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Quantitative characterization of the global philicity patterns of common diene/dienophile pairs in cycloaddition reactions II: the interacting pair model

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ABSTRACT

We present a unified model of electrophilicity and nucleophilicity that considers the electrophile/nucleophile pair in an interacting regime, thereby avoiding the arbitrariness of defining them as the opposite ends of a unique reactivity scale. The model is validated against rate coefficients for the cycloaddition of azomethine ylides towards substituted acetylenes and Michael addition of a series of 1-(*X*-substituted phenyl)-2-propyn-1-ones towards hydrazine.

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Introduction

In a previous paper[1] one of us in collaboration with Domingo, proposed an empirical scale of electrophilicity and nucleophilicity framed on the global electrophilicity index formerly introduced by Maynard et al.[2] and formally derived later by Parr et al.,[3] within the framework of density functional theory (DFT). That scale considered electrophilicity and nucleophilicity numbers as the opposite ends of a unique scale of global electrophilicity: strong electrophiles were classified as species displaying electrophilicity numbers within the range [9.0–1.5 eV]; moderate electrophiles labelling was used for species having electrophilicity numbers within the range [1.4–0.8 eV] and those compounds showing electrophilicity numbers below 0.8 eV were classified as marginal electrophiles or nucleophiles.

This scale of reactivity (philicity), yet arbitrary, turned out to be very useful for an important number of applications in organic chemistry that include: organic synthesis,[4] reaction mechanisms of polar and non polar processes,[5] excited state reactivity (luminescence),[6] selectivity and stereochemistry,[7] redox reactions[8] and theoretical extensions of the electrophilicity or nucleophilicity scales.[9] The impossibility of defining an independent nucleophilicity scale within the same DFT framework was traced to the fact that the second order $\{\Delta E, \Delta N\}$ parabola model proposed by Parr et al., became no longer applicable to nucleophiles because it was associated with positive values of the electronic chemical potential, a negatively definite quantity in DFT.[10] Several scales of nucleophilicity have been proposed up to date, but there still remains the problem that these scales are not comparable to the electrophilicity scale based on Parr et al., index. Consider for instance, the nucleophilicity scales based on the frontier molecular orbital theory, ionization potentials, molecular electrostatic potential and others scales. The electrophilicity/nucleophilicity scale proposed in the previous paper[1] was set up as a static reactivity scale, in the sense that the electrophilicity numbers were obtained from the ground state properties of molecules imbedded in an electronic bath at constant electronic chemical potential. The model we present in this Letter has a different background: it does incorporate the complementary partner for nucleophiles and electrophiles in an interacting regime and can be justified using the fundamental concepts of the Frontier Molecular Orbital (FMO)[11] reactivity theory. We describe in what follows, a simple model with the minimum mathematical details. The proposed model is validated, against kinetic data, to illustrate some of the advantages of the present model with reference to that previously presented.

Theoretical concepts

The change in energy accompanying the interaction between the nucleophile (Nu^-) and electrophile (E^+) pair may be derived by using the expansion proposed by Pearson et al.[12] Their results:

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$$\Delta E = -\frac{(\mu_n^\circ - \mu_e^\circ)^2}{2(\eta_n^\circ - \eta_e^\circ)} \qquad (1)$$

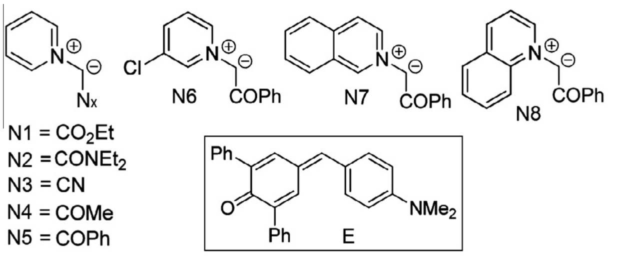
where μ is the electronic chemical potential and η is the chemical hardness of reagents. This equation differs from that proposed by Pearson. The denominator of Pearson's equation contains the sum of the hardnesses, whereas in the expression proposed herein, the denominator contains the difference between the hardness of the nucleophile and electrophile. The detailed derivation of Eq. 1 is given as Supplementary material (SM). The fundamental difference between both equations lies in the fact that: (i) the difference in hardness of the interacting pair emphasizes the very fact that nucleophiles and electrophiles retain their fragment properties as electron releasing and electron accepting species, respectively, and (ii) the control for an effective interaction lies on the electrophile moiety. This concept may be readily illustrated as follows if:

$$\eta_n > \eta_e \text{ then } \frac{1}{S_n} > \frac{1}{S_e} \text{ or } S_e > S_n \qquad (2)$$

