FULL PAPER

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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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.
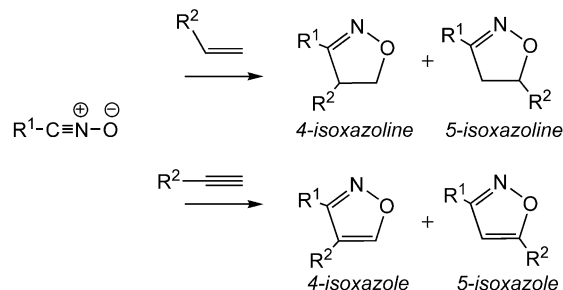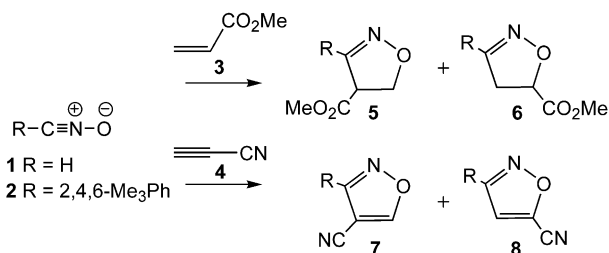

Scheme 1.

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]
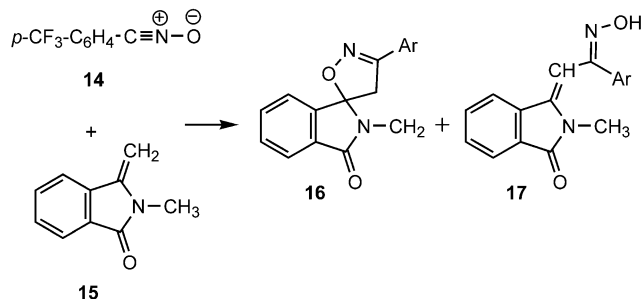

Scheme 2.

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-regiosiomers. 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.[8]
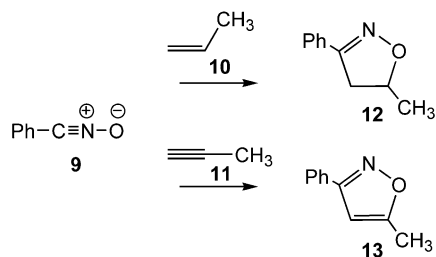
Scheme 3.

In addition, we have studied the 13DC reaction of the electrophilically activated NBO **14** with 3-methylenephthalimine (**15**) by using density functional theory (DFT) methods (see Scheme 4).[9] 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-methylenephthal-

imine (**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-methylenephthalimine (**15**), $N = 3.05$ eV.
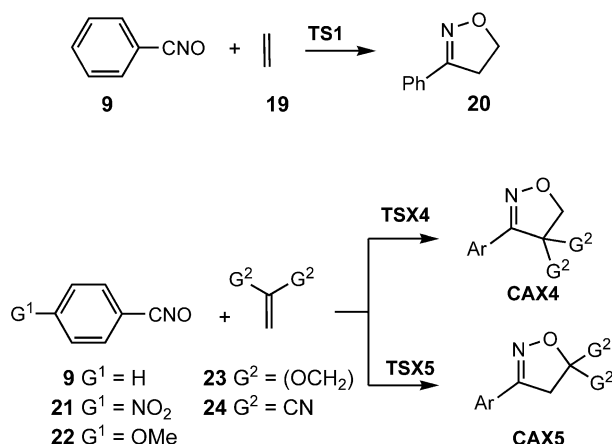

Scheme 4.

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, μ, of the two fragments as a first step. The regioselectivity was predicted through the local charge transfer (ΔN) 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, ω, introduced by Parr et al.[15] in a unique electrophilicity scale.[16] The $\Delta\omega$ value of the diene/dienophiles 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, ω_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 ω 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, f_k^-,[20] was the descriptor used as a measure of this property.

