1,3-Dipolar Cycloaddition Reactions: A DFT and HSAB Principle Theoretical Model

Francisco Méndez*,†

Departamento de Química, División de Ciencias Básicas e Ingeniería, Universidad Autónoma Metropolitana-Iztapalapa, A.P. 55-534, México, D.F. 09340, Mexico

Joaquín Tamariz

Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala, México, D.F. 11340, Mexico

Paul Geerlings

Eenheid Algemene Chemie (ALGC), Faculteit Wetenschappen, Vrije Universiteit Brussel, Pleinlaan2, 1050 Brussel, Belgium

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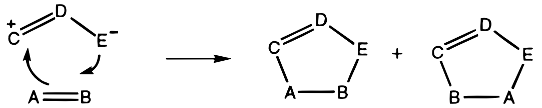
The hard and soft acids and bases principle is used together with the condensed fukui function to analyze the regioselectivity and reactivity of two model 1,3-dipolar cycloaddition reactions. Results obtained for benzonitrile oxide with vinyl *p*-nitrobenzoate or 1-acetyl vinyl *p*-nitrobenzoate illustrate the value of these concepts to describe their inherent reactivity. The calculations of the interaction energy by density functional theory using a perturbative, orbital independent method suggest the specific direction of the electronic process at each of the reaction sites. The electrophilic nature of the 1,3-dipole and the nucleophilic nature of the two dipolarophiles was determined by this model. The partitioning of the interaction energy in a term resulting from the chemical potential equalization principle at constant external potential and a term resulting from the maximum hardness principle at constant chemical potential show that the former term, arising from the charge-transfer process, contributes to a lesser extent than the term arising from the reshuffling of the charge distribution. The use of density functional theory concepts and the hard and soft acids and bases principle is a promising alternative to frontier orbital theory.

Introduction

1,3-Dipolar cycloaddition reactions have been used frequently to obtain five-membered heterocyclic compounds,[1] complex natural products,[2] and bioactive molecules.[3] It was proposed also that they operate in the ozonolysis and oxidation of olefins by OsO_4 and $KMnO_4$.[4]

The reaction involves the addition of 1,3-dipolar compounds (1,3-dipoles) to double bounds (dipolarophiles) and can be represented by the following scheme.



The addition can be regioselective, and it depends on steric and electronic effects.[1] The specific direction of the electronic interaction is not well-defined, and identifying unequivocally electrophilic and nucleophilic centers has been difficult.[5]

The regioselectivity observed has been explained, in general, in terms of frontier molecular orbital theory (FMO).[1b,6] However, although HOMO−LUMO interactions have proved to be very useful in explaining the chemical reactivity and regioselectivity of Diels−Alder reactions, a satisfactory rationalization[7,8] of 1,3-dipolar cycloaddition reactions is not available. The choice of a single pair of frontier orbitals is sometimes difficult, and the fact that some frontier orbitals are not strongly polarized forces one to judge each case carefully.

Orbital perturbation theory has also been used to study reactivity and regioselectivity in 1,3-dipolar cycloaddition reactions. Klopman et al[9] classified the 1,3-dipolar cycloaddition reaction as an "electron exchange reaction". They suggested that electron transfer occurs between the 1,3-dipole and the dipolarophile, but the specific direction of the electronic transfer process was undefined. Sustman and Sicking[10] showed that electrostatic interactions may be more important than the frontier orbitals involved to rationalize the reactivity and regioselectivity in the cycloaddition of the 1,3-dipoles diazomethane and formyl nitrile oxide. Craig and Stone[11] showed that electrostatic and repulsion terms are more important than charge-transfer effects in some Diels−Alder reactions. They suggested that the frontier orbital component is only a small part of the charge-transfer term.

An alternative to orbital perturbation theory to address the reactivity and regioselectivity in 1,3-dipolar cycloadditions is the formulation of the interaction energy in terms of density functional theory (DFT)[12−17] and the hard and soft acids and bases principle (HSAB).[18,19] The interaction energy between two chemical species, A and B, is considered in two steps, which can be taken as happening in succession. The first step, which

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[*] To whom correspondence should be sent.

[†] On sabbatical leave in Eenheid Algemene Chemie (ALGC), Faculteit Wetenschappen, Vrije Universiteit Brussel, Pleinlaan2, 1050 Brussel, Belgium.

