

DFT-HSAB Prediction of Regioselectivity in 1,3-Dipolar Cycloadditions: Behavior of (4-Substituted)benzonitrile Oxides towards Methyl Propiolate**

Alessandro Ponti*^[a] and Giorgio Molteni^[b]

Abstract: The regioselectivity of 1,3-dipolar cycloadditions between (4-substituted)benzonitrile oxides and methyl propiolate cannot be rationalized on the basis of the electron demand of the reactants or frontier molecular-orbital theory. To this problem, we have applied a quantitative formulation of the

hard-soft acid-base principle developed within the density functional theory. Global and local reactivity indi-

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ces were computed at B3LYP/6-311+G(d,p) level. The details of charge transfer upon the reactive encounter have been elucidated, and the computed regioselectivity has been shown to be in good agreement with experimental data.

Introduction

Since the first isoxazole synthesis in 1936,^[1] nitrile oxide cycloaddition chemistry has been continuously developed.^[2] The astonishing array of latent functionalities presented by isoxazole cycloadducts make them versatile starting materials in the synthesis of acyclic structures,^[3] aldols,^[4] enones,^[5] γ -aminoalcohols,^[6] and so on.^[7] Later, stereoselective nitrile oxide cycloaddition methodologies^[8] provided further valuable targets in the field of isoxazole synthesis. Most of the successful applications of nitrile oxide cycloaddition chemistry in synthesis are intimately linked with theory. Early findings by Houk's group were based on a frontier molecular orbital (FMO) theory^[9] that worked well for monosubstituted ethylenic dipolarophiles.^[10]

In general, FMO theory has been successfully applied to many organic reactions and is still one of the most preferred theoretical tools utilized by the organic chemist. However, despite its broad success, it is an approximate theory deeply rooted in the Hartree-Fock approach. For instance, the use

of coefficients in the frontier LCAO-MO (LCAO = linear combination of atomic orbitals) to describe regioselectivity, suffers from the fact that MOs are defined to within a rotation in the orbital basis set, so that the MO coefficients are not uniquely defined, even in a minimal basis calculation. Furthermore, when modern multiple-zeta polarized basis sets are used, it is far from clear how MO coefficients should be handled. As a consequence, even in a recent comparative study of theoretical tools to predict regioselectivity,^[11] FMO coefficients were taken from HF/STO-3G calculations, although large-basis, high-level calculations were used throughout the study.

In the last decade, many important concepts and indices that are useful for the understanding of chemical reactivity have been rationalized within the framework of density functional theory.^[12] Well-known examples^[13] are the electron chemical potential $\mu = (\partial E / \partial N)_{v(r)}$, which is defined as the "marginal" electronic energy and represents the escaping tendency of molecular electrons (E = molecular energy and N = the number of molecular electrons), and the global softness $S = (\partial N / \partial \mu)_{v(r)}$, which describes the ability of the molecule to take or loose electrons in response to a change in μ . Within DFT, any reaction can be considered to be split in two steps as follows:^[14,15] 1) As soon as reactant molecules approach each other they form a weakly-interacting, promoted complex^[16-18] in which charge is transferred between the reactants to equalize the electron chemical potential at constant external (nuclear) potential. 2) A charge reshuffling at constant electron chemical potential occurs in which the promoted complex either evolves toward the product(s) or back to the reactants. If the second step can

[a] Dr. A. Ponti
Consiglio Nazionale delle Ricerche
Istituto di Scienze e Tecnologie Molecolari
via Golgi 19, 20133 Milano (Italy)
Fax: (+39)02-5031-4300
E-mail: alessandro.ponti@istm.cnr.it

[b] Dr. G. Molteni
Università degli Studi di Milano,
Dipartimento di Chimica Organica e Industriale
via Venezian 21, 20133 Milano (Italy)

[**] HSAB = hard-soft acid-base principle

be neglected, the most favorable situation occurs when the reactants have equal softness. This is the DFT formulation^[14,19] of Pearson's hard-soft acid-base (HSAB) principle.^[20]

