontier molecular orbitals, reflected by the orbital coefficients, should also be taken into account when discussing the relative reactivities of different reaction sites in the reactants (related to the regiochemistry). Even though FMO theory is very successful in addressing reactivity, it can only qualitatively explain or predict a reaction rate. Only limited quantitative analysis using FMO has been reported.[9h,i]

Considering that the Mayr equation can give quantitative indexes of reactivities while FMO theory gives qualitative ones, we wondered whether there is an inherent relationship between the Mayr equation and the FMO theory, and consequently if the Mayr equation and its nucleophilicity and electrophilicity can be understood by the FMO theory. We further wondered whether the Mayr equation and the FMO theory can be combined to provide a new approach to quantify or semi-quantify reactivities. If this could be achieved, we could get the Mayr nucleophilicities and electrophilicities of new species by just computing these species' frontier molecular orbital energies, and consequently we could greatly expand the data sets of Mayr nucleophilicities and electrophilicities. Herein, we show that the Mayr equation and FMO theory are equivalent if electronic effects dominate reactivities of the studied molecules. We further demonstrate that the nucleophilicity and electrophilicity in the Mayr equation are related to the HOMO and LUMO energies of a nucleophile and an electrophile, respectively. A general quantitative scheme of reaction rate with regard to HOMO of a nucleophile and LUMO of an electrophile is also proposed.

Abstract in Chinese: 获得分子的化学反应活性（比如它们的亲电性和亲核性）在化学研究中非常重要。Mayr发展了一种可以定量描述反应速率与反应物的亲电性和亲核性相关的方程(即 Mayr 方程),并用此方程在实验上测量了许多反应物的亲电性和亲核性。在本文中，我们从前线轨道理论（FMO）出发,并结合过渡态理论中的 Eyring 方程，推导出 Mayr 方程和 FMO 理论在原理上是一致的。我们的理论表明，当在比较一系列分子的反应活性时,如果影响这些分子的反应性主要是由于它们的不同取代基的电子效应所引起的,那么,一个亲核分子的亲核性和该分子的最高占据轨道（HOMO）相关，而一个亲电分子的亲电性则与该分子的最低空轨道（LUMO）相关。通过对一系列反应活性主要受到取代基的电子效应影响的反应物的前线轨道能量进行量子化学计算，我们验证了亲电分子的 LUMO 能量和它们的 Mayr 亲电性常数（E），亲核分子的 HOMO 轨道能量和它们的 Mayr 亲核性常数（N）分别存在线性关系。如果其它效应(如立体位阻效应)在较高程度上影响反应物的亲电性和亲核性，那么这样的线性关系将不易获得。我们这一研究将可以用于预测许多反应物质的 Mayr 亲电性和亲核性，从而大大扩展 Mayr 的亲电性和亲核性数据库.

Results and Discussion

1. FMO Understanding of the Mayr Equation

Let's begin by showing that the Mayr equation can be understood by the FMO theory when the reactivities of a set of molecules are considered. These molecules could be either electrophiles or nucleophiles with different reactivities mainly dictated by the electronic effects of their different substituents.

$$\log k_{\mathrm{i/j}} = s_{\mathrm{j}}(E_{\mathrm{i}} + N_{\mathrm{j}}) \tag{1}$$

$$\ln k_{\mathrm{i/j}} = 2.303\, s_{\mathrm{j}}(E_{\mathrm{i}} + N_{\mathrm{j}}) \tag{1a}$$

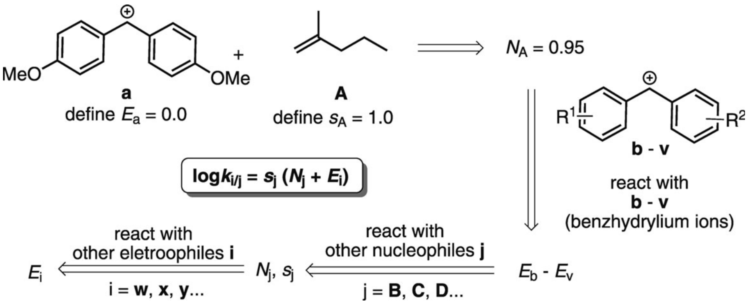
In the Mayr equation (1), $k_{\mathrm{i/j}}$ is the experimentally measured rate constant between electrophile i (i = **a**, **b**, **c**, ...) and nucleophile j (j = **A**, **B**, **C**, ...), s_{j} is a nucleophile-specific sensitivity parameter for the nucleophile j, N_{j} is the nucleophilicity of nucleophile j and E_{i} is the electrophilicity of electrophile i.

Before we derive the theoretical basis, let's first review how the Mayr equation was derived experimentally (Scheme 1).[6c] Initially, Mayr and co-workers measured the reaction rate of $(p\text{-MeOC}_6\text{H}_4)_2\text{CH}^+$ (**a**) with 2-methyl-1-pentene (**A**). By defining the nucleophile-specific parameter $s_{\mathrm{A}} = 1$ for nucleophile **A** and defining the electrophilicity of electrophile **a** as $E_{\mathrm{a}} = 0$, they obtained the nucleophilicity of **A** as $N_{\mathrm{A}} = 0.95$ by entering the measured reaction rate into Equation (1). Then they measured the reaction rates of a series of electrophiles of **b**–**v** (see structures of these species in the Supporting Information) toward nucleophile **A**. By using these experimental rates in Equation (1), they obtained the E_{i} values of all these electrophiles **b**–**v**. Mayr and co-workers then used these measured electrophilicities of the electrophiles **a**–**v** to obtain the nucleophilicities of other nucleophiles (**B**, **C**, **D**, ...) by entering the measured reaction rates into Equation (1). Consequently, the nucleophilicities (N_{B}, N_{C}, N_{D}, ...) and the nucleophile-specific parameters (s_{B}, s_{C}, s_{D}, ...) were obtained.