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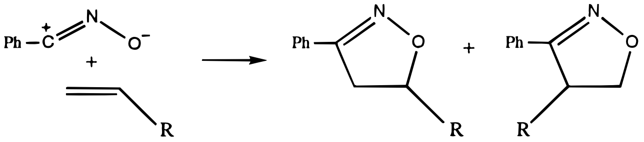
results from the chemical potential equalization principle,[20] corresponds to the charge-transfer process between A and B at constant external potential (i.e., fixed nuclear positions). The second step is equivalent to a redistribution of the charge at constant chemical potential, and it is a manifestation of the maximum hardness principle.[21,22] The term *electronic reshuffling* has been suggested to describe the second step.[13] This DFT and HSAB formulation has the advantage of being an orbital-independent method. It takes into account the electronic densities of the isolated reactants and products and the contribution of the electron density when the reactants are at a given distance. Interesting results have been obtained with this methodology while studying the reactivity of enolate anions[15] and pyridine derivatives.[16]

Since 1,3-dipolar cycloaddition reactions play a fundamental role in many organic reactions, we believe that it may be valuable to use this formulation and molecular orbital theory electronic structure calculations to obtain the interaction energy for some 1,3-dipolar cycloadditions reactions for the first time. An interesting example studied experimentally by Jiménez et al.[23] is the cycloaddition of benzonitrile oxide and vinyl derivatives to obtain isoxazolines.



As discussed below, the values of the interaction energy give the specific direction of the electronic transfer. An electrophilic nature for the 1,3-dipole and a nucleophilic nature for the dipolarophiles are obtained. For terminal alkenes, the energetically favored interaction is the interaction between the nucleophilic unsubstituted carbon atom in the dipolarophile and the electrophilic carbon atom in the 1,3-dipole. The regioselectivity obtained is in good agreement with experimental results. The interaction energy is dominated by the reshuffling of the charge distribution term rather than by the charge-transfer process, which contributes less. Reshuffling of the charge distribution interactions is more important to rationalize the reactivity and regioselectivity than frontier orbital theory which, in this case, fails to describe the regioselectivity observed.

Theory

According to density functional theory,[17] the interaction energy ΔE_{int} between a stable molecule A (formed by the bonding of K atoms with a total number of electrons N_{A}) and a stable molecule B (formed by the bonding of L atoms with a total number of electrons N_{B}) is given by

$$\Delta E_{\mathrm{int}} = E[\rho_{\mathrm{AB}}] - E[\rho_{\mathrm{A}}] - E[\rho_{\mathrm{B}}] \qquad (1)$$

where ρ_{AB}, ρ_{A}, and ρ_{B} are the ground-state electron densities of the product AB and the reactants A and B, respectively. Products and reactants are characterized by their corresponding density functionals $E[\rho_{\mathrm{AB}}]$, $E[\rho_{\mathrm{A}}]$, and $E[\rho_{\mathrm{B}}]$.

It has been shown[12-14] that eq 1 can be written in the form

$$\Delta E_{\mathrm{int}} = \Delta E_v + \Delta E_\mu \qquad (2)$$

where ΔE_v and ΔE_μ are the energy change at constant external potential and constant chemical potential, respectively.

In a global viewpoint, which does not specify the interaction sites for A and B, ΔE_v and ΔE_μ are given by

$$\Delta E_v \approx -\frac{1}{2}\frac{(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^2}{S_{\mathrm{A}} + S_{\mathrm{B}}} S_{\mathrm{A}} S_{\mathrm{B}} \qquad (3)$$

and

$$\Delta E_\mu \approx -\frac{1}{2}\frac{\lambda}{S_{\mathrm{A}} + S_{\mathrm{B}}} \qquad (4)$$

Equation 2 becomes

$$\Delta E_{\mathrm{int}} \approx -\frac{1}{2}\frac{(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^2}{S_{\mathrm{A}} + S_{\mathrm{B}}} S_{\mathrm{A}} S_{\mathrm{B}} - \frac{1}{2}\frac{\lambda}{S_{\mathrm{A}} + S_{\mathrm{B}}} \qquad (5)$$

where μ_{A} is the electronic chemical potential and S_{A} is the global softness of the molecule A. These quantities represent the global properties of molecule A as a whole and have the same value everywhere within each molecule.