Clearly, a local (atomic) reactivity index is needed to study regioselectivity. The best suited for this purpose is local softness $s(\mathbf{r}) = (\partial \rho(\mathbf{r}) / \partial \mu)_{v(\mathbf{r})}$, which represents the sensitivity of the molecular electron density ρ at point $\mathbf{r}$ to a change in μ . The physical significance of $s(\mathbf{r})$ can be made clearer by writing $s(\mathbf{r}) = [(\partial \rho(\mathbf{r}) / \partial N)(\partial N / \partial \mu)]_{v(\mathbf{r})} = f(\mathbf{r})S$.^[13] The derivative with respect to N is the Fukui function $f(\mathbf{r})$ defined by Parr and Yang^[21] and represents how the electron density $\rho(\mathbf{r})$ rearranges as a consequence of a change in the number of molecular electrons, irrespective of what causes such change. The other derivative is the global softness representing the charge transfer due to a change in μ , which in our case is brought about by the collision between the reactants. Therefore, $s(\mathbf{r})$ describes both the charge transfer between the reactants and how charge is redistributed within the reactants themselves. A local HSAB principle^[22] can then be devised as follows: a regioisomer is favored when the new bonds form between atoms with equal softness. The local HSAB principle has provided many reliable *qualitative* predictions of regioselectivity for 1,3-dipolar cycloadditions (1,3-DC),^[23–29] as recently discussed in detail.^[11]

The modern theory of regioselectivity just outlined under the name of "local HSAB principle" does not stand against FMO theory, rather it improves the latter in several respects by abandoning the wavefunction approach and the related concept of orbital. FMO theory can be regarded as a special case of the more general theory of chemical reactivity provided by DFT. For instance, the electron chemical potential μ is usually computed in the finite-difference approximation as $\mu \cong -(I+A)/2$, for which I and A are the vertical ionization potential and electron affinity, respectively. Similarly, $S \cong (I-A)^{-1}$. If one neglects the relaxation of the electron density upon ionization, then one can write $\mu \cong (\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})/2$ and $S \cong (\epsilon_{\text{HOMO}} - \epsilon_{\text{LUMO}})^{-1}$, so that a clear parallel between the two theories appears. The accuracy loss due to the neglect of electron relaxation is, however, significant when chemical accuracy is the target. Furthermore, the HOMO and LUMO can be regarded as an approximation to the finite-difference expression of the Fukui function, for example, for the case of electrophilic attack $f^-(\mathbf{r}) \cong \text{HOMO}$. However, the FMOs are a poor approximation of the Fukui function.^[13,30] Finally, the DFT-based theory should not be considered as a mere refining of the FMO theory as it relies on a quite different theoretical basis and, as we will soon discuss, it is amenable to a quantitative formulation of regioselectivity.

It is assumed that when two reactants approach each other the interaction occurs between pairs of atoms located in different molecules. Charge is transferred within such pairs in the very first step of the bond-forming interaction between the specific atoms. Such transfer equalizes the electron chemical potential and induces a variation $\Delta\Omega$ of the grand potential (i.e., the natural thermodynamic quantity used to describe the behavior of the reactants' atoms, which

are open subsystems freely exchanging energy and electrons) of the system. The contribution to $\Delta\Omega$ due to the interaction between atom i in molecule P and atom k in molecule Q is

$$\Delta\Omega_{\text{Ok}}^{\text{Pi}} = -\frac{1}{2}(\mu_{\text{P}} - \mu_{\text{Q}})^2 \frac{s_{\text{Pi}}s_{\text{Ok}}}{s_{\text{Pi}} + s_{\text{Ok}}} \quad (1)$$