We now demonstrate herein that the Mayr equation can be understood by using FMO theory assuming that electronic effects are the dominant factor affecting reactivity. FMO theory suggests that the nucleophilic reaction between **A** and the electrophile i should be faster if the HOMO of the nucleophile is higher while the LUMO of electrophile is lower.[10] Therefore, we propose that the activation enthalpies ($\Delta H^{\neq}_{\mathrm{i/A}}$) of these reactions should approximately obey Equation (2):

$$\Delta H^{\neq}_{\mathrm{i/A}} = m_{\mathrm{A}} L_{\mathrm{i}} - n_{\mathrm{A}} H_{\mathrm{A}} + C_{\mathrm{A}} \tag{2}$$

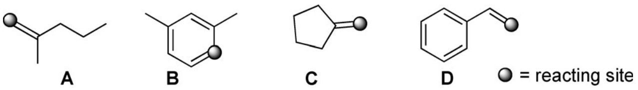
where H_{A} is the HOMO energy of nucleophile **A** and L_{i} is the LUMO energy of electrophile i, m_{A} and n_{A} are defined as LUMO and HOMO sensitivity factors for **A**, respectively, and C_{A} is a constant for all these nucleophilic reactions of **A** to i, which can be roughly regarded as a contribution from filled orbital interactions from reactants **A** and i, and the distortion energies of the reactants.[11–13] Equation (2) indicates that the higher/lower the HOMO/LUMO gap is, the higher/lower the activation enthalpy of the reaction is. In traditional FMO theory, the contributions of HOMO and LUMO energies to the activation energy of the reaction are the same (based on perturbation theory),[9h] but we propose that their contributions could be different, and we use LUMO and HOMO sensitivity factors *m* and *n* to quantify those different contributions to the reactivity.



Scheme 1. Procedure of measuring N_{j} and E_{i} using the Mayr equation.

DFT calculations at the B3LYP/6-31G(d)[15,16] level in the gas phase supported the validity of the application of the FMO theory to the nucleophilic addition reactions between **A** and electrophiles **a**–**v**[6c] (Table 1). We found that these quantitative relationships also hold for the nucleophilic reactions between **B**–**D** and **a**–**v** (Table 1). It is interesting to note that the computed rate constants (k_{cal}) and experimentally measured ones (k_{exp}) correlate very well.

Table 1. The linear relationship between the activation energies and LUMO energies (L_{i}) of electrophiles for the nucleophilic reactions of **A**–**D** towards **a**–**v** (see Scheme 1).



j	$\Delta H^{\neq}/L_{\mathrm{i}}$	$\Delta S^{\neq}$ [cal mol^{-1}K^{-1}]	$\ln k_{\mathrm{cal}}/\ln k_{\mathrm{exp}}$
A	$\Delta H_{i/\mathrm{A}}{}^{\neq} = 8.99\,L_{\mathrm{i}} + 70.3$	−41.3 to −42.3	$\ln k_{\mathrm{cal}} = 1.40 \ln k_{\mathrm{exp}} - 13.20$
B	$\Delta H_{i/\mathrm{B}}{}^{\neq} = 8.93\,L_{\mathrm{i}} + 76.2$	−46.3 to −49.2	$\ln k_{\mathrm{cal}} = 0.86 \ln k_{\mathrm{exp}} - 15.22$
C	$\Delta H_{i/\mathrm{C}}{}^{\neq} = 9.09\,L_{\mathrm{i}} + 49.7$	−39.1 to −41.9	$\ln k_{\mathrm{cal}} = 1.29 \ln k_{\mathrm{exp}} - 19.24$
D	$\Delta H_{i/\mathrm{D}}{}^{\neq} = 10.8\,L_{\mathrm{i}} + 81.3$	−40.5 to −42.5	$\ln k_{\mathrm{cal}} = 1.58 \ln k_{\mathrm{exp}} - 9.13$

After obtaining Equation (2) from FMO theory, we can submit this equation into the Eyring equation [Eq. (3)] of the transition state theory to get Equation (3 a):

$$\ln k_{\mathrm{i/A}} = -\frac{\Delta H^{\neq}_{\mathrm{i/A}}}{RT} + \frac{\Delta S^{\neq}_{\mathrm{i/A}}}{R} + \ln \frac{k_B T}{h} \tag{3}$$

$$\ln k_{\mathrm{i/A}} = -\frac{m_{\mathrm{A}}}{RT} L_{\mathrm{i}} + \frac{n_{\mathrm{A}}}{RT} H_{\mathrm{A}} - \frac{C_{\mathrm{A}}}{RT} + \frac{\Delta S^{\neq}_{\mathrm{i/A}}}{R} + \ln \frac{k_{\mathrm{B}} T}{h} \tag{3a}$$

In Equation (3), k_{B} is the Boltzman constant. The last three terms in Equation (3 a) can be regarded as constants, because all these reactions are conducted at almost the same temperature, and the activation entropies for all of them are very close (see Table 1). The activation entropies are very close because the structures of transition states are very similar. If the last three terms can be divided arbitrarily into two constants, namely, we can have $C1_{\mathrm{A}} + C2_{\mathrm{A}} = \frac{-C_{\mathrm{A}}}{RT} + \frac{\Delta S^{\neq}_{\mathrm{i/A}}}{R} + \ln \frac{k_B T}{h}$, Equation (3 a) can be written as Equation (3 b):

$$\ln k_{\mathrm{i/A}} = \left(-\frac{m_{\mathrm{A}}}{RT} L_{\mathrm{i}} + C1_{\mathrm{A}}\right) + \left(\frac{n_{\mathrm{A}}}{RT} H_{\mathrm{A}} + C2_{\mathrm{A}}\right) \tag{3b}$$

