An Analysis of the Regioselectivity of 1,3-Dipolar Cycloaddition Reactions of Benzonitrile N-Oxides Based on Global and Local Electrophilicity and Nucleophilicity Indices

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Keywords: Nitrile N-oxides / Cycloaddition / Regioselectivity / Electrophilicity / Nucleophilicity / Heterocycles

The regioselectivity of the 1,3-dipolar cycloaddition (13DC) reactions of benzonitrile N-oxides (BNOs) with electrophilic and nucleophilic alkenes has been analyzed by using global and local nucleophilicity and electrophilicity reactivity indices defined within the conceptual DFT. The BNOs react with electron-deficient and electron-rich ethylenes, but the regioselectivities of these polar reactions are different. Whereas the reactions with electron-rich ethylenes are completely regioselective, yielding 5-isoxazolines, a change in the regioselectivity is observed in the reactions with electron-deficient ethylenes, which yield a mixture of 4- and 5-isoxazolines. Analysis of the energies, geometries, and electronic structures of the transition-state structures involved in the 13DC reactions between the BNOs and two electronically activated ethylenes are in complete agreement with the analysis of the global and local electrophilicity and nucleophilicity reactivity indices.

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Introduction

Cycloaddition reactions are one of the most important processes in organic chemistry with considerable interest shown in both synthetic and mechanistic aspects. The current understanding of the underlying principles of 1,3-dipolar cycloaddition (13DC) reactions has grown from an interplay between theory and experiment.[1] The general concept of 13DCs was introduced by Huisgen in the early 1960s.[2] Huisgen outlined the basis for understanding the mechanism of concerted cycloaddition reactions. The development of 13DC reactions has in recent years entered a new stage as control of the stereo- and regiochemistries of the addition step is now the major challenge. Given the importance of these reactions, considerable effort has been directed towards the characterization of the reagents of these cycloaddition reactions as well as the elucidation of the reaction mechanisms.[3]

Nitrile oxides have been widely utilized as dipoles in 13DC reactions because they allow the rapid preparation of isoxazolines and isoxazoles by reactions with alkenes and alkynes, respectively.[4] This method is fairly general and complements classical condensation methods because of its greater functional group compatibility and the use of milder reaction conditions. Owing to the asymmetry of nitrile oxides, their reactions with asymmetric alkenes and alkynes can yield two 4- and 5-regioisomeric [3+2] cycloadducts (see Scheme 1). Experimentally it has been found that whereas 13DC reactions with electron-rich (ER) π systems only give 5-regioisomers, reactions involving electron-deficient (ED) π systems usually yield a mixture of 4- and 5-regioisomers.

Scheme 1.

The 13DC reactions of nitrile oxides have also been theoretically studied.[5–8] The regioselectivity of the 13DC reactions of benzonitrile N-oxides (NBOs) with ED alkynes and alkenes has been studied by Hu and Houk.[7] The transition-state structures (TSs) for the reactions of fulminic acid (1) and mesitonitrile oxide (2) and the ED methyl propiolate (3) and cyanoacetylene (4) have been studied at the B3LYP/6-31G* level of theory (see Scheme 2). The activation barriers associated with these cycloaddition reactions were calculated to generally be about 13–14 kcal/mol.[7] These 13DCs presented poor regioselectivity, yield-

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ing a mixture of two regioisomeric cycloadducts. Thus, for the 13DC reactions between the BNO 2 and the dipolarophile 3 or 4, the TSs associated with the formation of the 5-regioisomers 6 and 8 were found to be 0.5 and 1.3 kcal/mol, respectively, lower in energy than those associated with the formation of the 4-regioisomers 5 and 7. These lower energies, together with the large polar character of the more unfavorable TSs, suggested that solvent effects could change the regioselectivity of these 13DCs.\[7\]

More recently, Wagner and co-workers\[8\] studied the 13DC reactions of benzonitrile oxide (9) with propene (10) and propyne (11) at the same level of theory (see Scheme 3). Note that the methyl group nucleophilically activates these π systems. The activation barriers were between 14–19 kcal/mol. These 13DC reactions showed complete regioselectivity, the TSs involved in the formation of the 5-regioisomers 12 and 13 being 3.6 and 3.0 kcal/mol lower in energy than those involved in the formation of the 4-regioisomers. Interestingly, an analysis of the MOs involved in these cycloaddition reactions indicated that they could not involve the HOMO and LUMO, but the HOMO-2 and LUMO+2 pairs. They proposed that these orbitals conserve the delocalization energy of the system as far possible.\[9\]

