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Local nucleophile-electrophile interactions in [3+2] cycloaddition reactions between benzonitrile N-oxide and selected conjugated nitroalkenes in the light of MEDT computational study

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A B S T R A C T

The regioselectivity of the [3+2] cycloaddition reactions between benzonitrile N-oxide as three-atom component and two series of *para*-substituted β-nitrostyrene analogues was analysed in the framework of a Molecular Electron Density Theory. All of the considered processes were found to be initiated by the attack of the most nucleophilic oxygen atom in the benzonitrile N-oxide on the most electrophilic carbon atom (C_α) in the nitroalkenes. This type of interaction favours the formation of 4-nitro-substituted Δ^2-isoxazolines.

1. Introduction

Recently, the interest of heterocyclic compounds has been growing steadily. Due to the fact that most of them have biological effects, they are being tested for pharmacological uses. In this group, isoxazolines (4,5-dihydroisoxazoles) are one of the most important 5-membered heterocycles. They are a precursors of synthesis of to many multi-functional compounds such as β-hydroxyketones and nitriles, α,β-unsaturated ketones and oximes, β-amino acids.[1-3] In addition, they are also substrates to obtain azaheterocycles.[4,5] Isoxazolines widely spread out as biological and pharmacological substances.[6] They show potency to fight bacteria[7,8] and antiviral,[9] so therefore they are commonly used as an anti-inflammatory[10-12] and analgesic drugs.[11-13] Isoxazolines can also be successfully used in antipsychotic therapy drugs for the treatment of schizopchrenia, bipolar disorder and irritability associated with autism.[14] The most popular medicines such as *Zonisamid*[15] and *Risperidone*,[16] contain isoxazoline ring in their structure. Moreover, isoxazolines, like the others compounds of azoles group, are reported to possess anticancer.[17,18]

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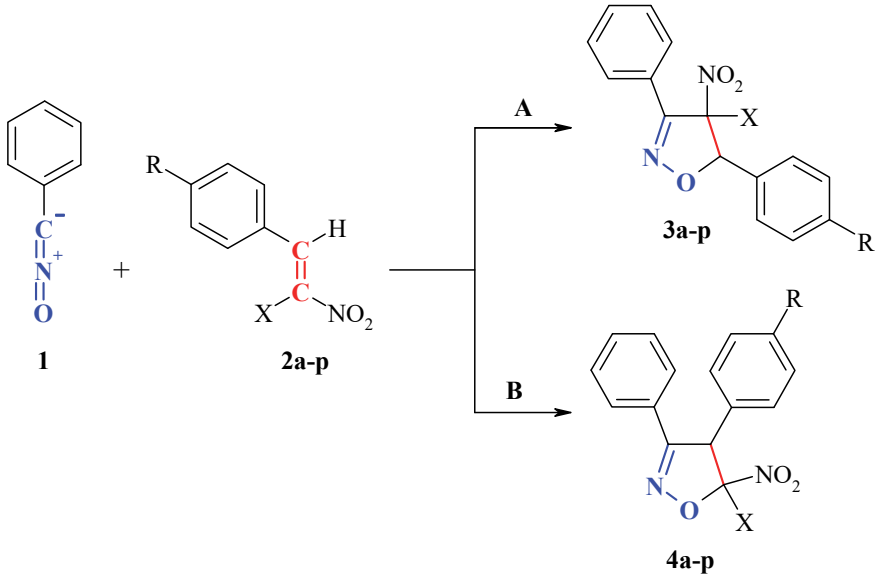
A several methods for the synthesis of isoxazolines are known, but one of the most prevalent is [3+2] cycloaddition process (32CA).[19-20] Reaction allows obtaining isoxazolines with *"full atomic economy"* and retention of primary conformation of substrates.[21-22] Most of the synthesis reactions of isoxazolines in a course of [3+2] cycloaddition are realised under mild, non catalyst, condition giving high yields.[21-23] These conditions approach one of the main principles of green chemistry. Moreover, using conjugated nitroalkenes as one of the addents, allows the reaction to proceed in a highly regioselective.[24] Additionally, the usage of this type of alkenes is interesting due to several aspects. On one hand, the introduction of a nitro group into the ring, provides the possibility of transformation isoxazolines via *Nef* reaction,[25] *Mukuiyama* reaction,[26] *Henry* reaction and many others.[25-26] On the other hand, the presence of a nitro group in a chemical compounds stimulate their biological activity.[27] That fact makes nitroalkenes even more attractive in terms of pharmacological applications.[28]

In this paper we decided to analyze regioselectivity of the reaction with the participation of representative conjugated nitroalkenes and the model of nitrile N-oxide. For this purpose, we explored the nature of the global and local interaction between the addents in an elementary cycloaddition step. In a role of dipolarophile, we selected two series of *para*-substituted β-nitrostyrene analogues (**2a-p**). These nitroalkenes has been popular tested in different cycloaddition reactions.[21,27,29] In turn, as three atoms component (TAC), we decided to apply benzonitrile N-oxide (**1**). For such selected addents the [3+2] cycloaddition reaction may theoretically proceed via two competitive reaction channels giving 4- and 5-nitro-substituted Δ^2-isoxazolines (respectively **3a-p** and **4a-p**) (see **Scheme 1**). We hope that our study will be helpful for better understanding the nature of 32CA including electron deficient ethenes.