This equation is similar to the Mayr equation. Therefore, we can define Equation (3 c) and Equation (3 d):

$$2.303\,E_{\mathrm{i}} = \frac{-m_{\mathrm{A}}}{RT} L_{\mathrm{i}} + C1_{\mathrm{A}} \tag{3c}$$

$$2.303\,N_{\mathrm{A}} = \frac{n_{\mathrm{A}}}{RT} H_{\mathrm{A}} + C2_{\mathrm{A}} \tag{3d}$$

Then Equation (3 b) can be transformed to Equation (3 e):

$$\ln k_{\mathrm{i/A}} = 2.303\,(E_{\mathrm{i}} + N_{\mathrm{A}}) = 2.303\,s_{\mathrm{A}}(E_{\mathrm{i}} + N_{\mathrm{A}}) \tag{3e}$$

where $s_{\mathrm{A}} = 1$ is defined with respect to nucleophile **A** so that Equation (3 e) and Equation (1 a) have the same form.

The nucleophilic reactions of nucleophile (**B**) toward electrophiles **a**–**v** also follow Equation (4), based on the FMO theory, as supported by calculations shown in Table 1, entry 2. By following the previous procedure, we arrive at Equations (4 b) and (4 c).

$$\Delta H^{\neq}_{\mathrm{i/B}} = m_{\mathrm{B}} L_{\mathrm{i}} - n_{\mathrm{B}} H_{\mathrm{B}} + C_{\mathrm{B}} \tag{4}$$

$$\ln k_{\mathrm{i/B}} = \left(-\frac{m_{\mathrm{B}}}{RT} L_{\mathrm{i}} + C1_{\mathrm{B}}\right) + \left(\frac{n_{\mathrm{B}}}{RT} H_{\mathrm{B}} + C2_{\mathrm{B}}\right) \tag{4b}$$

$$\ln k_{i/B} = \frac{m_B}{m_A}\left[\left(-\frac{m_A}{RT}L_i + C1_A\right) + \left(\frac{m_A}{m_B}\frac{n_B}{RT}H_B + \frac{m_A}{m_B}C2_B\right)\right] \quad (4c)$$

Equation (4b) has been written in another form, Equation (4c), in which, we tried to introduce $2.303\,E_i = -\frac{m_A}{RT}L_i + C1_A$ so that the electrophile indexes for the nucleophilic reactions of nucleophiles **A** and **B** towards electrophiles **a**–**v** are the same. In Equation (4c), we have $C1_B = (m_B/m_A)\,C1_A$ and $C1_B + C2_B = \frac{-C_B}{RT} + \frac{\Delta S^{\neq}_{i/B}}{R} + \ln\frac{k_B T}{h}$

Thus, we can define the nucleophilicity of **B** as $2.303\,N_B = \frac{m_A}{m_B}\frac{n_B}{RT}H_B + \frac{m_A}{m_B}C2_B$, and the nucleophile-specific slope is $s_B = m_B/m_A$.

Consequently, we get Equation (4d):

$$\ln k_{i/B} = 2.303\,s_B(E_i + N_B) \quad (4d)$$

Based on the above derivation, we can generalize the Mayr nucleophilicity N_j of any nucleophile j, together with its nucleophile-specific slope s_j (using nucleophile **A** as the reference nucleophile) as in Equation (5):

$$\ln k_{i/j} = \frac{m_j}{m_A}\left[\left(-\frac{m_A}{RT}L_i + C1_A\right) + \left(\frac{m_A}{m_j}\frac{n_j}{RT}H_j + \frac{m_A}{m_j}C2_j\right)\right] \quad (5)$$

Equation (5) can be simplified to Equation (5b):

$$\ln k_{i/j} = s_j\big(f_i(L_i) + f_j(H_j)\big) = s_j(E_i + N_j) \quad (5b)$$

where [Eqs. (6)–(8)]:

$$f_i(L_i) = 2.303\,E_i = -\frac{m_A}{RT}L_i + C1_A \quad (6)$$

$$s_j = \frac{m_j}{m_A} \quad (7)$$

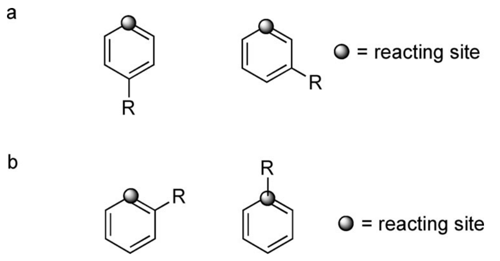
$$f_j(H_j) = 2.303\,N_j = \frac{m_A}{m_j}\frac{n_j}{RT}H_j + \frac{m_A}{m_j}C2_j \quad (8)$$

Thus, Equations (5)–(8) derived from the FMO theory implicate that the Mayr equation [Eq. (1)] can be well understood by the FMO theory, and Equation (5) can be regarded as a quantified FMO expression of the Mayr equation (or this can be simplified as Equation (5b), which invokes two functions $f_i(L_i)$ and $f_j(H_j)$ with L_i and H_j as variables).

Equation (7) suggests that the nucleophile-specific parameter s_j is related to the HOMO sensitivity factor m_j of nucleophile j. Nucleophiles j and **A** could usually have similar HOMO sensitivity factors and s_j is then close to 1, as found by Mayr in the Mayr equation. The theoretical values of s_A, s_B, s_C and s_D calculated on this basis are 1.0, 1.0, 1.0, and 1.2 (m_j/m_A, m_j are the slopes in Table 1). The values measured by Mayr are 1.0, 1.62, 0.90, and 0.95, respectively. The difference between the theoretical and experimental values of s is due to the difference between the computed k_{cal} and the experimentally measured k_{exp} (this relationship is $\ln k_{cal} = x_j \ln k_{exp} + y_j$; x_j and y_j are correction coefficients, Table 1). With this consideration, the nucleophile-specific parameter can be computed as $s_j = \frac{m_j}{m_A}\frac{x_A}{x_j}$, and the computed values of s_A, s_B, s_C and s_D are then 1.0, 1.64, 1.03, and 1.06, close to the trend of Mayr's experimentally measured values.