In addition, we have studied the 13DC reaction of the electrophilically activated NBO 14 with 3-methyleneephthalimine (15) by using density functional theory (DFT) methods (see Scheme 4).\[10\] Two different channels leading to the formation of the spiro-cycloadduct 16 and two isomeric (E)- and (Z)-oximes 17 were characterized for this reaction. The 13DC reaction was completely regioselective, giving only the \( [3+2] \) cycloadduct 16.\[10\] This 13DC reaction proceeded by a two-stage mechanism\[11\] with a large polar character. The unique highly asynchronous TS found in the one-step 13DC reaction was associated with nucleophilic attack of the methylene carbon of the 3-methyleneephthalimine (15) on the carbon atom of the electrophilically activated NBO 14. This was in agreement with the high electrophilic character of the NBO 14, \( \omega = 1.94 \) eV, and the high nucleophilic character of the 3-methyleneephthalimine (15), \( N = 3.05 \) eV.

Recently, Ponti and Molteni\[12\] studied the regioselectivity of the cycloaddition reactions of 4-substituted benzonitrile oxides and methyl propiolate based on the Pearson’s hard–soft acid–base (HSAB) principle.\[13\] The charge transfer (CT) between the two reagents in these 13DC reactions was analyzed in terms of the electronic chemical potentials, \( \mu \), of the two fragments as a first step. The regioselectivity was predicted through the local charge transfer (\( \Delta N \)) in the grand canonical ensemble by using the locally condensed softness, \( s_k \), of the atoms involved in the bond-forming step. The results showed that in these 13CD reactions, the oxygen atom behaves as a donor, whereas the nitrile oxide carbon is an acceptor, in agreement with previous results.\[14\]

A few years ago, we classified the common dienes and dienophiles involved in Diels–Alder reactions through the known electrophilicity index, \( \omega \) introduced by Parr et al.\[15\] in a unique electrophilicity scale.\[16\] The \( \Delta \omega \) value of the diene/dienophile pairs was proposed as a measure of the polar character of the reactions.\[16\] A quantitative extension of the global electrophilicity to obtain the local electrophilicity, \( \omega_k \), at specific sites in Diels–Alder reagents was proposed by Domingo et al.\[17\] As a consequence, dipoles and dipolarophiles commonly used in 13DC reactions were classified by using the \( \omega \) index.\[18\] Later, the regioselectivities of a series of 13DC reactions were studied by using the global and local reactivity indices.\[19\] The theoretical results indicated that the regioselectivity of a polar cycloaddition reaction could be explained by the most favorable two-center interactions between the highest nucleophilic and electrophilic sites of the reagents. The corresponding reaction channel favors the maximum CT from the nucleophilic to the electrophilic reagent in the course of the polar cycloaddition reaction. Not having at this moment an appropriate local nucleophilicity index, the nucleophilic Fukui function, \( \mu^+ \), was the descriptor used as a measure of this property. Very recently, we proposed a nucleophilicity index, \( N_k \), based on the HOMO energy in order to explain the participation of captodative ethylenes in polar cycloaddition reactions.\[21\] Analysis of the local electrophilicity,\[17\] \( \omega_k \), and nucleophilicity,\[22\] \( N_k \), indices in polar cycloaddition reactions...
of carbonyl ylides has allowed the regioselectivity observed experimentally to be explained.\textsuperscript{[23]} These local indices are the product of the corresponding global indices, $\omega$ and $N$, and the corresponding Fukui function\textsuperscript{[20]} for nucleophilic, $f_k^+$, and electrophilic, $f_k^-$, attacks, respectively. Thus, whereas the Fukui functions account for the regioselectivity, the local electrophilicity and nucleophilicity indices account for the local activation within a molecule.

Our interest in the study of the mechanisms of cycloaddition reactions and, more specifically, of 13DC reactions encouraged us to perform a theoretical study of the regioselectivity of the 13DC reactions of electronically activated BNOs by using global and local nucleophilicity and electrophilicity reactivity indices defined within the conceptual DFT. For this purpose, the 13DC reactions of the unsubstituted BNO (9), the electrophilic $p$-nitrobenzonitrile N-oxide (21), and the nucleophilic $p$-methoxybenzonitrile N-oxide (22) with two activated ethylenes, the nucleophilic 2-methylene-1,3-dioxolane (23) and the electrophilic 1,1-dicyanoethylene (24)\textsuperscript{[21]} will be analyzed to determine the regioselectivity of these 13DC reactions (see Scheme 5).