This immediately entails $\Delta E(N) < 0$. Therefore, if we accept that the interaction energy criterion proposed by Klopman[11] may become a reactivity index by itself, then we have now the possibility that this interaction may result in stabilizing ($\Delta E(N) < 0$) or destabilizing ($\Delta E(N) > 0$) events. Note moreover that having the sum of hardness in Pearson's equation implies that the interaction is driven by the electronic chemical potential, whereas in the model described by Eq. 1, the electrophile–nucleophile interaction depends on both, hardness and electronic chemical potential differences. A relationship with the maximum hardness principle (MHP)[13] is harder to establish for it involves the global hardness of the non interacting electrophile–nucleophile pair. In round words, the present model establishes the additional rule that for stabilizing interactions the electrophile should be the softer (i.e., the more polarizable) moiety. Note further that in the limiting case where the hardness of the nucleophile–electrophile pair is close to each other, the $\Delta E(N)$ value will become largely negative, thereby implying the Hard and Soft Acids and Bases (HSAB)[11] rule.

Results and discussion

The appraisal of the usefulness and reliability of the present model will be illustrated on a more quantitative basis, because experimental data regarding rate coefficients for cycloadditions are available in literature.[14] A wide survey on nucleophile/electrophile interactions in organic chemistry may be found in Mayr's et al. extensive work. Therein, experimental nucleophilicity/electrophilicity numbers have been reported.[15] Geometry optimization of the series depicted in Scheme 1, were performed at the m062x/6-311+G(d,p) level of theory with SMD solvation corrections to mimic DMSO as solvent, using the GAUSSIAN 03 package of programs.[16] Using the one electron energy levels of HOMO and LUMO, we can easily evaluate the electronic chemical potential and hardness μ and η, respectively, to be used as input to our model Eq. 1. The results are presented in Table 1.



Scheme 1. Structures of pyridinium ylides Nx and reference electrophile E.

The implementation of the interacting pair model demands the definition of a reference molecule because the present scale of nucleophilicity is now relative not absolute. In the present case, ethylene (E) is taken as a reference system, because most of the cycloaddition reactions kinetically evaluated involve this system towards 1,3-dipolar electron donor systems of varying nucleophilicity. The systems used are showed in Scheme 1 and the information required to evaluate the reaction energy from Eq. 1 is depicted in Table 1, together with the available reaction rate coefficients.

A first sight to Table 1 reveals that the electronic chemical potential of E is smaller than all the remaining compounds within the series. This result is relevant for, it permits to unambiguously label E as electrophile. Note that in the previous classification the systems were arbitrarily labelled as strong/moderate electrophiles or nucleophiles. Note further that being the hardness of E the smallest within the series the ΔE values are consistently predicted as negative, thereby implying a stabilizing interaction and as a result the ΔE values nicely correlate with the experimental reaction coefficients. The comparison between the interaction energy index versus Ln k_2 is shown in Figure 1.

Another application highlighting this time the reliability of the present model to assess the direction of the electronic flux (i.e., normal vs inverse electron demand patterns) and inductive substituent effects was performed on a series of cycloaddition reactions involving dipole **1** and dipolarophiles **2**, **3** and **4**.[17] Geometry optimization of the series depicted in Scheme 2, were performed at the m062x/6-311+G(d,p) level of theory, using the GAUSSIAN 03 package of programs[16] to evaluate the electronic descriptors μ and η. The results obtained from our model Eq. 1 are presented in Table 2.

Table 1
Electronic chemical potential (μ), hardness (η), reaction energy (ΔE in Eq. 1) and rate constants[14] for the reaction of 1,3-dipolar nucleophiles towards electrophile E

System	μ (eV)	η (eV)	ΔE (kcal/mol)	Ln(k_2)
N2	−3.331	5.280	−7.931	8.07
N3	−3.571	5.404	−3.209	5.37
N1	−3.518	5.375	−4.020	4.95
N4	−3.652	5.492	−2.083	4.04
N7	−3.874	4.867	−1.248	3.59
N5	−3.757	5.375	−1.352	3.30
N8	−3.992	4.699	−0.407	2.88
N6	−3.922	5.280	−0.375	2.76
E	−4.086	4.452		