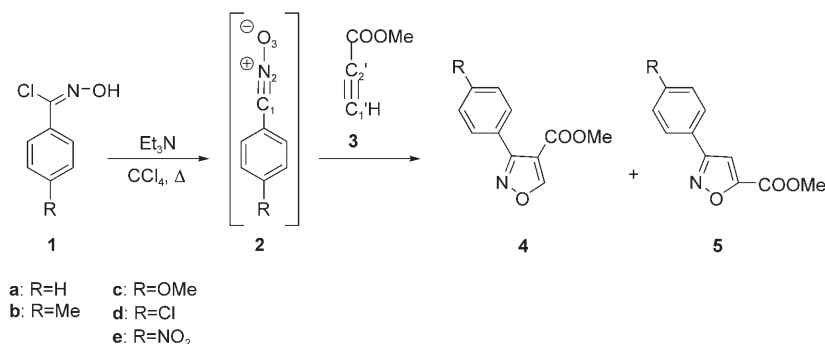
For the case of concerted 1,3-DCs, we can obtain $\Delta\Omega$ for each regioisomer as the sum of two bond-forming interactions and their difference $\delta\Delta\Omega$ describes the relative stabilization of the two regioisomeric promoted complexes. Given that in 1,3-DCs the relative energy of transition states is paralleled by the relative energy of the weakly interacting complexes forming in the early stage of the reaction,^[10] the neglect of the charge reshuffling term is reasonable.^[31,32] Moreover, the many successful qualitative predictions of regioselectivity found in the literature suggest that the interaction energy between the reactants forming the activated complex should be closely related to the transition-state energy. For the above reasons, $\Delta\Omega$ is expected to be proportional to the transition-state energy and to provide a *quantitative* prediction of regioselectivity without the need to locate the transition state. On these grounds, a generalization of the local HSAB principle has been introduced,^[33] which enables one to compute the relative stabilization of the two regioisomeric transition states from μ and s of the reactants only. This method has been successfully applied by us to the 1,3-DC between nitrilimines and alkynyl or alkenyl dipolarophiles,^[34–36] and between arylazides and methyl propiolate.^[37]

Some qualitative predictions of the regiochemistry of the 1,3-DCs of nitrile oxides to electron-deficient acetylenes, based on DFT calculations, have been reported.^[38] In order to have a clearer and more systematic picture of the substituent effect on the regioselectivity of the 1,3-DC of nitrile oxides to methyl propiolate, we present here a quantitative study of the regioselectivity observed in the cycloadditions between (4-substituted)benzonitrile oxides and methyl propiolate (see Scheme 1). The present study is based upon the DFT theory and the HSAB principle, and does not involve the location of the transition structure and the calculation of the activation energy. The latter point is important as the calculation of the activation barrier for the 1,3-DC of nitrile oxides is very sensitive to the treatment of electron correlation, both for alkynyl^[39] and alkenyl^[40] dipolarophiles.

Results and Discussion

It has been known for a long time that the 1,3-DCs between (4-substituted)benzonitrile oxides **2** and methyl propiolate **3** give mixtures of regioisomeric 4-methoxycarbonyl-3-(4-substituted)phenylisoxazoles **4** and 5-methoxycarbonyl-3-(4-substituted)phenylisoxazoles **5**.^[41]

The regioselectivity and total yield presently observed for the 1,3-DCs of **2a–e** and **3** (Scheme 1) in refluxing CCl_4 are



Scheme 1.

Table 1. Experimental yield ratios for **4:5** and total yields for the cycloaddition reactions between benzonitrile oxides **2** and methyl propiolate **3** in CCl₄ at 77 °C.

	R	Yield ratio ^[a] 4:5	Yield [%] 4+5
a	H	29:71	> 95
b	Me	32:68	90
c	MeO	40:60	88
d	Cl	28:72	95
e	NO ₂	30:70	83

[a] Determined by NMR spectroscopic analysis of the crude reaction mixture.

reported in Table 1. The yield ratio was obtained from NMR spectroscopic analysis of crude reaction mixtures.

This regioselective outcome cannot be fully rationalized on the basis of the electronic demand of the reactants. When the substituents are ordered by the yield ratio of **4:5**, one obtains MeO < Cl < Me < NO₂ < H. Even if the most electron-donating group, MeO is at one end, and at the other end one finds the “null” substituent H. Linear regression of the yield ratio versus Hammett σ_p values^[42] results in a scattered plot with a very low correlation coefficient, $\rho = 0.47$. As for FMO theory, the FMO energies at the B3LYP/6-311+G(d,p) level are reported in Table 2. For **2a–d** the HOMO-dipole–LUMO-dipolarophile difference (ranging from 4.5 to 5.1 eV) is 1–2 eV smaller than the LUMO-dipole–HOMO-dipolarophile difference (ranging from 6.1 to 6.7 eV), whereas the latter difference (4.6 eV) is 1.1 eV smaller than the former (5.7 eV) for nitro-substituted **2e**.

Both FMO interactions can thus be effective, and one can only predict that a regioisomeric mixture will result. Pushing FMO theory a little further, major HOMO-dipole control can be associated with the 1,3-DCs between **2a–d** and **3**,

Table 2. Frontier MO energies of dipole benzonitrile oxides **2** and dipolarophile methyl propiolate **3** at the B3LYP/6-311+G(d,p) level.