The above derivations [Eqs. (5)–(8)] indicate that the Mayr nucleophilicity of a nucleophile is related to the HOMO energy of the nucleophile, while the Mayr electrophilicity is related to the LUMO energy of an electrophile. If both E_i/L_i and N_j/H_j display linear relationships, we can then greatly expand the data sets of Mayr nucleophilicities and electrophilicities by using the calculated H_j and L_i energies.

Here we want to point out that our derivation of Equations (5)–(8) is based on FMO theory. It is well known that FMO theory has its limitations. For example, FMO theory is not quantitative and does not take into consideration steric effects, solvent effects, distortion effects, and so forth.[10] Also for diffusion-controlled reactions,[10h] our FMO approach has problems describing the reactivities of reactants appropriately. In principle, we can include some additional terms in Equation (2) to take account of all these non-electronic effects, which will be a subject of future study. At present, we will only consider sets of species that have different nucleophilicities or electrophilicities, mainly due to their different frontier molecular orbitals induced by their different substituents remote to the reacting sites. In Scheme 2, we use the hypothetical reactivities of substituted benzenes to depict the scope of using Equations (5)–(8). For the set of species in Scheme 2a, R groups affect the reactivities mainly through electronic effects, the FMO theory can be applied, and consequently, Equations (5)–(8) can be used. For those species whose reactivities are dominated mainly by both steric and electronic effects, the FMO approach cannot be used to quantify reactivities (the hypothesized species in Scheme 2b). Obtaining reactivity parameters here is similar to getting substitution parameters from benzoic acid derivatives by Hammett,[17]



Scheme 2. A schematic description of scope of the application of FMO to Equation (5)–(8). a) FMO can be applied; electronic effects dominate reactivity. Equations (5)–(8) can be applied. b) FMO cannot be applied; both electronic and steric effects affect reactivity. Equations (5)–(8) should be modified.

where the substituents can only be in the *para* or *meta* position of the benzoic acid.

Below, we will show that the present FMO approach can greatly expand the data sets of the Mayr equation in many systems if electronic effects are dominant in affecting reactivity.

2. Computational Support of the Relationship between LUMO and Electrophilicity[14]

Equation (6) should obey a linear relationship between E_i and L_i because the coefficients are constants, as supported by the data shown in Table 1, independent of electrophile i. We were pleased to observe (Figure 1) that the LUMO energies[14] of benzhydrylium ions (**a**–**v**) have a very excellent liner relationship with the experimentally measured Mayr electrophilicities, thus confirming the validity of Equation (6).[15,16] Such linear relationship was also observed by Liu et al.[8i] Similar linear relationships were also found for Michael acceptors, and this discussion will be given in Section 5 below.[18] The good correlation here is quite understandable considering that the species in Figure 1 differ in reactivity mainly in electronic effects (it is obvious that the steric effects caused by R group in **a**–**v** can be ignored).

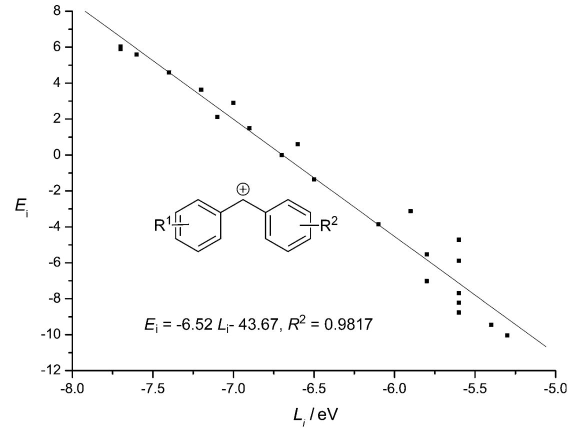


Figure 1. Correlation between experimentally measured electrophilicity (E_i) and B3LYP/6-31G(d) computed LUMO energy (L_i) of electrophile i (carbocations **a**–**v**) with $E_\mathrm{i}=-6.52\,L_\mathrm{i}-43.67$, $R^2=0.9817$.

3. Computational Support of the Relationship Between HOMO and Nucleophilicity

Since N_j, m_j, n_j, and $C2_\mathrm{j}$ are different for different nucleophiles j, in principle, a general linear relationship cannot be obtained between H_j and N_j [Eq. (8)]. This situation suggests that we can have very random distribution of H_j and N_j for compounds **A**–**D** (Table 1) and their derivatives, which also explains why Liu et al. could not obtain linear relationships.[8i] Not only electronic effects but also other effects influence the reactivities of compounds **A**–**D**. Consequently, Equation (8) cannot be used, and no linear relationship can be found.

However, a set of similar nucleophiles in which the reactivity differences are governed mainly by electronic effects could have very similar values of m_j, n_j, $C2_\mathrm{j}$, and consequently a good relationship of N_j and H_j could be obtained (only electronic effects of R groups are dominant in affecting reactivity. This is the case (a) in Scheme 2). In other words, very different nucleophiles can be divided into several subsets, and in each subset, a good relationship between nucleophilicities (N_j) and HOMO energies (H_j) could be obtained. We calculated the H_j values of the arene compounds[6c,19] as an example to show a linear relationship between HOMO energies and the experimentally measured nucleophilicities. We were excited to find that there is a linear correlation between N_j and H_j after classifying all aromatic compounds into either the five-membered heteroaromatic subset (**E1**–**E7**) or the benzene derivative subset (**B** and **F1**–**F4**; Figure 2). We observed that the nucleophilicities of five-membered heteroaromatics and benzene derivatives cover a range of more than seven orders of magnitude in nucleophilicity. Furthermore, plotting H_j versus N_j of indoles[20] also gave two separate linear correlations for 2-methylindoles (**G1**–**G4**) and indoles (**H1**–**H11**; Figure 2c,d).