![Scheme 5](image)

**Results and Discussion**

First, the 13DC reactions between the simplest BNO 9 with ethylene (19), and the BNOs 9, 21, and 22 with the ethylene derivatives 23 and 24 were studied. Then an analysis based on the reactivity indices of the reagents involved in the 13DC reactions of BNOs was performed to systematize the regioselectivity of these 13DC reactions.

**Mechanistic Details of the 13DC Reactions of Benzonitrile N-Oxides**

**Study of the 13DC Reaction between Benzonitrile N-Oxide (9) and Ethylene (19)**

An analysis of the stationary points involved in the 13DC reaction between BNO (9) and 19 indicates that this cycloaddition has a one-step mechanism (see Scheme 5). Therefore, one TS, TS1, and one cycloadduct, 20, were located and characterized. The activation barrier associated with TS1 is 12.4 kcal/mol. This value is closer to that obtained for the TS associated with the 13DC reaction between fulminic acid (1) and ethylene (19); 11.3 kcal/mol.\textsuperscript{[9]} This cycloaddition is strongly exothermic, $-42.9$ kcal/mol (see Table 1). To validate the B3LYP energies, single-point calculations at the MP3 and CCSD(T) levels of theory were performed by using the same standard 6-31G* basis set (see Table 1). This comparative study indicates that the B3LYP calculations give activation and reaction energies in reasonable agreement with the very expensive CC calculations.\textsuperscript{[9]}

The geometry of TS1 is shown in Figure 1. The lengths of the two forming bonds in the TS are 2.258 (C–C) and 2.342 Å (C–O). Similar geometrical parameters were found for the TS associated with the 13DC reaction between fulminic acid (1) and ethylene (19): 2.235 (C–C) and 2.413 Å (O–C).\textsuperscript{[9]}

![Figure 1](image)

**Figure 1.** Structure of the transition state TS1 involved in the one-step reaction between benzonitrile N-oxide (9) and ethylene (19). The distances are given in Å.

The extent on bond formation in the TS is provided by the bond order (BO). In TS1, the BO values for the two forming bonds are 0.29 (C–C) and 0.22 (C–O). In this concerted process, the C–C bond formation is slightly more advanced than the C–O one. Finally, the electronic nature of this 13DC reaction was also evaluated by analyzing the CT in the TS. The natural charges in TS1 were shared between the frameworks of BNO (9) and ethylene (19). The charges on both fragments are $-0.02e$ at 9 and 0.02e at 19. This negligible CT in TS1 points to a nonpolar cycloaddition process.\textsuperscript{[9]}

<table>
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<tbody>
<tr>
<td>9</td>
<td>$-399.639891$</td>
<td>$-398.427465$</td>
<td>$-398.508248$</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>19</td>
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<td>$-78.305958$</td>
<td>$-78.321852$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS1</td>
<td>$-478.207537$</td>
<td>$12.4$</td>
<td>$-476.708114$</td>
<td>$15.9$</td>
<td>$-476.814212$</td>
<td>$10.0$</td>
</tr>
<tr>
<td>20</td>
<td>$-478.295640$</td>
<td>$-42.9$</td>
<td>$-476.823399$</td>
<td>$-56.5$</td>
<td>$-476.908891$</td>
<td>$-49.4$</td>
</tr>
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</table>
These results, which are similar to those obtained for the 13DC reaction between fulminic acid (1) and ethylene (19), seem to show that the inclusion of the phenyl group in the nitrile oxide apparently does not modify the cycloaddition reaction. However, this apparently low activation could be related to the poor ability of ethylene (19) to act as an electrophile or nucleophile in a polar reaction (see later). Consequently, only the nonpolar mechanism similar to that for the reaction of fulminic acid (1) and ethylene (19) is feasible for this 13DC reaction.

**Study of the 13DC Reactions between Benzonitrile N-Oxide (9) and the Electronically Activated Benzonitrile N-Oxides 21 and 22 with the Ethylene Derivatives 23 and 24**

An analysis of the stationary points involved in the two regioisomeric paths associated with the 13DC reactions of the BNOs 9, 21, and 22 with the activated ethylenes 23 and 24 indicates that these cycloaddition reactions have one-step mechanisms (see Scheme 5). Therefore, eight TSs, TSX4 and TSX5 (X = 2-5), and the corresponding [3+2] cycloadducts, CA4X and CA5X, were located and characterized. Note that the reactive channels X4 and X5 are associated with the formation of the 4- and 5-regioisomeric cycloadducts.