The chemical potential μ_{A} and global softness S_{A} appear in a natural way as response functions of the electronic energy of molecule A to changes in the number of electrons N_{A} and the external potential, $v_{\mathrm{A}}(\mathbf{r})$ (i.e., due to the nuclei),[17] respectively. The chemical potential[24] μ_{A} is the change of the energy E_{A} with the number of electrons N_{A}, $\mu_{\mathrm{A}} = (\partial E_{\mathrm{A}}/\partial N_{\mathrm{A}})_{\mathrm{v}}$ and was identified as negative of the electronegativity. The global softness[25] S_{A} is the inverse of the global hardness η_{A}, $S_{\mathrm{A}} = 1/(2\eta_{\mathrm{A}})$, and the global hardness[26] η_{A} is the change of the chemical potential μ_{A} with respect the number of electrons N_{A}, $\eta_{\mathrm{A}} = (1/2)(\partial^2 E_{\mathrm{A}}/\partial N_{\mathrm{A}}^2)_v$. In a finite difference approximation to these derivatives, μ, η, and S can be evaluated from the electron affinity (A) and ionization potential (I) [17]

$$\mu \approx -\frac{(I + A)}{2} \qquad (6)$$

$$\eta \approx \frac{(I - A)}{2} \qquad (7)$$

and

$$S \approx \frac{1}{(I - A)} \qquad (8)$$

The first term ΔE_v in eq 2, resulting from the chemical potential equalization principle, corresponds to the charge-transfer process between A and B at constant external potential $v(\mathbf{r})$.[20] The second term, ΔE_μ, being equivalent to a reshuffling of the charge distribution at constant chemical potential μ, is usually a manifestation of the maximum hardness principle.[21,22] The (positive) factor λ has been shown to be proportional to an *effective number of valence electrons*[13,14] taking part in the reaction between A and B. Also, λ bears information on the system AB out of equilibrium (when A and B are far away from each other) and the system AB at equilibrium.

Invoking a local viewpoint for A (local properties represent the properties of different sites within the molecule A) and a global viewpoint for B (global properties represent the properties of molecule B as a whole, and it has the same value in B) in an effort to study the chemical reactivity of different atoms of A with respect to different reagents B, ΔE_v and ΔE_μ become

$$\Delta E_v \approx -\frac{1}{2}\frac{(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^2}{S_{\mathrm{A}} f_{\mathrm{Ak}} + S_{\mathrm{B}}} S_{\mathrm{B}} S_{\mathrm{A}} f_{\mathrm{Ak}} \qquad (9)$$

and

$$\Delta E_{\mu} \approx -\frac{1}{2}\frac{\lambda}{S_{\mathrm{A}} f_{\mathrm{Ak}} + S_{\mathrm{B}}} \tag{10}$$

The interaction energy ΔE_{int}, eq 5, adopts the form [15,16]

$$(\Delta E_{\mathrm{int}})_{\mathrm{A}}^{\mathrm{k}} \approx -\frac{1}{2}\frac{(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^2}{S_{\mathrm{A}} f_{\mathrm{Ak}} + S_{\mathrm{B}}} S_{\mathrm{B}} S_{\mathrm{A}} f_{\mathrm{Ak}} - \frac{1}{2}\frac{\lambda}{S_{\mathrm{A}} f_{\mathrm{Ak}} + S_{\mathrm{B}}} \tag{11}$$

where $(\Delta E_{\mathrm{int}})_{\mathrm{A}}^{\mathrm{k}}$ is the interaction energy when the atom k of molecule A reacts with a whole molecule B. The local property f_{Ak} is the condensed fukui function and reflects the reactivity of the atom k within the molecule A, and S_{B} characterizes the nature of molecule B via its global softness. The condensed fukui f_{Ak} is given for nucleophilic, electrophilic, and radical attack[27]

$$f_{\mathrm{Ak}}^{+} = q_{\mathrm{Ak}}(N_{\mathrm{A}} + 1) - q_{\mathrm{Ak}}(N_{\mathrm{A}}) \quad \text{for nucleophilic attack} \tag{12}$$