We must point out here that the HOMO is usually the reacting orbital considered in FMO theory. But in some special cases, the HOMO-1 or HOMO-2 could be the frontier molecular orbitals as the reacting orbitals. Therefore, in this case, we have to use HOMO-1 or HOMO-2 orbitals in Equation (8). An example for this special case is found for *para*-substituted pyridines (**I1**–**I6**, Figure 3), where some species have their HOMO-1 orbitals as the reacting orbitals (the lone pair orbitals of the nitrogen atoms).[21] Here we see again that Equation (8) is kept in the present case.

4. Further Consideration of the FMO and Mayr Nucleophilicity: The Orbital Coefficients Are also Important

In the above development, we did not consider the contribution of orbital coefficients, with the assumption that the orbital coefficients of the reaction centers in HOMO (or LUMO) are very close for a set of similar nucleophiles (or electrophiles). This assumption proved to be true in most cases (see the Supporting Information for more discussion). In addition, for most nucleophiles, the HOMO orbital coefficients at the reacting centers are much higher than those of the LUMOs. Similarly, for most electrophiles, the HOMO orbital coefficients at the reacting centers are lower than LUMO coefficients. Therefore, the orbital shapes of HOMOs and LUMOs are not considered in obtaining nucleophilicities and electrophilicities for most nucleophiles and electrophiles.

However, for some nucleophiles, the orbital coefficients in their LUMOs are not small and negligible, and it is necessary to consider the orbital coefficients to get a better re-

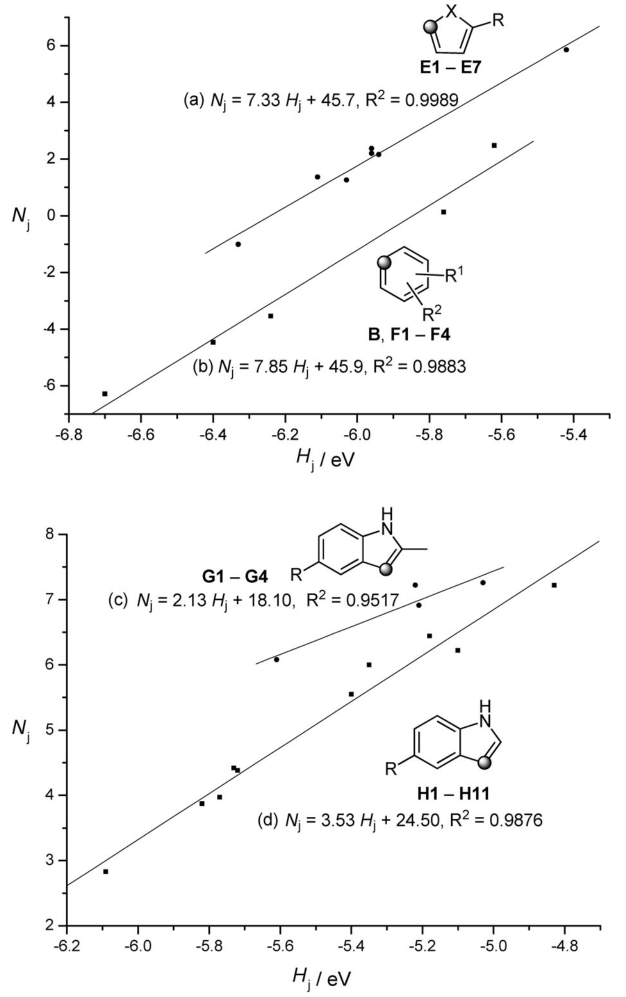


Figure 2. Correlation between nucleophilicity (N_j) and the HOMO energy (H_j) computed at the B3LYP/6-31G(d) level. a) The five-membered heteroaromatic (**E1–E7**) subset; $N_j = 7.33H_j + 45.7$, with $R^2 = 0.9989$. b) The benzene derivative (**B** and **F1–F4**) subset; $N_j = 7.85H_j + 45.9$, with $R^2 = 0.9883$. c) The 2-methylindole derivatives (**G1–G4**) subset; $N_j = 2.13H_j + 18.10$, with $R^2 = 0.9517$. d) The indoles derivative (**H1–H11**) subset; $N_j = 3.53H_j + 24.50$, with $R^2 = 0.9876$.

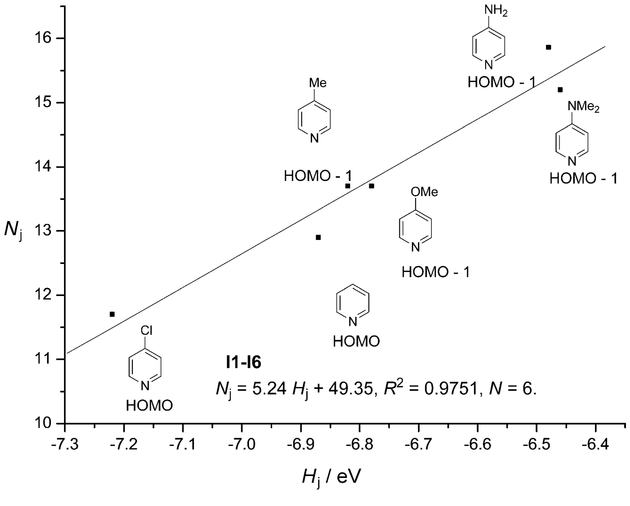


Figure 3. Correlation between N_j and H_j for *para*-substituted pyridines (**I1–I6**); $N_j = 5.24H_j + 49.35$, with $R^2 = 0.9751$.