The activation barriers associated with these 13DC reactions are 25.7 (TS24), 11.0 (TS25), 10.3 (TS34), 10.6 (TS35), 24.4 (TS44), 8.8 (TS45), 8.4 (TS54), and 10.2 (TS55) kcal/mol (see Table 2). Some interesting conclusions can be drawn from these energy values. i) The activation barriers for the 13DC reactions between the unsubstituted BNO 9 and the activated ethylenes 23 and 24 are only 1.4 and 1.8 kcal/mol lower in energy than that for the reaction between the BNO 9 and ethylene. ii) Electronic activation of the BNO 9 decreases the activation barriers for the more favorable reactive channels by around 4 kcal/mol. iii) There is a change in the regioselectivity of the 13DC reactions of these BNOs with the activated ethylenes 23 and 24. Whereas in the 13DC reactions with the nucelophic ethylene 23 the reactive channels yielding the 5-isoxazolines are clearly favored, the reactions with the electrophilic ethylene 24 yield 4-isoxazolines. iv) Although the 13DC reactions with 23 are totally regioselective, ΔΔEa > 15 kcal/mol, in the reactions with 24, mixtures of the 4- and 5-isoxazolines are expected, ΔΔEa < 2 kcal/mol. The low regioselectivity found for the 13DC reactions involving ED ethylenes indicates that solvent effects or steric effects in the TSs can modify the ratio of the 4- and 5-isoxazolines. v) The regioselectivity of the reactions with ED ethylenes increases with the nucleophilic character of the NBO. Finally, as all these cycloaddition reactions are strongly exothermic, between -29 and -47 kcal/mol, they can be considered irreversible. That is, these energetic results suggest that the regioisomeric isoxazolines are formed as a result of kinetic control.

The geometries of the TSs involved in these 13DC reactions are shown in Figure 2 and Figure 3. The lengths of the two forming bonds in the TSs are 2.222 (C-C) and 2.181 Å (C-O) for TS24, 2.223 (C-C) and 2.725 Å (C-O) for TS25, 2.415 (C-C) and 1.892 Å (C-O) for TS34, 2.113 (C-C) and 2.498 Å (C-O) for TS35, 2.265 (C-C) and 2.170 Å (C-O) for TS44, 2.247 (C-C) and 2.823 Å (C-O) for TS45, 2.444 (C-C) and 1.871 Å (C-O) for TS54, and 2.102 (C-C) and 2.460 Å (C-O) for TS55. Some interesting conclusions can be drawn from these values. i) The electronic activation of the BNO 9 by the strong electron-releasing OCH3 and strong electron-withdrawing NO2 groups does not produce any significant changes in the TS geometries. ii) Although the more unfavorable TSs associated with the 13DC reactions of the ER ethylene 23, TS24 and TS44, correspond to synchronous processes, the more favorable TSs, TS25 and TS45, correspond to asynchronous processes. For the reactions with the ED ethylene 24, all the TSs are asynchronous. iii) In these 13DC reactions, the shortest forming bond corresponds to that at the β-conjugated position of the activated ethylene. iv) The high activation barrier associated with the synchronous TSs TS24 and TS44 and the bonding geometrical parameters are in good agreement with the low electrophilic activation of the oxygen atom (see later), which accounts for the complete regioselectivity of the reactions of these BNOs with ER ethylenes.