Very recently, we proposed a nucleophilicity index, N, 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] ω_k, and nucleophilicity,[22] N_k, indices in polar cycloaddition reactions

of carbonyl ylides has allowed the regioselectivity observed experimentally to be explained.[23] These local indices are the product of the corresponding global indices, ω and N, and the corresponding Fukui function[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**),[21] will be analyzed to determine the regioselectivity of these 13DC reactions (see Scheme 5).

Scheme 5.

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).[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.[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).[9]
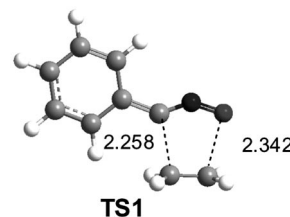

Figure 1. Structure of the transition state **TS1** involved in the one-step reaction between benzonitrile *N*-oxide (**9**) and ethylene (**19**). The distances are given in Å.

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 –0.02*e* at **9** and 0.02*e* at **19**. This negligible CT in **TS1** points to a nonpolar cycloaddition process.[9]

Table 1. B3LYP/6-31G*, MP3/6-31G*//B3LYP/6-31G* and CCSD(T)//B3LYP/6-31G* total (*E*) and relative (Δ*E*, relative to **9** + **19**) energies of the stationary points of the 13DC reaction between benzonitrile oxide **9** and ethylene **19**.

| | B3LYP | | MP3 | | CC | |
	E [a.u.]	Δ*E* [kcal/mol]	*E* [a.u.]	Δ*E* [kcal/mol]	*E* [a.u.]	Δ*E* [kcal/mol]
9	–399.639891		–398.427465		–398.508248	
19	–78.587457		–78.305958		–78.321852	
TS1	–478.207537	12.4	–476.708114	15.9	–476.814212	10.0
20	–478.295640	–42.9	–476.823399	–56.5	–476.908891	–49.4

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, **CAX4** and **CAX5**, 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 nucleophilic 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, $\Delta\Delta E^{\#} > 15$ kcal/mol, in the reactions with **24**, mixtures of the 4- and 5-isoxazolines are expected, $\Delta\Delta E^{\#} < 2$ kcal/mol. The low regioselectivity found for the 13DC reactions involving ED ethylenes indicates that solvent effects[7] or steric effects[6b] in the TSs can modify the ratio of the 4- and 5-isoxazolines. iv) 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)

Table 2. B3LYP/6-31G* total (E) and relative (ΔE) energies in the gas phase and in DCM, and gas-phase dipole moments (DM given in debye units) of the stationary points involved in the 13DC reactions of the NBOs **9**, **21**, and **22** with the activated ethylenes **23** and **24**.

	Gas phase			Solvent	
	E [a.u.]	ΔE [kcal/mol]	DM	E_{DCM} [a.u.]	ΔE_{DCM} [kcal/mol]
9	–399.639891		4.4	–399.658470	
21	–604.138406		0.9	–604.150762	
22	–514.163814		5.6	–514.173446	
23	–306.441320		2.9	–306.447315	
24	–263.062684		4.2	–263.072971	
TS24	–706.040320	25.7[a]	5.1	–706.051678	27.7[a]
TS25	–706.063668	11.0[a]	1.6	–706.074819	13.2[a]
CA24	–706.131735	–31.7[a]	4.6	–706.143509	–29.9[a]
CA25	–706.153519	–45.4[a]	2.7	–706.166124	–44.1[a]
TS34	–662.686213	10.3[b]	3.7	–662.702058	12.2[b]
TS35	–662.685650	10.6[b]	9.0	–662.703480	11.3[b]
CA34	–662.746273	–27.4[b]	1.5	–662.759647	–24.0[b]
CA35	–662.749425	–29.4[b]	6.4	–662.764383	–26.9[b]
TS44	–910.540828	24.4[c]	4.3	–910.545538	26.8[c]
TS45	–910.565736	8.8[c]	7.2	–910.580721	10.9[c]
CA44	–910.633057	–33.5[c]	6.6	–910.648241	–31.5[c]
CA45	–910.654767	–47.1[c]	6.9	–910.670845	–45.7[c]
TS54	–777.213102	8.4[d]	5.0	–777.229774	10.4[d]
TS55	–777.210267	10.2[d]	10.7	–777.229146	10.8[d]
CA54	–777.271838	–28.5[d]	2.7	–777.285871	–24.8[d]
CA55	–777.273971	–29.8[d]	7.6	–777.289707	–27.2[d]

[a] Relative to **9** + **23**. [b] Relative to **9** + **24**. [c] Relative to **21** + **23**. [d] Relative to **22** + **24**.