lationship between the Mayr equation and FMO theory. For example, we found that anionic nucleophiles unexpectedly exhibited a loose correlation between H_j with N_j (see the Supporting Information). In this case, we built a new modified HOMO energy (H'_j) by considering both the orbital coefficients of FMOs at the reaction centers and the HOMO and LUMO energies of the electrophile [Eq. (9)]:

$$H'_j = \frac{(c_H)^2 H_j + (c_L)^2 L_j}{(c_H)^2 + (c_L)^2} \tag{9}$$

where c_H and c_L are the molecular orbital coefficients of $\mathrm{HOMO_j}$ and $\mathrm{LUMO_j}$, respectively, of the carbon atom in the reaction center of the nucleophile. If $c_H \gg c_L$, $H'_j \approx H_j$. in this case, there is no need to consider the LUMO, and this is confirmed by the results from nucleophiles in Figure 2. For those nucleophiles with significant LUMO contributions, the relative coefficients of the HOMOs and LUMOs at the reaction centers play an important role the in reactivity (Figure 4).

A linear correction can be obtained between the modified HOMO energies (H'_j) and the nucleophilicities, as demonstrated by the case of aryl acetonitrile anions (Figure 4a).[22a] The data in Figure 4b give a regression coefficient of 0.9977, while it is 0.88 (before the correction) in Figure 4a. For trifluoromethylsulfonyl stabilized carbanions (**K1–K5**)[22b] and sulfur ylides (**L1–L5**),[22c] the linear relationships between the modified HOMO energies and nucleophilicities are shown in Figure 4c, d.

5. Relationship of E_i/L_i for Sets of Michael Acceptors

Similar to the analysis of the relationship N_j/H_j, we explored whether a linear E_i/L_i relationship can be found for Michael acceptors. The electrophilicities of these Michael acceptors were obtained using the Mayr equation, where the reaction rates were measured by the reactions of these Michael acceptors toward carbocations (**a–v**) with known nucleophilicities (Scheme 1). We found that when electrophiles are divided into different sets, for example, the **x1–x10**,[18a–c] **y1–y4**,[18d] and **z1–z7**[18e] sets, a linear relationship between LUMO energies and electrophilicities can be obtained in each subset (Figure 5). This result is a further support of Equation (6) and suggests that for electrophiles, we can have different sets of electrophiles within which the electrophiles have different reactivities due to electronic reasons. In each subset, the Mayr electrophilicities and the HOMOs correlate well.

6. Influences of Steric Effects on the Correlation Between HOMOs and Nucleophilicities

In Figures 1–5, the substituents affect the reactivity mainly through electronic effects, and Equations (5)–(8) hold in all these cases. In this part, we will show that when both electronic and steric effects are considered, linear relationship between HOMO and nucleophilicity cannot be obtained.