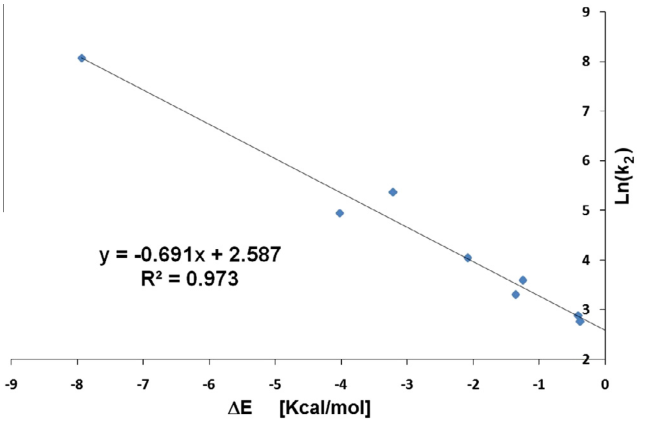
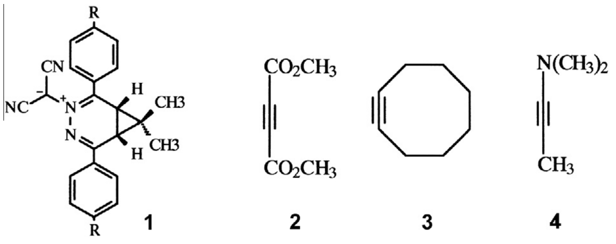


Figure 1. Comparison between reaction energy and rate coefficients for the reaction of E towards the 1,3-dipolar nucleophiles quoted in Table 1. The comparison presented here corresponds to best fit obtained after a cross validation procedure. This procedure is presented in SM.



Scheme 2. Structures of dipole **1** and dipolarophiles **2**, **3**, **4**.

Table 2
Global properties of dipole **1** and dipolarophiles **2**, **3** and **4**, in eV units

R	μ(**1**)	η(**1**)	μ(**2**)	η(**2**)	ΔE	Ln(k_2)
*Reaction between systems **1+2***						
CF_3	−4.882	4.405	−5.390	9.464	0.6	2.04
Cl	−4.616	4.436	−5.390	9.464	1.4	1.63
H	−4.382	4.491	−5.390	9.464	2.4	1.39
CH_3	−4.335	4.514	−5.390	9.464	2.6	1.38
OCH_3	−4.152	4.492	−5.390	9.464	3.6	1.08
R	μ(**1**)	η(**1**)	μ(**3**)	η(**3**)	ΔE	Ln(k_2)
*Reaction between systems **1+3***						
CF_3	−4.882	4.405	−3.912	8.658	−2.6	7.64
Cl	−4.616	4.436	−3.912	8.658	−1.4	6.68
H	−4.382	4.491	−3.912	8.658	−0.6	6.08
CH_3	−4.335	4.514	−3.912	8.658	−0.5	5.48
OCH_3	−4.152	4.492	−3.912	8.658	−0.2	4.80
R	μ(**1**)	η(**1**)	μ(**4**)	η(**4**)	ΔE	Ln(k_2)
*Reaction between systems **1+4***						
CF_3	−4.882	4.405	−3.264	7.342	−10.3	9.64
Cl	−4.616	4.436	−3.264	7.342	−7.3	8.55
H	−4.382	4.491	−3.264	7.342	−5.1	7.67
CH_3	−4.335	4.514	−3.264	7.342	−4.7	7.09
OCH_3	−4.152	4.492	−3.264	7.342	−3.2	6.35

Reaction energy in kcal/mol.

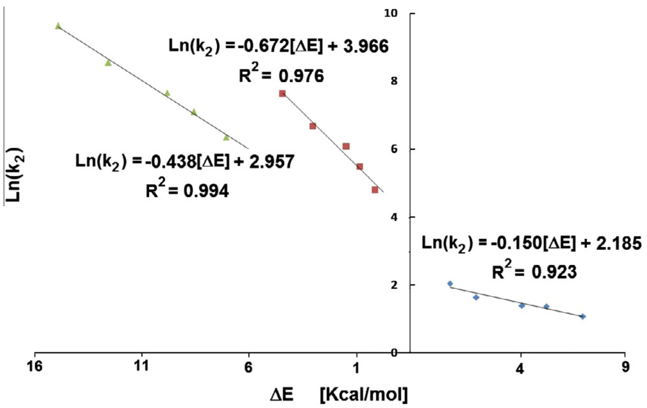


Figure 2. Relationship between reaction energy and natural logarithm of rate constants between dipole **1** and dipolarophiles **2** (blue points), **3** (green points) and **4** (red points).

For the sake of clarity we have ordered the series of reactions (**1**+**2**), (**1**+**3**) and (**1**+**4**) in order of decreasing electron withdrawing power of the substituent R on the dipole 1, passing through the reference compound with R = H and including two substituents displaying electron donating abilities. A first sight at Table 2 reveals that for the reaction **1**+**2**, the electronic chemical potential of 2 is less than the electronic chemical potential of the series of dipoles thereby indicating that these reactions may be classified as an inverse electron demand (IED) process. On the other hand for reactions **1**+**3** and **1**+**4**, the opposite response is obtained and these processes are classified as normal electron demand (NED) cycloadditions. Note further that the reaction energy index suggests that the first series **1**+**2** will have a destabilizing interaction and therefore kinetically less favoured. This result is in agreement with the observed rate coefficients depicted in the last column of Table 2. For the series **1**+**3** and **1**+**4**, the reaction energy index becomes increasingly negative.