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 OCH_3 and strong electron-withdrawing NO_2 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 ethylenes. 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-
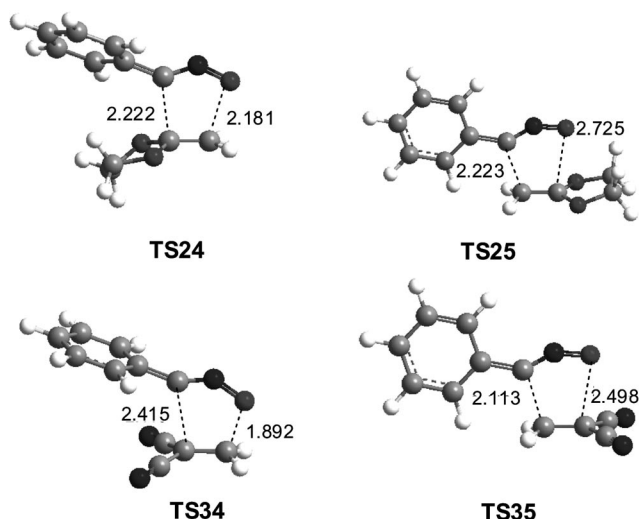
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Figure 2. Structures of the transition states involved in the 13DC reactions between the BNO **9** and the ethylene derivatives **23** and **24**. The distances are given in Å.
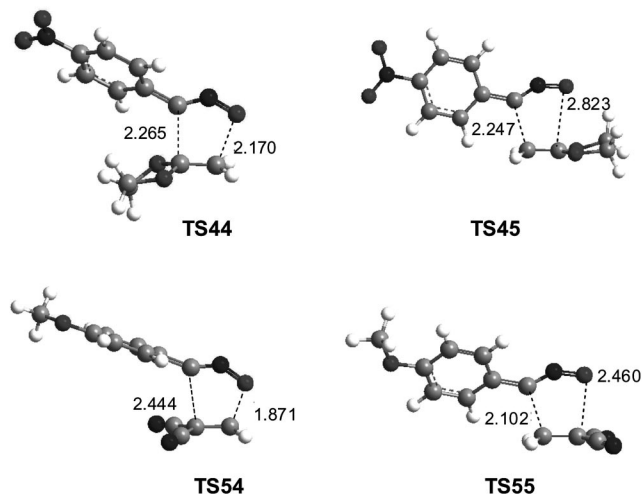

Figure 3. Structures of the transition states involved in the 13DC reactions between the electronically activated BNOs **21** and **22** and the ethylene derivatives **23** and **24**. The distances are given in Å.

sions obtained from the analysis performed on the geometrical parameters. As can be seen, electronic activation of the BNO **9** does not produce any significant changes in the bond-formation process. These BO values point to a high asynchronicity of the favorable **TS45**. Analysis of the IRC from **TS45** to **CA45** indicates that this 13DC reaction occurs by a two-stage mechanism.[11] In the first stage of the cycloaddition, only the C–C bond is formed during the nucleophilic attack of the ER ethylene **23** on the carbon atom of the nitrile oxide, whereas the second C–O bond forms in the second stage of the reaction.[9] From the analysis of the IRC from **TS45** to **CA45** it is interesting to note the structure named half-point (**HP**), the reaction coordinate of which is shared by the two stages of the reaction.[9] The structure of **HP** is shown in Figure 4. The length of the C–C bond in this structure is 1.608 Å, whereas the distance

between the C and O atoms is 2.295 Å. The corresponding BO values, 0.91 and 0.35, indicate that whereas the formation of the C–C bond is complete, the C–O forming bond is very delayed.
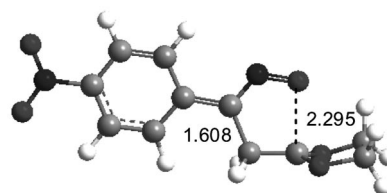

Figure 4. Structure of the half point (**HP**) of the IRC from **TS45** to **CA45**.