$$f_{\mathrm{Ak}}^{-} = q_{\mathrm{Ak}}(N_{\mathrm{A}}) - q_{\mathrm{Ak}}(N_{\mathrm{A}} - 1) \quad \text{for electrophilic attack} \tag{13}$$

and

$$f_{\mathrm{Ak}}^{\circ} = (1/2)[q_{\mathrm{Ak}}(N_{\mathrm{A}} + 1) - q_{\mathrm{Ak}}(N_{\mathrm{A}} - 1)] \quad \text{for radical attack} \tag{14}$$

where $q_{\mathrm{Ak}}(N_{\mathrm{A}} - 1)$, $q_{\mathrm{Ak}}(N_{\mathrm{A}})$, and $q_{\mathrm{Ak}}(N_{\mathrm{A}} + 1)$ are the Mulliken charge population of the atom k in the cation, neutral, and anion of molecule A, respectively.

Since the exact value of λ is difficult to obtain with a simple model, eqs 5 and 11 were first studied as a function of λ. Moreover, within the present model, a determination of the value of λ is not necessary. We therefore rewrite eq 2 (and its analogues eqs 5 and 11) in a shorthand notation in a global and local−global viewpoint respectively, as

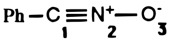
$$\Delta E_{\mathrm{int}}(\lambda) = \Delta E_{v} + \lambda \Delta E'_{\mu} \quad \text{with} \quad \Delta E'_{\mu} = \Delta E_{\mu}(\lambda = 1) \tag{15}$$

and

$$(\Delta E_{\mathrm{int}})_{\mathrm{A}}^{\mathrm{k}} = \Delta E_{v} + \lambda \Delta E'_{\mu} \quad \text{with} \quad \Delta E'_{\mu} = \Delta E_{\mu}(\lambda = 1) \tag{16}$$

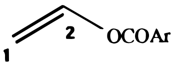
Results and Discussion

The molecules chosen to study 1,3-dipolar cycloaddition reactions were benzonitrile oxide (BNO) as the 1,3-dipole (molecule A) and vinyl *p*-nitrobenzoate and its acetyl derivative as the dipolarophiles **1** and **2**, respectively (molecules B). These were selected in view of their importance in the synthesis of the isoxazolines and because FMO theory does not provide a satisfactory rationalization to explain their reactivity.



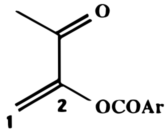
$\mathrm{Ph{-}\underset{1}{C}{\equiv}\underset{2}{N^{+}}{-}\underset{3}{O^{-}}}$

1,3-Dipole (BNO)



Dipolarophile 1

Ar = C_6H_4*p*-NO_2



Dipolarophile 2

Ar = C_6H_4*p*-NO_2

TABLE 1: Global Properties Values for 1,3-Dipole and Dipolarophiles 1 and 2 (Values in eV)

global properties	1,3-dipole	dipolarophile **1**	dipolarophile **2**
chemical potential[a] (μ)	−3.022	−4.340	−4.563
global hardness[b] (η)	4.339	4.327	4.647
global softness[c] (S)	0.115	0.115	0.107

[a] Calculated with eq 6. [b] Calculated with eq 7. [c] Calculated with eq 8. Value in eV^{-1}.

TABLE 2: Values of the Condensed Fukui Function f_{k} and f_{l} at the Relevant Atoms for the Interactions between 1,3-Dipole and Dipolarophiles 1 and 2, Respectively

fukui function	1,3-dipole		dipolarophile **1**		dipolarophile **2**	
	C-1	O-3	C-1	C-2	C-1	C-2
f_{k}^{+} or f_{l}^{+} [a]	−0.0016	0.1690	0.0392	−0.0417	0.0344	−0.0592
f_{k}^{-} or f_{l}^{-} [b]	0.3292	0.4093	−0.0764	0.0135	−0.0672	−0.0351

[a] Nucleophilic attack. Calculated with eq 12. [b] Electrophilic attack. Calculated with eq 13.