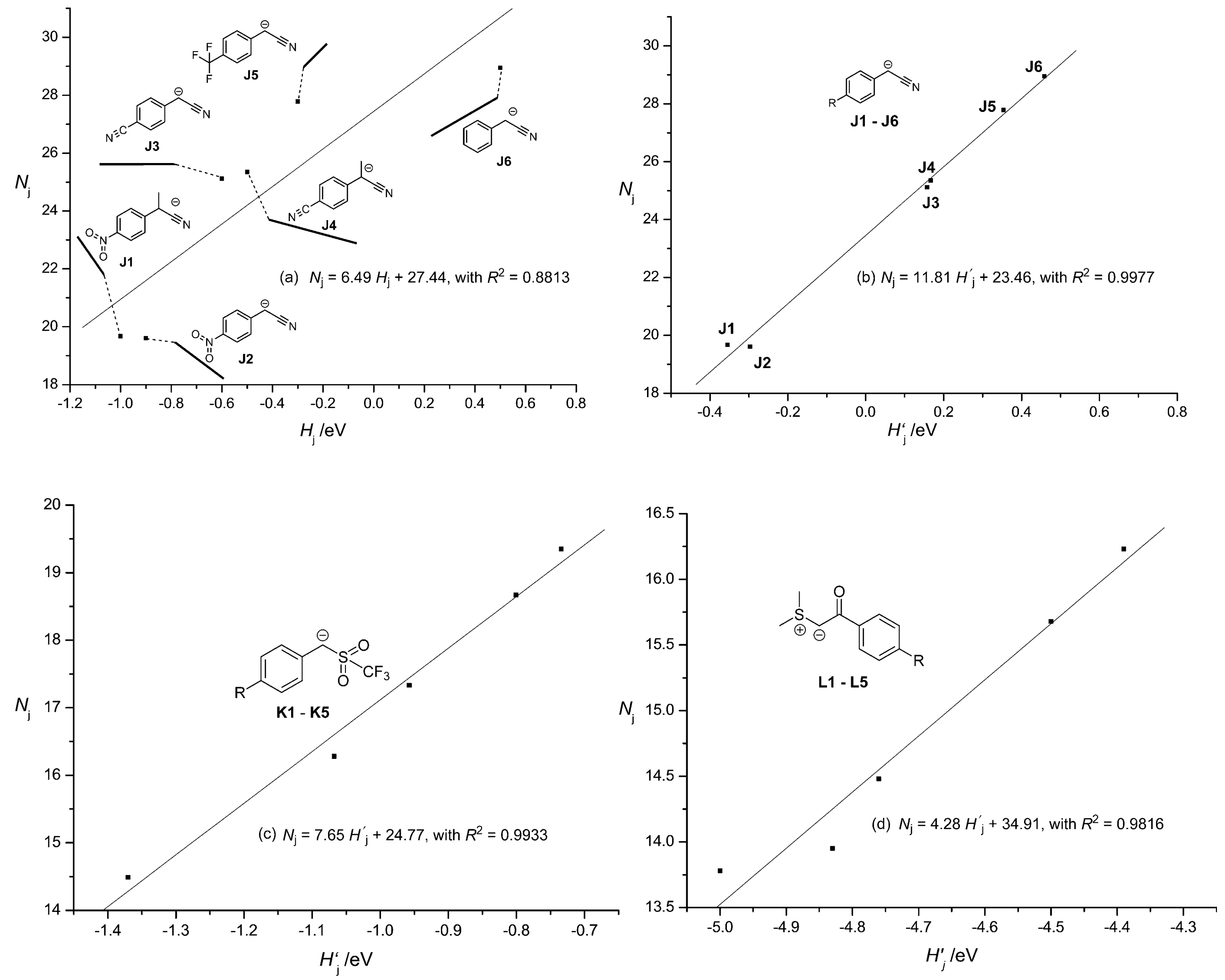


Figure 4. a) Correlation between N_j and H_j of for aryl acetonitrile anions (**J1**–**J6**); $N_j = 6.49 H_j + 27.44$, with $R^2 = 0.8813$. b–d) Correlation between N_j and H'_j (the modified HOMO energy computed by the B3LYP/6-31G(d) method, see Equation (9)) for aryl acetonitrile anions (**J1**–**J6**), $N_j = 11.81 H'_j + 23.46$, with $R^2 = 0.9977$ (b); for trifluoromethylsulfonyl stabilized carbanions (**K1**–**K5**), $N_j = 7.65 H'_j + 24.77$, with $R^2 = 0.9933$ (c); and for sulfur ylides (**L1**–**L5**), $N_j = 4.28 H'_j + 34.91$, with $R^2 = 0.9816$ (d).

For example, for **M**,[23a] a linear relationship is obtained in a wide range since the electronic effects are dominant in affecting their reactivities (Figure 6a). However, the HOMO energies in **M2**–**M8** are close but different for steric reasons (and maybe other possible reasons such as distortions in the transition states or solvation), and no satisfactory linear relationship can be found. Also for **N**,[23b] **O**,[23c] and **P**,[23d] we believe that steric effects introduced by the substituents are very significant, and consequently, the N values and HOMO energies are not correlated well in these cases. (Figure 6b–d)

Conclusions

In conclusion, we have proposed herein a new understanding of the Mayr equation based on FMO theory and the Eyring equation and suggest a new approach by combining FMO theory and the Mayr equation to quantify nucleophilicity and electrophilicity. We have derived that the nucleophilicity of a nucleophile is related to the HOMO energy of the nucleophile, while the electrophilicity is related to the LUMO energy of an electrophile. Calculation results support these linear relationships between LUMO energies and the Mayr electrophilicities (*E*s) and HOMO energies and the Mayr nucleophilicities (*N*s) for sets of electrophiles and nucleophiles, respectively. For each set of nucleophiles or electrophiles, the different reactivities are mainly controlled by the electronic effects of the substituents. If other effects such as sterics play a role in affecting reactivity for a set of similar electrophiles or nucleophiles, the linear relationships between HOMO levels and N values and LUMO levels and E values cannot be secured. The theory herein and Equations (5)–(8), which are based on the existing and well-accepted principles of chemical reactions, are very powerful tools to understand the Mayr equation and its cor-

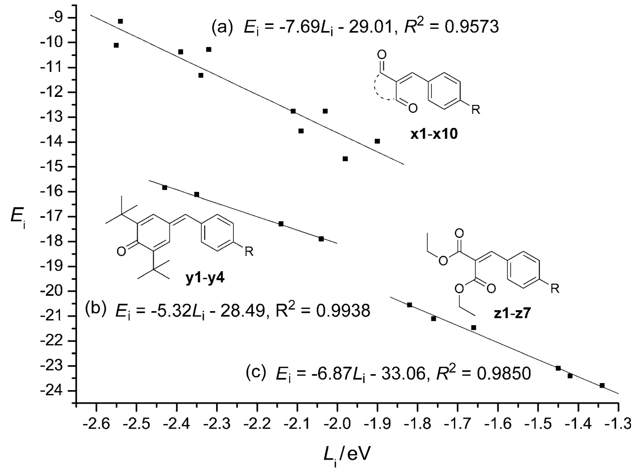


Figure 5. Correlation between experimentally measured electrophilicity (E_i) and B3LYP/6-31G(d) computed LUMO energy (L_i) of Michael acceptors i. a) **x1–x10** subset, $E_i = -7.69\,L_i - 29.01$, $R^2 = 0.9573$; b) **y1–y4** subset, $E_i = -5.32\,L_i - 28.49$, $R^2 = 0.9938$; c) **z1–z7** subset with $E_i = -6.87\,L_i - 33.06$, $R^2 = 0.9850$.

responding nucleophilicities and electrophilicities. The present discovery also suggests that we can predict the reactivities of new species that share similar reaction patterns and steric effects but differ by electronic effects (induced by the different substituents) relative to the experimentally measured species in the data sets from the Mayr group. The Mayr nucleophilicities and electrophilicities can be easily obtained by computing these new species' frontier molecular orbitals and then correlating these calculated orbital energies with the experimentally measured Mayr parameters. In addition, implementation of the semi-quantitative FMO expression of activation energy [Eq. (2)] can be envisioned in many areas of chemistry. Further studies to include more effects into Equation (2) to investigate a molecule's reactivity are ongoing.