The BO values of the forming bonds in these TSs are 0.31 (C-C) and 0.30 (C-O) for TS24, 0.30 (C-C) and 0.10 (C-O) for TS25, 0.20 (C-C) and 0.44 (C-O) for TS34, 0.36 (C-C) and 0.15 (C-O) for TS35, 0.31 (C-C) and 0.30 (C-O) for TS44, 0.29 (C-C) and 0.09 (C-O) for TS45, 0.18 (C-C) and 0.45 (C-O) for TS54, and 0.36 (C-C) and 0.16 (C-O) for TS55. These BO values validate the main conclu-
The electronic nature of these cycloaddition reactions was also evaluated by analyzing the CT in the TS. The natural charges in the TS are shared between the BNOs 9, 21, or 22 and the ethylene derivative 23 or 24. The charges on the two BNO fragments in the TSs are −0.08e for TS24, −0.17e for TS25, 0.17e for TS34, 0.13e for TS35, −0.13e for TS44, −0.18e for TS45, 0.19e for TS54, and 0.14e for TS55. These values, which are larger than that found in TS1, point to some zwitterionic character. The CT increases slightly with the electronic activation of the BNO 9. The lower CT corresponds to the more unfavorable TS24 and TS44. Although in the 13DC reactions with the ER ethylene 23, the CT fluxes from 23 to the BNOs 9 and 21, in the 13DC reactions with the ED ethylene 24, the CT fluxes from the BNO 9 and 22 to the ethylene 24. In addition, the CT is slightly larger in the more favorable regioisomeric TSs.

Along the IRC from TS45 to CA45 the CT increases to that of the HP structure, −0.46e. After this point the CT decreases as a consequence of back-donation in the cyclization process. Thus, this two-stage cycloaddition can be viewed as a nucleophilic attack of the conjugated position of the ER ethylene 23 on the carbon atom of the ED BNO 21 followed by concomitant ring-closure. A similar result was obtained for the 13DC reaction between the electrophilically activated CF3PhCNO (14) and 3-methylene-phthalimine (15). Note that the mechanism of these polar cycloaddition reactions, which take place through very asynchronous TSs, cannot proceed through a pericyclic mechanism because the formation of the C–O bond is not initialized in the first stage of the reaction.

**Solvent Effects on the Regioselectivity of the 13DC Reactions of NBOs**

Some authors have suggested that polar solvents can modify the regioselectivity of the 13DC reactions of NBOs. To investigate whether this proposal has any validity, the solvent effects of dichloromethane (DCM) were studied through single-point energy calculations of the gas-phase stationary points involved in the 13DC reactions between the BNOs 9, 21, and 22 and the activated ethylenes 23 and 24 using PCM methods. The results are given in Table 2.

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**Figure 2.** Structures of the transition states involved in the 13DC reactions between the BNO 9 and the ethylene derivatives 23 and 24. The distances are given in Å.

**Figure 3.** Structures of the transition states involved in the 13DC reactions between the electronically activated BNOs 21 and 22 and the ethylene derivatives 23 and 24. The distances are given in Å.

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The electronic nature of these cycloaddition reactions was also evaluated by analyzing the CT in the TS. The natural charges in the TS are shared between the BNOs 9, 21, or 22 and the ethylene derivative 23 or 24. The charges on the two BNO fragments in the TSs are −0.08e for TS24, −0.17e for TS25, 0.17e for TS34, 0.13e for TS35, −0.13e for TS44, −0.18e for TS45, 0.19e for TS54, and 0.14e for TS55. These values, which are larger than that found in TS1, point to some zwitterionic character. The CT increases slightly with the electronic activation of the BNO 9. The lower CT corresponds to the more unfavorable TS24 and TS44. Although in the 13DC reactions with the ER ethylene 23, the CT fluxes from 23 to the BNOs 9 and 21, in the 13DC reactions with the ED ethylene 24, the CT fluxes from the BNO 9 and 22 to the ethylene 24. In addition, the CT is slightly larger in the more favorable regioisomeric TSs.

Along the IRC from TS45 to CA45 the CT increases to that of the HP structure, −0.46e. After this point the CT decreases as a consequence of back-donation in the cyclization process. Thus, this two-stage cycloaddition can be viewed as a nucleophilic attack of the conjugated position of the ER ethylene 23 on the carbon atom of the ED BNO 21 followed by concomitant ring-closure. A similar result was obtained for the 13DC reaction between the electrophilically activated CF3PhCNO (14) and 3-methylene-phthalimine (15). Note that the mechanism of these polar cycloaddition reactions, which take place through very asynchronous TSs, cannot proceed through a pericyclic mechanism because the formation of the C–O bond is not initialized in the first stage of the reaction.