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.[23] 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-methylenephthalimine (**15**).[9] 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.[5a,7] To investigate whether this proposal has any validity, the solvent effects of dichloromethane (DCM) were studied through single-point energy calculations of the gasphase 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.

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, $\Delta\Delta E^{\#} < 1.8$ kcal/mol, and the higher polar character of the more unfavorable TSs, **TS35** and **TS55** (see Table 2). Therefore, polar solvents can diminish $\Delta\Delta E^{\#}$, 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 $\Delta\Delta E^{\#}_{DCM}$ as a consequence of the low regioselectivity in the gas phase, $\Delta\Delta E^{\#} = 0.3$ kcal/mol. However, in the 13DC reactions involving ER ethylenes, the large regioselectivity found in these reactions, $\Delta\Delta E^{\#} > 15.6$ 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, μ, chemical hardness, η, global electrophilicity, ω, and global nucleophilicity, N, for BNO dipoles and ethylene dipolarophiles are presented in Table 3.

Table 3. Electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), and global nucleophilicity (N) for BNOs and substituted ethylenes.

	μ [a.u.]	η [a.u.]	ω [eV]	N [eV]
NO$_2$PhCNO (**21**)	−0.1851	0.1480	3.15	2.07
CH$_2$=C(CN)$_2$ (**24**)	−0.2074	0.2075	2.82	0.65
CF$_3$PhCNO (**14**)	−0.1590	0.1775	1.94	2.38
Isoindole derivative **15**	−0.1394	0.1674	1.58	3.05
PhCNO (**9**)	−0.1406	0.1847	1.46	2.78
CH$_3$PhCNO (**25**)	−0.1356	0.1825	1.37	2.95
(CH$_3$)$_3$PhCNO (**2**)	−0.1311	0.1791	1.31	3.12
MeOPhCNO (**22**)	−0.1259	0.1804	1.19	3.24
Ethylene (**19**)	−0.1239	0.2855	0.73	1.86
HCNO (**1**)	−0.1249	0.2919	0.73	1.75
Propene (**10**)	−0.1133	0.2692	0.65	2.37
CH$_2$=C(OCH$_2$)$_2$ (**23**)	−0.0712	0.2682	0.26	3.53

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 process 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 π 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 π molecular orbitals in a narrow range of energy, that is, C–C and C–N triple bonds[8] or aromatic systems,[22b] the approximation based on HOMOs and LUMOs cannot provide the expected reactivity. This is the case with BNO derivatives in which some π 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

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

				f_k^-				f_k^+	
		HOMO–3	HOMO–2	HOMO–1	HOMO	LUMO	LUMO+1	LUMO+2	LUMO+3
NO$_2$PhCNO (**21**)	C	0.0046	0.0000	0.3407	0.1852	0.0111	0.0001	0.0698	0.4147
	N	0.0004	0.0000	0.0752	0.0811	0.0496	0.0000	0.0924	0.3191
	O	0.0058	0.0000	0.5349	0.3735	0.0430	0.0000	0.0534	0.1461
PhCNO (**9**)	C	0.1704	0.0000	0.3399	0.1600	0.0633	0.0001	0.4147	0.1552
	N	0.0063	0.0000	0.0745	0.0852	0.1197	0.0000	0.3178	–0.0851
	O	0.1826	0.0000	0.5450	0.3609	0.0789	0.0000	0.1438	0.0033
CH$_3$OPhCNO (**22**)	C	0.1600	0.0392	0.3415	0.0981	0.0706	0.0012	0.4110	0.1274
	N	0.0104	0.0033	0.0727	0.0794	0.1206	0.0015	0.3181	–0.0676
	O	0.1948	0.0498	0.5468	0.2744	0.0762	0.0009	0.1441	0.0024