Scheme 1. Theoretically possible paths for [3+2] cycloadditions between benzonitrile N-oxide (**1**) and
para-substituted β-nitrostyrene analogues (**2a-p**).

2. Computational methods

All quantum-chemical calculations reported in this paper were performed using the B3LYP functional along with the 6-31G(d) basis set included in the GAUSSIAN 09 package.[30]

Global reactivity indices (electronic chemical potential μ, chemical hardness η, global electrophilicity ω, global nucleophilicity N) were estimated according to the equations recommended by *Parr*[31] and *Domingo*.[32-34] In particular, the electronic chemical potential and chemical hardness of the reactants studied here were evaluated in terms of the one-electron energies of the frontier molecular orbitals using the following equations:[32,33]

$$\mu \approx (E_{HOMO} + E_{LUMO})/2$$
$$\eta \approx E_{LUMO} - E_{HOMO}$$

Next, the values of μ and η were then used for the calculation of global electrophilicity (ω) according to the formula:[34]

$$\omega = \mu^2/2\eta$$

The local electrophilicity (ω_k) condensed to atom k was calculated by projecting the index ω onto any reaction centre k in the molecule by using *Parr* functions P^+_k:[35]

$$\omega_k = P^+_k \cdot \omega$$

The global and local electronic properties of the reactants considered in this work are collected in **Table 1** and **Table 2**.

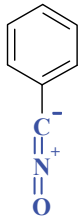


Table 1. Global and local electronic properties of benzonitryle N-oxide (**1**).

No	Global properties			Local properties			
	μ (eV)	η (eV)	ω (eV)	P^-_O	P^-_C	N_O (eV)	N_C (eV)
1	−3.83	5.02	1.46	0.54	0.01	1.49	0.03

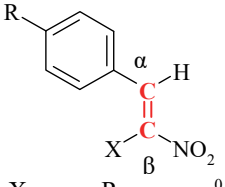


Table 2. Global and local electronic properties of *para*-substituted β-nitrostyrene analogues (**2a–p**).

X	R	σp^0	No	Global properties			Local properties			
				μ	η	ω	$P^+_{C\alpha}$	$P^+_{C\beta}$	ω_α	ω_β
H	**NMe_2**	−0.83	**2a**	−3.85	3.45	2.15	0.06	0.27	0.57	0.13
	OMe	−0.27	**2b**	−4.35	3.92	2.42	0.07	0.26	0.55	0.16
	Me	−0.17	**2c**	−4.63	4.18	2.56	0.09	0.24	0.51	0.18
	H	0.00	**2d**	−4.79	4.31	2.66	0.09	0.24	0.51	0.19
	Cl	0.23	**2e**	−4.90	4.16	2.88	0.10	0.22	0.47	0.22
	CF_3	0.54	**2f**	−5.18	4.38	3.06	0.11	0.20	0.42	0.25
	CN	0.66	**2g**	−5.32	4.19	3.38	0.13	0.15	0.33	0.27
	NO_2	0.78	**2h**	−5.58	4.21	3.70	0.11	0.11	0.24	0.24
Br	**NMe_2**	−0.83	**2i**	−3.94	3.31	2.35	0.04	0.31	0.73	0.09
	OMe	−0.27	**2j**	−4.41	3.72	2.62	0.06	0.30	0.70	0.14
	Me	−0.17	**2k**	−4.65	3.93	2.75	0.07	0.28	0.66	0.16
	H	0.00	**2l**	−4.79	4.04	2.84	0.07	0.28	0.66	0.16
	Cl	0.23	**2m**	−4.91	3.92	3.07	0.09	0.26	0.61	0.21
	CF_3	0.54	**2n**	−5.14	4.08	3.23	0.10	0.24	0.56	0.23
	CN	0.66	**2o**	−5.29	3.93	3.56	0.12	0.20	0.47	0.28
	NO_2	0.78	**2p**	−5.49	3.92	3.85	0.10	0.15	0.35	0.23

3. Results and Discussion

To investigate the regioselectivity of [3+2] cycloaddition reactions between benzonitrile N-oxide (**1**) and para-substituted analogues of β-nitrostyrene (**2a-p**), we analyzed electronic intermolecular interactions in the framework of Molecular Electron Density Theory (MEDT). The respective global

and local indices were then estimated using equations defined on the basis of conceptual density functional theory.[36-39] Recently, similar approach was successfully used to explain the paths followed by a number of different biomolecular processes (see for example[40-43]).