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In DCM the activation barriers associated with these 13DC reactions increase by between 0.6 and 2.4 kcal/mol as a consequence of a larger solvation of the reagents than of the TSs. DCM exerts different effects on the regioselectivities of these 13DC reactions, depending on the electronic nature of the reactants. In the cycloaddition reactions involving ED ethylenes, polar solvents can modify the ratio of the 4- and 5-regioisomeric cycloadducts as a consequence of the low regioselectivity of these 13DC reactions, $\Delta \delta < 1.8$ kcal/mol, and the higher polar character of the more unfavorable TS, $\text{TSS}$ and $\text{TSSS}$ (see Table 2). Therefore, polar solvents can diminish $\Delta \delta$, and even invert the relative energies.\[7\] Note that in the 13DC reaction between the unsubstituted BNO 9 and the ED ethylene 24 there is an inversion of $\Delta \delta_{DCM}$ as a consequence of the low regioselectivity in the gas phase, $\Delta \delta = 0.3$ kcal/mol. However, in the 13DC reactions involving ER ethylenes, the large regioselectivity found in these reactions, $\Delta \delta > 15.6$ kcal/mol, cannot be substantially modified by solvent effects. As a consequence, these 13DC reactions remain completely regioselective.

### Analysis of the Reactivity Indices in the Ground State of the BNOs

#### Analysis of the Global Reactivity Indices of the BNOs

Recent studies of Diels–Alder and 13DC reactions have shown that the reactivity indices defined within the conceptual DFT are powerful tools for establishing the polar character of the reactions.\[24\] The static global properties, electronic chemical potential, $\mu$, chemical hardness, $\eta$, global electrophilicity, $\omega$, and global nucleophilicity, $N$, for BNO dipoles and ethylene dipolarophiles are presented in Table 3.

<table>
<thead>
<tr>
<th>NO$_2$PhCNO (21)</th>
<th>CH$_3$C=C(CN)$_2$ (24)</th>
<th>CF$_3$PhCNO (14)</th>
<th>Isoindole derivative 15</th>
<th>PhCNO (9)</th>
<th>CH$_3$PhCNO (25)</th>
<th>(CH$_3$)$_2$PhCNO (2)</th>
<th>MeOPhCNO (22)</th>
<th>Ethylene (19)</th>
<th>HCN$\delta$ (1)</th>
<th>Propene (10)</th>
<th>CH$_2$=C(OCH$_3$)$_2$ (23)</th>
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<td>0.1851</td>
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<td>-0.1259</td>
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<td>2.82</td>
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<td>1.46</td>
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<td>1.75</td>
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<tr>
<th>$\mu$ [a.u.]</th>
<th>$\eta$ [a.u.]</th>
<th>$\omega$ [eV]</th>
<th>$N$ [eV]</th>
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Both the electrophilicity\[15\] and nucleophilicity\[21\] indices for the simplest nitrile oxide, fulminic acid (1), have very low values, $\omega = 0.73$ eV and $N = 1.75$ eV. These values, which are similar to those of ethylene (19), $\omega = 0.73$ eV and $N = 1.86$ eV, allow these molecules to be classified as poor electrophiles and nucleophiles. This accounts for the participation of these species in nonpolar cycloaddition reactions with a large biradical character.\[9\]

The substitution of the hydrogen atom in fulminic acid by a phenyl group produces important changes in reactivity. With the BNO 9, the two reactivity indices increase significantly, $\omega = 1.46$ eV and $N = 2.78$ eV. As a consequence, the BNO 9 can be classified as a good electrophile\[16,18\] and a good nucleophile,\[25\] allowing its participation in polar processes with good nucleophiles and electrophiles. Note that the phenyl group produces a larger nucleophilic activation and therefore it is expected that it will react better with ED alkenes.

Weak electron-releasing and -withdrawing groups, for example, CH$_3$ and CF$_3$, respectively, on the aromatic ring activate the corresponding BNOs for polar processes. Thus, whereas the nucleophilicity of CH$_3$PhCNO (25) increases to 2.95 eV, the electrophilicity of CF$_3$PhCNO (14) increases to 1.94 eV. The presence of three methyl groups on the aromatic ring increases the nucleophilicity of mesitonitrile oxide (2) to 3.12 eV. A more activating effect is observed when the aromatic ring is substituted by functional groups that interact directly with the molecular $\pi$ system of the BNO. Thus, the nitro derivative 21 and the methoxy derivative 22 have the largest electrophilic and nucleophilic activation: $\omega = 3.15$ eV (21) and $N = 3.24$ eV (22), respectively. Note that the nucleophilicity of the trimethyl derivative 2, which possesses three electron-releasing methyl groups, is slightly lower than that for the methoxy derivative 22.