Entry	R	HOMO energy [eV]	LUMO energy [eV]
2a	H	−6.7	−1.8
2b	Me	−6.5	−1.6
2c	MeO	−6.3	−1.4
2d	Cl	−6.8	−2.0
2e	NO ₂	−7.4	−3.5
3		−8.1	−1.7

and therefore a predominance of **4a–d** is expected. Conversely, the 1,3-DC between **2e** and **3** is subject to major LUMO-dipole control and **5e** is expected to be the major product. Comparison with the experimental data in Table 1 shows that FMO prediction is correct only for **2e+3**, as regioisomer **5** predominates in any case. Hence, to better understand the regioselectivity of the cycloaddition between **2** and **3**, we

turned our attention to the local HSAB principle, as formulated within DFT. The main results of our DFT calculations at the B3LYP/6-311+G(d,p) level are reported in Table 3.

The electron chemical potential difference between **2** and **3** determines the direction of the overall charge flow upon the interaction of the reactants, as electrons flow towards re-

Table 3. Results of B3LYP/6-311+G(d,p) calculations: electron chemical potential difference between benzonitrile oxides **2** and methyl propiolate **3**, along with the $\delta\Delta\Omega$ difference^[a] and predicted yield ratios of **4:5** for their mutual cycloaddition.

R	$\mu(2) - \mu(3)$ [eV]	$\delta\Delta\Omega$ [kJ mol ^{−1}]	Predicted ratio of 4:5 ^[b]
H	0.70	−1.63	30:70
Me	0.87	−1.89	31:69
MeO	1.15	−5.01	40:60
Cl	0.57	−0.73	28:72
NO ₂	−0.49	−1.71	30:70

[a] Difference in grand potential variation for the pathways leading to isoxazoles **4** and **5**. [b] From computed $\delta\Delta\Omega$ and Equation (4); uncertainty $\pm 1\%$.

gions at low electron chemical potential μ . Charge flows from the substituted benzonitrile oxide to methyl propiolate in the reaction of **3** with **2a–d** and vice versa in the reaction of **3** with **2e**, that is, **2a–d** act as nucleophiles, whereas **2e** acts as electrophile. Note also that **2a–b** and **2e** show very similar regioselectivity, although the very different electron-demand properties of the substituents make the $\mu(2) - \mu(3)$ difference largely unequal and opposite in sign. As it depends only on global indices, the direction of the overall charge flow is the same irrespective of regiochemistry.

The local charge transfer, that is, the transfer of electrons between interacting atoms can be computed as^[22]

$$\Delta N(C_1 \rightarrow C_2) = [\mu(3) - \mu(2)] s(C_1) s(C_2) [s(C_1) + s(C_2)]^{-1} \quad (2)$$

$$\Delta N(O_3 \rightarrow C_1) = [\mu(3) - \mu(2)] s(O_3) s(C_1) [s(O_3) + s(C_1)]^{-1}$$

in which ΔN is the degree of electron population transferred from the dipole atom to the dipolarophile atom and the atoms are numbered as illustrated in Scheme 1 (these equations are easily generalized so that they can be transferred

to other interacting atom pairs). The actual direction of local electron flow to alkynes in the 1,3-DC of HCNO has recently been debated.^[18,43–46] Our calculations show that at the beginning of the reaction, the oxygen atom behaves as a donor and the nitrile oxidic carbon atom as an acceptor, the only exception being **2e**+**3**→**4e**, for which the reverse behavior is observed. Our results are thus in agreement with spin-coupled valence-bond calculations,^[45,47] but they also imply that the amount and direction of both global and local electron transfer depends on the substituent present in the reactants.^[44]

We now turn to regioselectivity and, as selectivity criterion, use the grand potential change due to two bond-forming interactions between **2** and **3**,^[33] because of the general agreement about the concertedness of 1,3-DC reactions. The grand potential change for the pathway leading to 4-methoxycarbonyl-3-(4-substituted)phenylisoxazole **4** is

$$\Delta\Omega(\mathbf{4}) = (1/2) [\mu(\mathbf{3}) - \mu(\mathbf{2})] [\Delta N(\text{C}_1 \rightarrow \text{C}_{2'}) + \Delta N(\text{O}_3 \rightarrow \text{C}_{1'})] \quad (3)$$