TABLE 3: Interaction Energy Values ΔE_{int} for Global−Global Interactions between 1,3-Dipole and Dipolarophiles 1 and 2 (Values in kJ/mol), Calculated with Eqs 3, 4, and 15

ΔE	1,3-dipole vs dipolarophile **1**	1,3-dipole vs dipolarophile **2**
ΔE_{v}	−4.83	−6.37
$\Delta E'_{\mu}$	−209.75	−217.30
ΔE_{int}	$-4.83 - 209.75\lambda$	$-6.37 - 217.30\lambda$

Jiménez et al. showed that thermal cycloaddition of BNO to **2** provides exclusively the regioisomer 5-acetyl-3-arylisoxazole,[23] which is formed by interaction of carbons C-1 of both cycloaddends and O-3 of BNO and C-2 of 2. Concerning **1**, to the best of our knowledge, no experimental details of its reaction with BNO are available.

The values of the condensed fukui function of the relevant atoms in the molecules (f_{k} for BNO and f_{l} for **1** and **2**) and the HSAB principle will be used. These have provided a rationalization of the chemical behavior of a wide variety of systems.[15,16,28−35]

With this goal, molecular orbital calculations for BNO and **1** and **2** were carried out at the Hartree−Fock−LCAO level with a 6-31G** basis set using GAUSSIAN 92.[36] The geometries of the neutral species were optimized at the RHF level. The electron affinity (A) and ionization potential (I) were obtained at the same level of calculations using UHF theory for the anion and cation. The geometries of the neutral species were used to calculate the electronic structure of the charged species in order to fulfill the demand for constant external potential $v(\mathbf{r})$. The chemical potential μ, global softness S, and global hardness η were evaluated from eqs 6−8, (Table 1).

Using the Mulliken population analysis for the cation, anion and neutral system, the condensed fukui function for nucleophilic and electrophilic attacks on the relevant atoms in BNO ($f_{\mathrm{C-1}}^{+}$, $f_{\mathrm{O-3}}^{+}$, $f_{\mathrm{C-1}}^{-}$, and $f_{\mathrm{O-3}}^{-}$) and **1** and **2** ($f_{\mathrm{C-1}}^{+}$, $f_{\mathrm{C-2}}^{+}$, $f_{\mathrm{C-1}}^{-}$, and $f_{\mathrm{C-2}}^{-}$) were also calculated from eqs 12 and 13, (Table 2).

Global−Global Interactions. Calculations of ΔE_{int} in a global viewpoint without specifying the interaction site between BNO and either **1** or **2** were made using eqs 3, 4, and 15. Table 3 shows the ΔE_{int} values. The interaction energy between BNO and **2** is favored approximately by 9 kJ/mol as compared to that between BNO and **1**. The value of the ΔE_{v} term is not the most important one; rather, it is $\Delta E'_{\mu}$. The reason for this can easily be traced back for the ΔE_{v} term in eq 3, owing to the small difference in chemical potentials μ. We can see that the average value of $(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^2/[2/\eta_{\mathrm{A}} + \eta_{\mathrm{B}})]$ is approximately 11 kJ/mol for both reactions ($(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^2[(S_{\mathrm{A}}S_{\mathrm{B}})/(S_{\mathrm{A}} + S_{\mathrm{B}})] = (\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^2/[2(\eta_{\mathrm{A}} + \eta_{\mathrm{B}})]$); the hardness values η are of the same

TABLE 4: Interaction Energy Values $(\Delta E_{\text{int}})^{\text{k}}_{\text{dipole}}$ for Local−Global Interactions between 1,3-Dipole and Dipolarophile 1 (Values in kJ/mol), Calculated with Eqs 9, 10, and 16

	nucleophilic attack at atom		electrophilic attack at atom	
ΔE	C-1	O-3	C-1	O-3
ΔE_v	0.01	−1.39	−2.38	−2.79
$\Delta E'_\mu$	−420.17	−358.85	−315.60	−297.66
$(\Delta E_{\text{int}})^{\text{k}}_{\text{dipole}}$	$0.01 - 420.17\lambda$	$-1.39 - 358.85\lambda$	$-2.38 - 315.60\lambda$	$-2.79 - 297.66\lambda$

TABLE 5: Interaction Energy Values $(\Delta E_{\text{int}})^{\text{k}}_{\text{dipole}}$ for Local−Global Interactions between 1,3-Dipole and Dipolarophile 2 (Values in kJ/mol), Calculated with Eqs 9, 10, and 16

	nucleophilic attack at atom		electrophilic attack at atom	
ΔE	C-1	O-3	C-1	O-3
ΔE_v	0.02	−1.88	−3.20	−3.74
$\Delta E'_\mu$	−451.64	−381.56	−333.03	−313.12
$(\Delta E_{\text{int}})^{\text{k}}_{\text{dipole}}$	$0.02 - 451.64\lambda$	$-1.88 - 381.56\lambda$	$-3.20 - 333.03\lambda$	$-3.74 - 313.12\lambda$

order of magnitude as the chemical potentials (see Table 1). In FMO theory this term is large, but when introducing higher order contributions[10] its magnitude is rectified.