Finally, the ethylene derivatives 24 and 23 have high electrophilicity and nucleophilicity values, $\omega = 2.82$ eV and $N = 3.53$ eV, respectively.\[21\] Therefore, it is expected that the 13DC reactions of electronically activated BNOs with these ethylene derivatives will take place through polar mechanisms.

### Analysis of the Regioselectivity Based on the Local Reactivity Indices

The values of the condensed-to-atoms Fukui functions, $f_{k}^-$ and $f_{k}^+$, are obtained from the most simple approximation, from the HOMO and LUMO frontier molecular orbitals, respectively.\[26\] However, in the cases of complex molecules having several $\pi$ molecular orbitals in a narrow range of energy, that is, C–C and C–N triple bonds\[29\] or aromatic systems,\[220\] the approximation based on HOMOs and LUMOs cannot provide the expected reactivity. This is the case with BNO derivatives in which some $\pi$ molecular orbitals are located in a narrow band. In addition, specific substitutions can modify the relative positions of these MOs.\[22b\] To clarify this effect, we computed the electrophilic and nucleophilic Fukui functions for the BNOs 9, 21, and 22. For this analysis we considered the Fukui functions obtained from the first four FMOs.\[27\] The corresponding Fukui functions for the carbon, nitrogen, and oxygen atoms of the nitrile oxide group are presented in Table 4.

Analysis of the Fukui functions obtained for the unsubstituted BNO 9 shows that the values obtained from the
The presence of an electron-releasing CH$_3$O group at the para position of benzene in the BNO 22 does not modify either the relative position of the MO involved in the 13DC reaction or the regiochemistry (compare the values with those of the unsubstituted BNO 9). On the other hand, the presence of a strong electron-withdrawing NO$_2$ group at the para position of benzene in the BNO 21 destabilizes the MO involved in the 13DC reaction. However, the regioselectivity of the reaction is not modified; the carbon atom is the preferred center for a nucleophilic attack. This analysis is in reasonable agreement with the regiochemistry observed for the reaction of BNO 21 with the ER ethylene 23.

These results show that the regioselectivity of the reactions of these BNOs is not substantially modified by substitution: Although BNOs will react with electron-rich ethylenes to yield unique 5-substituted isoxazolines, they will react with electron-deficient ethylenes to yield a mixture of 4- and 5-substituted isoxazolines in which the latter predominate.

With the selected Fukui functions for these 13DCs, the local electrophilicity and nucleophilicity values can be calculated for the BNOs 9, 21, and 22. The results are given in Table 5. Note that both the local indices and the Fukui functions account for the regioselectivity of these 13DC reactions. However, analysis of the local indices provides information about the local electronic activation of these BNOs. Thus, although the local electrophilicity index for the carbon atom of the BNO 21 is twice that for the unsubstituted BNO 9, the local nucleophilicity index for the oxygen atom of the BNO 22 is only 1.2 times that for the unsubstituted BNO 9. These results indicate that an electron-withdrawing substituent on the benzene will produce a larger electronic activation than an electron-releasing substituent.

Finally, the ED ethylene 24 and the ER ethylene 23 have the largest electrophilic and nucleophilic activation at the unsubstituted β position, $\omega_k = 1.41$ eV and $N_k = 1.96$ eV, respectively (see Table 5). Therefore, the β position of these ethylene derivatives will be the more electrophilic and nucleophilic centers, respectively, in clear agreement with the asynchronicity found for the corresponding TSs.

### Conclusions

The reactivity and regioselectivity of the 13DC reactions of the BNOs with electronically activated ethylenes have been analyzed by using the global and local electrophilicity and nucleophilicity indices defined within the conceptual DFT. The BNOs react with both ER and ED ethylenes, but the regioselectivities are different. Whereas with ER ethylenes the reactions are completely regioselective, yielding 5-isoxazolines, the reactions with ED ethylenes give mixtures of 4- and 5-isoxazolines. Analysis of the energies, geometries, and electronic structures of the transition-state structures involved in the 13DC reactions of the BNO 9 and two electronically activated BNOs, 21 and 22, has allowed the reactivity and regioselectivity of these 13DC reactions to be explained. Although electronic activation of the BNO 9

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### Table 4. Electrophilic ($f_k^-$) and nucleophilic ($f_k^+$) Fukui functions for the BNOs 9, 21, and 22.