ΔN for this equation is defined in Equation (2). $\Delta\Omega(\mathbf{5})$ can be obtained by exchanging $\text{C}_{1'}$ and $\text{C}_{2'}$. Each new bond contributes to the stabilization of the promoted complex by a term consisting of the amount of electrons transferred between the relevant atoms multiplied by the electron chemical potential difference. The stabilization difference $\delta\Delta\Omega = \Delta\Omega(\mathbf{5}) - \Delta\Omega(\mathbf{4})$ is reported in Table 3. The negative sign of $\delta\Delta\Omega$ shows that cycloadduct **5** is the major one, in line with experimental results.

The regioselective similarity of the **2e**+**3** cycloaddition to that of the 1,3-DCs involving **2a** and **2b** is now clearly explained by our DFT-HSAB approach, as the relevant promoted-complexes have similar computed stabilization. This is the result of two opposite effects: the large difference in the amount of charge transferred upon the formation of the two possible regioisomeric complexes for **2e**+**3** (comparable to that observed in **2c**+**3**) is counterbalanced by the smaller (in absolute value) difference $\mu(\mathbf{2e}) - \mu(\mathbf{3})$, which makes the charge transfer less effective in producing energetic stabilization.

We now proceed one step further by demonstrating that $\delta\Delta\Omega$ is a quantitative regioselectivity index for the present 1,3-DC reactions. The difference in activation energy, $\delta\Delta E^\ddagger$ of the two reaction paths can be obtained as $\delta\Delta E^\ddagger = -RT \log(Y)$ in which T is the reaction temperature (350 K) and Y is the experimental ratio of **4**:**5**. Estimating the error in Y at $\pm 1\%$, weighted least-squares linear regression results in

$$\delta\Delta\Omega = (2.7 \pm 0.3) \delta\Delta E^\ddagger - (8.1 \pm 0.9) \text{ kJ mol}^{-1}, \rho = 0.99 \quad (4)$$

in which ρ is the linear correlation coefficient (Figure 1). The predicted ratio of **4**:**5** (Table 3), obtained from the computed $\delta\Delta\Omega$ by using Equation (4), is in very good agreement with the experimental values (Table 1).

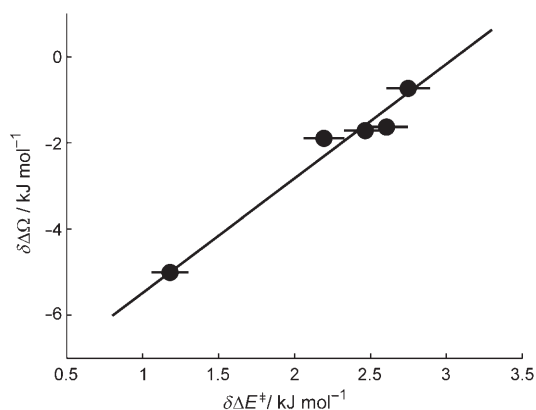


Figure 1. Linear relationship between the computed difference $\delta\Delta\Omega$ in grand potential variation for the pathways leading to cycloadducts **4** and **5**, and the correspondent difference in activation energy $\delta\Delta E^\ddagger$, computed from the experimental yield ratio of **4**:**5**. The error bars illustrate the uncertainty in $\delta\Delta E^\ddagger$ due to the error in the yield ratio, estimated at 1%.

The negative intercept in the equation above implies that there is a preference towards the 5-methoxycarbonylisoxazoles **5**, as $\delta\Delta E^\ddagger < 0$ when $\delta\Delta\Omega = 0$. Such a preference is independent of the specific electronic interaction between the reactants and the individual reacting sites. It might be tentatively attributed to steric hindrance between the aryl and the carbomethoxy moieties that become close to each other when approaching to form regioisomer **4**. The slope in Equation (4) is significantly larger than 1. This means that the difference in transition-state energy is about one third of the computed energy difference between the promoted complexes. Given that in our previous studies of aryl nitrilimines^[34] and aryl azides^[37] the regression slope was always ≤ 1 , we checked whether the neglected constant electron potential term $\Delta\Omega_\mu$ (charge reshuffling) could counter-balance the constant external potential term $\Delta\Omega$ of Equation (3) and reduce the slope. To this end, we computed the grand-potential contribution of the step at constant electron chemical potential as