HOMO and LUMO do not account for the reactivity of this molecule in 13DC reactions.[8] In this case, it is necessary to analyze the f_k^- value obtained from the HOMO-1 and the f_k^+ value obtained from the LUMO+2 to explain its reactivity. Thus, analysis of f_k^- indicates that the oxygen atom will be the more favorable center for an electrophilic attack ($f_k^- = 0.5450$), whereas analysis of the corresponding f_k^+ indicates that the carbon atom will be the more favorable center for a nucleophilic attack ($f_k^+ = 0.4147$). In addition, analysis of the f_k^- functions indicates that the carbon atom is also susceptible to electrophilic attack, and as a consequence, a lower regioselectivity will be expected for the 13DC reactions of BNO **9** with electrophiles.

The presence of an electron-releasing CH$_3$O group at the *para* position of benzene in the NBO **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 NBO **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.

Table 5. Local electrophilicity (ω_k) and nucleophilicity (N_k) indices of the BNOs, **9**, **21**, and **22** and the activated ethylenes **23** and **24**.

		ω_k [eV]	N_k [eV]
NO$_2$PhCNO (**21**)	C	1.31	
	N	1.01	
	O	0.46	
PhCNO (**9**)	C	0.60	0.95
	N	0.46	0.21
	O	0.21	1.52
CH$_3$OPhCNO (**22**)	C		1.11
	N		0.24
	O		1.77
ED ethylene (**24**)	C$_\alpha$	0.59	
	C$_\beta$	1.41	
ER ethylene (**23**)	C$_\alpha$		0.62
	C$_\beta$		1.96

Finally, the ED ethylene **24** and the ER ethylene **23** have the largest electrophilic and nucleophilic activation at the unsubstituted β position, $\omega_\beta = 1.41$ eV and $N_\beta = 1.96$ 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**

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, $\Delta\Delta E^{\#} < 2.0$ kcal/mol, can be affected by steric or polar solvent effects to produce greater stabilization of the more polar TS. Thus, mixtures of regioisomeric 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 check the energy profiles connecting each TS to the two associated minima of the proposed mechanism by using the second-order González–Schlegel integration method.[35] The electronic structures of the stationary points were analyzed by the NBO method.[36] All calculations were carried out with the Gaussian03 suite of programs.[37]

Solvent effects were considered at the same level of theory by performing single-point energy calculations on the gas-phase structures using a self-consistent reaction field (SCRF)[38] based on the polarizable continuum model (PCM) of Tomasi and co-workers.[39] Dichloromethane ($\varepsilon = 8.93$) was selected as a polar solvent.

The global electrophilicity index,[15] ω, is given by the following simple expression,[15] $\omega = (\mu^2/2\eta)$, where μ is the electronic chemical potential and η the chemical hardness. Both quantities may be approached through the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively.[40] Recently, we introduced an empirical (relative) nucleophilicity index, N, based on the HOMO energies obtained from the Kohn–Sham scheme[41] and defined as $N = E_{HOMO(Nu)} - E_{HOMO(TCE)}$.[21] The nucleophilicity index is referenced to tetracyanoethylene (TCE) because it has the lowest HOMO energy of a large number of molecules already investigated in the context of polar cycloaddition reactions. This choice has allowed us to conveniently handle a nucleophilicity scale of positive values.[21] Local electrophilicity[17] and nucleophilicity[22] indices, ω_k and N_k, were evaluated by using the following expressions: $\omega_k = \omega f_k^+$ and $N_k = N f_k^-$ where f_k^+ and f_k^- are the Fukui functions for nucleophilic and electrophilic attack, respectively.[26]

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