Computational Method

All calculations were performed with the Gaussian 03 program.[15a] All gas-phase stationary points were optimized using the B3LYP[15b,c] functional with the 6-31G(d) basis set for all atoms. Orbital energies were calculated by B3LYP/6-31G(d), B3LYP/6-31+G(d), HF/6-31G(d), HF/6-31+G(d), and BP86/6-31G(d) methods, based on the gas-phase geometries optimized at the B3LYP/6-31g(d) level. All the orbital energies discussed in the text are B3LYP/6-31G(d) values.[16] Full Hessian matrixes in Gaussian 03 were calculated to verify the nature of all stationary points as either

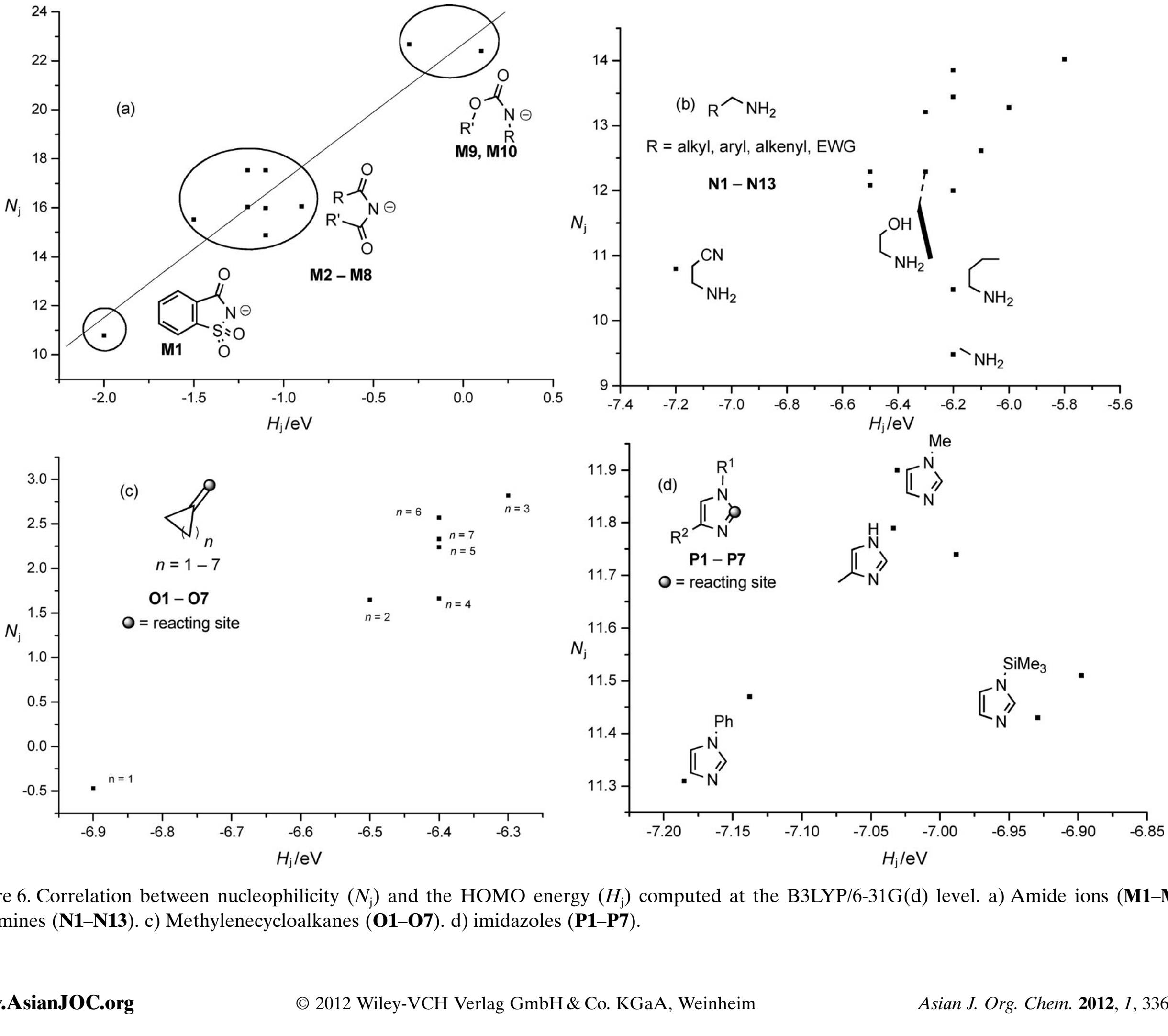


Figure 6. Correlation between nucleophilicity (N_j) and the HOMO energy (H_j) computed at the B3LYP/6-31G(d) level. a) Amide ions (**M1**–**M10**). b) Amines (**N1**–**N13**). c) Methylenecycloalkanes (**O1**–**O7**). d) imidazoles (**P1**–**P7**).

minima or first-order saddle points. The first-order saddle points were further characterized by intrinsic reaction coordinate (IRC)[15d–f] calculations to confirm that the stationary points are correctly connected to the corresponding reactants and products.

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[12] In principle, another FMO quantitative analysis using activation free energy $\Delta G^{\neq}_{i/A}$ could also be proposed as: $\Delta G^{\neq}_{i/A} = m_A L_i - n_A H_A + C'_A$ (2′)
This will give similar results as we have derived if we have $C_A{}'$ as a constant.

[13] The C_A is also dependent on the set of electrophiles i. These electrophiles are similar but are differ mainly through electronic effects introduced by their different R substituents, which are far away from the reacting sites of the electrophiles (see also Scheme 2).

[14] The LUMO orbitals here refer to the reacting orbitals responsible for the elecrophilicity. In calculations with different basis sets, these reaction orbitals could be changed to LUMO+1, LUMO+2 or others; in these cases, we have to use these corresponding reacting orbitals instead of the LUMO orbitals in Equation (6).

[15] All of the geometry optimizations and frequency calculations were performed with the B3LYP functional and the 6-31G(d) basis set implemented in Gaussian 03; a) Gaussian 03 (Revision C.02), M. J. Frisch, et al., Gaussian, Inc.: Pittsburgh, PA, **2004**; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; d) K. Fukui, *J. Phys. Chem.* **1970**, *74*, 4161; e) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, *90*, 2154; f) C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523.

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