According to the data in the **Table 1**, the global electrophilicity of benzonitrile N-oxide (**1**) is 1.46 eV. In *Domingo* scale compound (**1**) should be classified as a moderate electrophile.[33] According to the same scale,[33] the first series of tested *para*-substituted analogues of β-nitrostyrene (X=H) (**2a-h**) can be classified as a strong electrophiles (see **Table 2**), because their electrophilicity are in the range 2.15 – 3.70 eV. It should be noted that, benzonitrile N-oxide (**1**) is characterised by a relative lower global electrophilicity than the first series of nitroalkenes (X=H) (**2a-h**). In particular, analogues of β-nitrostyrene (X=H) (**2a-h**) substituted in the *para*-position in benzene ring by an electron-withdrawing group (EWG) have a relative higher value of the global electrophilicity (see **Table 2**). For instance, when β-nitrostyrene is substituted by electron donating dimethylamine group in *para*-position the global electrophilicity is 2.15 eV, for comparison for nitro group ω = 3.70 eV. Next, in the same way, we analysed a global electronic properties of β-bromosubstituted analogues of *para*-substituted analogues of β-bromo-β-nitrostyrene (X=Br) (**2i-p**). It was found, that the replacement of hydrogen atom with bromine atom increases the values of the electrophilic properties of the molecule about 0.2 eV (ω = 2.35 – 3.85 eV) compared to analogues of β-nitrostyrene (X=H) (**2a-h**) (see **Table 2**). Therefore, according to *Domingo* scale[33] β-bromo-β-nitroalkenes (X=Br) (**2i-p**) can be classified as strong electrophiles (see **Table 2**), because their electrophilicity is in the range 2.15 – 3.70 eV.

To sum up, in the analyzed reactions, benzonitrile N-oxide (**1**) will perform a role of an electron donor, while the *para*-substituted analogues of β-nitrostyrenes (**2a-p**) will perform a role of an electron acceptors. Moreover, according to the MEDT role, the interaction between the tested components should be evidently classified as polar processes.[36]

Next, we analyzed the local reactivity for different pairs of the reactants. In order to determine the values of the local reactivity of benzonitrile N-oxide (**1**) firstly, we calculated global nucleophilicity index (N) from the equation:[34]

$$\mathbf{N = E_{HOMO} - E_{HOMO\ (tetracyanoethene)}}$$

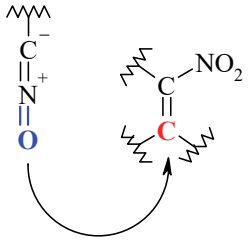
where the HOMO energy for tetracyanoethylene (TCE) is taken as a reference.

The local nucleophilicity (N_k) condensed to atom k was calculated using global nucleophilicity N and *Parr* functions P^-_k according to the formula:[35]

$$\mathbf{N_k = P^-_k \cdot N}$$

It was found, that the strongly nucleophilic reaction center for benzonitrile N-oxides (**1**) is situated on the oxygen atom on the CNO fragment (N_O = 1.49 eV). In turn, the strongest electrophilic reaction center for *para*-substituted analogues of β-nitrostyrene (**2a-p**) is always situated on the α atom of the nitrovinyl fragment in the nitroalkenes (ω_α = 0.24 – 0.73 eV). According to MEDT, the regioselectivity of cycloaddition can be determined by interaction more electrophilic center located on the electrtophile with more nucleophilic center from compound which is nucleophile for analysed reaction (see **Scheme 2**). If we assume that these centers govern the reaction path, more preferred one should be forming of 4-nitro-substituted Δ^2-isoxazolines (**3a-p**).

The obtained results are compatible with an experimental data. According to *Cholewka,*[44] in a reaction between benzonitrile N-oxide (**1**) and β-nitrostyrene (**2d**) both possible cycloadducts (**3d** and **4d**) are synthesized (see **Scheme 2**). In this process, 4-nitro-substituted Δ^2-isoxazoline (**3d**) is formed in excess with yield of 52%, while the second possible regioisomer, 5-nitro-substituted Δ^2-isoxazoline (**4d**), is formed with yield of 21%. Similar results were also presented by other Authors.[45]



Scheme 2. The local interaction of 32CA between nitrile N-oxides (**1**) and considered nitroalkenes (**2a-p**).

4. Conclusions

The Molecular Electron Density Theory analysis of global properties for all [3+2] cycloadditions has shown that benzonitrile N-oxides can be classified as a nucleophile, while tested *para*-substituted analogues of β-nitrostyrene play a role of electrtophile. DFT calculation also has shown that the more preferred reaction path is the formation of 4-nitro-substituted Δ^2-isoxazolines. The quantum-chemical calculations correlate well with observed regioselectivity.

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