$$\Delta\Omega_\mu(\mathbf{4}) = -(1/2) \lambda \{ [s(\text{C}_1) + s(\text{C}_{2'})]^{-1} + [s(\text{O}_3) + s(\text{C}_{1'})]^{-1} \} \quad (5)$$

in which $\Delta\Omega_\mu(\mathbf{5})$ can be obtained by exchanging $s(\text{C}_{1'})$ and $s(\text{C}_{2'})$ and λ is a positive parameter related to an effective number of valence electrons.^[25] As the value of λ is not precisely set by theory, we carried out a bilinear regression of $\delta\Delta E^\ddagger$ with $\delta\Delta\Omega$ and $\delta\Delta\Omega_\mu$ for which λ was considered a parameter to be optimized. Such regression does not reproduce the experimental data better than the linear one in Equation (4); the slope related to $\delta\Delta\Omega$ and the intercept are very close to that previously obtained, and the optimized factor, $\lambda = -1.4 \times 10^{-4}$ is clearly not significant. This confirms that in 1,3-DCs the relative transition-state energy depends on the relative energy of the promoted complex formed by charge transfer in the chemical-potential equalization step

and is not affected by the subsequent charge-reshuffling step. As for possible structural peculiarities in the benzonitrile oxide case, we note that the B3LYP/6-31G* optimized structures of the promoted complexes and transition states for the 1,3-DC between ethene and several 1,3-dipoles^[17] (including HCNO, HCNH, and HNNH) do not indicate any anomaly in the HCNO case. We have to conclude that, at present, we have no explanation for the peculiar slope observed, but it seems that the details of the 1,3-DC reaction path of (4-substituted)benzonitrile oxides to methyl propiolate differ from those of *N*-(4-substituted)phenylnitrile imines and (4-substituted)arylazides in that the substituent effect on the transition-state energy is only 37% of that affecting the promoted complex.

We have thus shown that the combined use of the DFT reactivity indices of the reactants with the local HSAB principle provides a quantitative rationalization of regioselectivity for a series of 1,3-DCs not amenable to FMO and electron-demand theory. No transition state has to be located and characterized. Indeed, the electron demand of the substituent is an important feature, but it only affects the electron chemical potential μ , which cannot fully account for regioselectivity. The latter can only be adequately rationalized when the substituent effect on the local variations of charge density upon the reactive encounter is taken into account.

Experimental Section

Cycloadditions between nitrile oxides 2 and methyl propiolate 3: Compounds **4a–e** and **5a–e** are known in the literature.^[36]

General procedure: A solution of **2** (5.0 mmol) and **3** (0.43 g, 5.0 mmol) in dry carbon tetrachloride (25 mL) was refluxed for 20 h. Evaporation of the solvent in vacuo gave a residue, which was separated by chromatography on a silica-gel column with EtOAc/hexane 3:7. The major product, 4-methoxycarbonylisoxazole **4** was eluted first, followed by the minor product, 5-methoxycarbonylisoxazole **5**. Crystallization from diisopropyl ether gave analytically pure **4** and **5**.

Computational methods: DFT calculations were performed with the Gaussian98^[48] program suite by means of a Beowulf PC cluster. The hybrid B3LYP functional was employed with the standard 6-311+G(d,p) basis set. The in-vacuo geometry of **2a–e** and **3** was fully optimized and characterized with vibrational analysis at the same level of theory. The anion and cation of **2a–e** and **3** were treated at the UB3LYP level by using the geometry of the neutral systems. Atomic electron populations were evaluated by the CHelp electrostatic scheme^[49] (including fitting of atom-centered dipoles), which has already proved to be a reliable method.^[50] Reactivity indices were computed within the finite difference approximation:^[12] $\mu = -(I+A)/2$ and $S = (I-A)^{-1}$ in which *I* and *A* are the (vertical) ionization potential and electron affinity, respectively. The local softness *s* (condensed to each individual atom^[51]) was computed as $s^+ = S[p(N_0+1)-p(N_0)]$ for electrophiles, and as $s^- = S[p(N_0)-p(N_0-1)]$ for nucleophiles in which $p(N)$, $N=N_0-1$, N_0 , and N_0+1 represent the atomic electron population of the cationic, neutral, and anionic system, respectively.

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