Table 3
Electronic chemical potential (μ), hardness (η), reaction energy (ΔE from Eq. 1) and rate coefficients[18] for the Michael addition of 1-(X-substituted phenyl)-2-propyn-1-ones electrophile towards hydrazine

Substituent X	μ (eV)	η (eV)	ΔE (kcal/mol)	Ln(k_2)
$-OCH_3$	−4.2899	6.8916	−0.984	1.233
$-CH_3$	−4.6150	7.2620	−3.038	1.418
–H	−4.8182	7.4829	−5.144	1.484
–Cl	−4.8954	7.1507	−5.216	1.712
–CN	−5.4227	7.1762	−11.459	2.293
Hydrazine	−3.7855	9.8732		

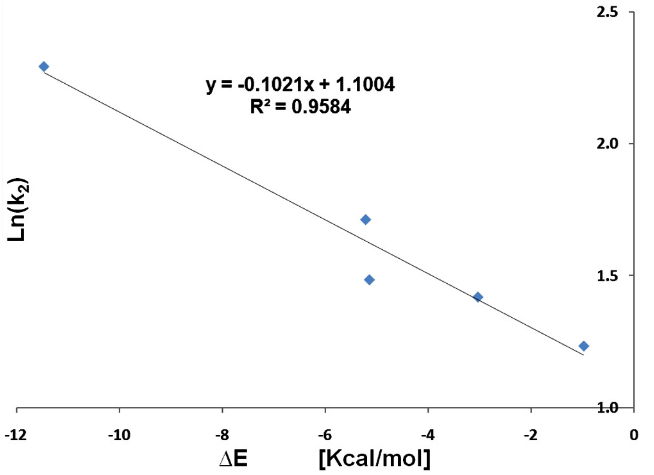


Figure 3. Comparison between reaction energy and rate coefficients for the Michael addition of 1-(X-substituted phenyl)-2-propyn-1-ones electrophile towards hydrazine.

A summary of the results obtained for these systems is shown in Figure 2. Note that each family of reactions is linearly correlated with Ln k_2.

In the process of manuscript revision, a reviewer asked for additional examples to test the reliability of the reactivity model condensed in Eq. 1, beyond the cycloadditions presented as illustrations. We choose the Michael addition of a series of 1-(X-substituted phenyl)-2-propyn-1-ones (electrophiles) towards hydrazine, for which rate coefficients have been reported by Um et al.[18] Geometry optimization of the series of electrophiles and hydrazine was performed at the m062x/6-311+G(d,p) level of theory, using the GAUSSIAN 03 package of programs. With the energy levels of HOMO and LUMO at the hand, we can readily evaluate the electronic chemical potential and hardness μ and η, respectively. These data together with reaction energies and rate coefficients are compiled in Table 3.

A first sight to Table 3 reveals that hydrazine displays the lowest value of chemical softness within the whole series of molecules, thereby reinforcing the idea that the order relationship quoted in Eq. 2 remains still valid, beyond the cycloadditions cases: the control of the reaction is still associated to the electrophilic moiety. The comparison between the reaction energy versus natural logarithm of second-order rate constant is shown in Figure 3. Note that, as in the case of cycloadditions, a nice linear comparison is again obtained.

In conclusion, we have presented a unified model of electrophilicity and nucleophilicity that considers the electrophile/nucleophile pair in an interacting regime. The present model contributes two novel aspects with respect to the previous formulation: the difference in hardness of the interacting pair emphasizes the very fact that nucleophiles and electrophiles retain their fragment properties as electron releasing and electron accepting species, respectively and that the control for an effective interaction lies on the electrophile moiety. The model successfully describes the kinetic data for the cycloaddition of azomethine ylides towards substituted acetylenes, a series of 1,3-dipolar cycloadditions and the Michael addition of a series of 1-(*X*-substituted phenyl)-2-propyn-1-ones (electrophiles) towards hydrazine. Our model shows that in preparing a reaction between an electrophile and a nucleophile. The reactivity rule quoted in Eq. 2 may be useful in preparing an experiment: for a more rapid process, a softer electrophile should be the first choice decision. Also, the computational implementation of the model Eq. 1 is also useful to anticipate the enthalpy of reaction and its *endo*/*exo* thermicity.

Acknowledgments

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Supplementary data

Supplementary data (detailed derivation of Eq. 1. Cross validation procedure to obtain Figure 1. Cartesian coordinates of the series depicted in Scheme 1. Complete author list of Ref. 16) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.199.

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