Local−Global Interactions. *(i) Carbon (C-1) and Oxygen (O-3) in the 1,3-Dipole.* To analyze the reactivity of the different atoms within the 1,3-dipole and study its nucleophilic or electrophilic properties, we take into account a local viewpoint for the BNO and a global viewpoint for **1** and **2** as a first approximation. It seems reasonable that the interaction energy ($(\Delta E_{\text{int}})^k_{\text{dipole}}$ in lieu of $(\Delta E_{\text{int}})^k_{\text{A}}$) will be dominated by the local properties of the carbon and oxygen atoms from BNO. The condensed fukui function represents the local reactivity properties of the carbon and oxygen atoms: $f^+_{\text{C}-1}$ and $f^+_{\text{O}-3}$, for nucleophilic attack, and $f^-_{\text{C}-1}$ and $f^-_{\text{O}-3}$ for electrophilic attack. The global softness of **1** and **2**, S_{B}, characterizes the global nature of the dipolarophiles.

Tables 4 and 5 show the $(\Delta E_{\text{int}})^k_{\text{dipole}}$ values calculated by eqs 9, 10, and 16. Both ΔE_v and $\Delta E'_\mu$ are negative in all cases (except for the nucleophilic attack at the C-1 atom, where ΔE_v terms are positive) and $\Delta E'_\mu$ larger in absolute value than the ΔE_v term. Note that the $\Delta E_v/\Delta E'_\mu$ ratio is even smaller than in the global−global case stressing the role of the fukui function when working at the local level (see Table 3). In both cases, the energetically favored interaction is when the dipolarophiles **1** and **2** undertake a nucleophilic attack at the C-1 atom of the 1,3-dipole. The BNO is the electrophile, and **1** and **2** are the nucleophiles. The C-1 atom is the electrophilic center in BNO without the nucleophilic center in **1** and **2** being known yet.

(ii) Carbon (C-1) and Carbon (C-2) in the Dipolarophiles. To analyze the reactivity of the two atoms within dipolarophiles, and to understand their nucleophilic or electrophilic properties, we take a local viewpoint for **1** and **2** and a global viewpoint for BNO. It seems reasonable that the interaction energy ($(\Delta E_{\text{int}})^{\text{l}}_{\text{dipolarophile1}}$ and $(\Delta E_{\text{int}})^{\text{l}}_{\text{dipolarophile2}}$) will be dominated by the local properties of the C-1 and C-2 carbons atoms in **1** and **2**. The condensed fukui function represents the local reactivity of the carbons atoms: $f^+_{\text{C}-1}$ and $f^+_{\text{C}-2}$, for nucleophilic attack, and $f^-_{\text{C}-1}$ and $f^-_{\text{C}-2}$ for electrophilic attack. The global softness of BNO, S_{A}, characterizes the global nature of the 1,3-dipole.

TABLE 6: Interaction Energy Values $(\Delta E_{\text{int}})^{\text{l}}_{\text{dipolarphile1}}$ for Local−Global Interactions between Dipolarophile 1 and 1,3-Dipole (Values in kJ/mol), Calculated with Eqs 9, 10, and 16

	nucleophilic attack at atom		electrophilic attack at atom	
ΔE	C-1	C-2	C-1	C-2
ΔE_v	−0.36	0.41	0.79	−0.12
$\Delta E'_\mu$	−403.67	−437.35	−454.20	−413.91
$(\Delta E_{\text{int}})^{\text{l}}_{\text{dipolarophie1}}$	$-0.36 - 403.67\lambda$	$0.41 - 437.35\lambda$	$0.79 - 454.20\lambda$	$-0.12 - 413.91\lambda$