<table>
<thead>
<tr>
<th></th>
<th>HOMO-3</th>
<th>HOMO-2</th>
<th>HOMO-1</th>
<th>HOMO</th>
<th>LUMO</th>
<th>LUMO+1</th>
<th>LUMO+2</th>
<th>LUMO+3</th>
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<tbody>
<tr>
<td>NO$_2$PhCNO (21)</td>
<td>C</td>
<td>0.0046</td>
<td>0.0000</td>
<td>0.3407</td>
<td>0.1852</td>
<td>0.0111</td>
<td>0.0001</td>
<td>0.0698</td>
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<td></td>
<td>N</td>
<td>0.0004</td>
<td>0.0000</td>
<td>0.0752</td>
<td>0.0811</td>
<td>0.0496</td>
<td>0.0000</td>
<td>0.0924</td>
</tr>
<tr>
<td>PhCNO (9)</td>
<td>C</td>
<td>0.0058</td>
<td>0.0000</td>
<td>0.5349</td>
<td>0.3735</td>
<td>0.0430</td>
<td>0.0000</td>
<td>0.0534</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>0.1704</td>
<td>0.0000</td>
<td>0.3399</td>
<td>0.1600</td>
<td>0.0633</td>
<td>0.0001</td>
<td>0.4147</td>
</tr>
<tr>
<td>CH$_3$OPhCNO (22)</td>
<td>C</td>
<td>0.0063</td>
<td>0.0000</td>
<td>0.0745</td>
<td>0.0852</td>
<td>0.1197</td>
<td>0.0000</td>
<td>0.3178</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>0.1826</td>
<td>0.0000</td>
<td>0.5450</td>
<td>0.3609</td>
<td>0.0789</td>
<td>0.0000</td>
<td>0.1438</td>
</tr>
</tbody>
</table>

---

### Table 5. Local electrophilicity ($\omega_k$) and nucleophilicity ($N_k$) indices of the BNOs, 9, 21, and 22 and the activated ethylenes 23 and 24.

<table>
<thead>
<tr>
<th></th>
<th>$\omega_k$ [eV]</th>
<th>$N_k$ [eV]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$PhCNO (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.31</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1.61</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>PhCNO (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.60</td>
<td>0.95</td>
</tr>
<tr>
<td>N</td>
<td>0.46</td>
<td>0.21</td>
</tr>
<tr>
<td>O</td>
<td>0.21</td>
<td>1.52</td>
</tr>
<tr>
<td>CH$_3$OPhCNO (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>1.77</td>
<td></td>
</tr>
<tr>
<td>ED ethylene (24)</td>
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</tr>
<tr>
<td>C$_e$</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>C$_p$</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>ER ethylene (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_e$</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>C$_p$</td>
<td>1.96</td>
<td></td>
</tr>
</tbody>
</table>
decreases the activation barrier by around 4 kcal/mol; the regioselectivity is not modified by substitution of the aromatic ring. The poor regioselectivity found in the reactions with ED ethylenes, ∆∆Ethr < 2.0 kcal/mol, can be affected by steric or polar solvent effects to produce greater stabilization of the more polar TS. Thus, mixtures of regiosomeric 4- and 5-isoxazolines are expected for these types of 13DC reactions.

Computational Methods

DFT calculations were carried out by using B3LYP[30] exchange-correlation functionals together with the standard 6-31G* basis set.[31] For the 13DC reaction between benzonitrile oxide (9) and ethylene, MP3[31] and CCSD(T)[32] single-point energy calculations were performed on the B3LYP-optimized structures to check the DFT relative energies. The geometry optimizations were carried out by using the Berny analytical gradient optimization method.[33] The stationary points were characterized by frequency calculations to verify that the TSs have one and only one imaginary frequency. The intrinsic reaction coordinate (IRC)[34] paths were traced to verify that the TSs have one and only one imaginary frequency. The geometry optimizations were carried out by using the Berny analytical gradient optimization method.[33]

Acknowledgments

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The Fukui functions can also be evaluated by using the finite difference approximation in terms of the cationic, neutral and anionic electronic densities. However, under this approximation, the Fukui functions of these NBOs yielded negative values (data not reported here), avoiding a proper rationalization of the regioselectivity of selected systems. These negative values can be traced back to the larger electronic relaxation effects expected in these systems.

The Fukui functions can also be evaluated by using the finite relaxation effects expected in these systems. Negative values can be traced back to the larger electronic relaxation of the regioselectivity of selected systems. These negative values can be traced back to the larger electronic relaxation effects expected in these systems.