TABLE 7: Interaction Energy Values $(\Delta E_{\text{int}})^{\text{l}}_{\text{dipolarphile2}}$ for Local−Global Interactions between Dipolarophile 2 and 1,3-Dipole (Values in kJ/mol), Calculated with Eqs 9, 10, and 16

	nucleophilic attack at atom		electrophilic attack at atom	
ΔE	C-1	C-2	C-1	C-2
ΔE_v	−0.40	0.76	0.87	0.44
$\Delta E'_\mu$	−406.49	−443.95	−447.48	−433.66
$(\Delta E_{\text{int}})^{\text{l}}_{\text{dipolarphile2}}$	$-0.40 - 406.49\lambda$	$0.76 - 443.95\lambda$	$0.87 - 447.48\lambda$	$0.44 - 433.66\lambda$

Tables 6 and 7 show the $(\Delta E_{\text{int}})^{\text{l}}_{\text{dipolarophile1}}$ and $(\Delta E_{\text{int}})^{\text{l}}_{\text{dipolarophile2}}$ values calculated by eqs 9, 10, and 16. In both cases the dominant term is the $\Delta E'_\mu$ term and not the ΔE_v term. The most important interaction will occur when BNO undertakes an electrophilic attack at the C-1 atom of **1** and **2**.

Using the local−global point of view for the interactions between BNO and **1** and **2**, we see that the maximum interaction will occur preferentially between atom C-1 from BNO and atom C-1 from **1** and **2**. Our conclusions confirm the experimental results at the cycloaddition of BNO with **2** and suggest that the reaction of BNO with **1** will give a similar adduct.[37]

It is interesting to note that both C-1 atoms have the lower values for the fukui function (they have negative values, see Table 2), but they are nevertheless the more reactive atoms in the molecules.[16,38]

Recently, an experimental paper appeared[39] briefly discussing the role of FMO theory in 1,3-dipolar cycloaddition reactions of the 1,3-dipole BNO with dipolarophilic thiones and terminal alkenes (adamantane derivatives). It was suggested that these reactions are controlled mainly by the LUMO (1,3-dipole)−HOMO (dipolarophile) interaction. However, only the frontier orbital properties of the 1,3-dipole were studied, and the frontier orbital properties of the dipolarophiles were not considered. Our FMO calculations show that the HOMO (1,3-dipole)−LUMO (dipolarophile) and the LUMO (1,3-dipole)−HOMO (dipolarophile) do not determine the chemical reactivity of the 1,3-dipole BNO and dipolarophiles **1** and **2**. FMO theory does not give satisfactory results.

Analyzing the λ expression in detail,[14] it is considered that the number of valence electrons taking part in the reaction between BNO and 1 should remain constant. The term λ depends on the number of valence electrons participating in the reaction, and it may be different for different 1,3-dipole-dipolarophile couples. In the original derivation of λ by Gázquez, its value was obtained by factors yielding at least an order of magnitude 1.

A final comment concerns the dependency of the values of the interaction energy with the λ parameter. Considering the linear equations for the global−global and local−global interactions in Tables 3−7, a graphical representation of the equations indicate that all the results mentioned above are valid as long as $\lambda > 0.2$, a condition, which in view of the discussion on λ presented above, is fulfilled.

Conclusions

As an alternative to frontier molecular orbital theory and orbital perturbation theory, we have used the formulation of the interaction energy in terms of density functional theory and the hard and soft acids and bases principle to study reactivity and regioselectivity in 1,3-dipolar cycloaddition reactions. Arguments based on global and a local−global points of view allow us to analyze the behavior of benzonitrile oxide with respect to vinyl derivatives.

The values of the interaction energy suggest an electrophilic nature for the 1,3-dipole and a nucleophilic nature for the dipolarophiles. The nucleophilic and electrophilic atoms involved in the reaction were identified. The regioselectivity obtained was in agreement with experimental results. The interaction energy was dominated by the reshuffling of the charge distribution term instead of the charge-transfer process, which contributes less. Reshuffling of the charge distribution interactions was more important to rationalize the reactivity and regioselectivity than FMO. The frontier orbital theory failed to describe the reactivity of these systems. Further applications of this approach, among others to reactions of ambident nucleophiles, are currently in progress.

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