Current Chemistry Letters 12 (2023) 421–430

Contents lists available atGrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

The global and local Reactivity of C,N-diarylnitryle imines in [3+2] cycloaddition processes with trans-β-nitrostyrene according to Molecular Electron Density Theory: A computational study

Mikołaj Sadowski[a], **Jolanta Utnicka**[a], **Adrianna Wójtowicz**[a] **and Karolina Kula**[a*]

[a]*Department of Organic Chemistry and Technology, Cracow University of Technology, Warszawska 24, 31-155, Cracow, Poland*

C H R O N I C L E

Article history:
Received July 3, 2022
Received in revised form
August 2, 2022
Accepted November 24, 2022
Available online
November 24, 2022

Keywords:
Nitrilimine
[3+2] Cycloaddition Reaction
Conceptual Density Functional Theory
Molecular Electron Density Theory
Regioselectivity

A B S T R A C T

The regioselectivity of the [3+2] cycloaddition reactions between *trans*-β-nitrostyrene and C,N-diarylnitryle imine analogues as three atom components (TACs) has been studied with the use of Conceptual Density Functional Theory in the framework of Molecular Electron density Theory. Global and local reactivity indices were determined. Presented quantum-chemical computations showed that, for the reaction of nitroalkene with diphenylnitryle imine, the most favourable reaction path is determined by the nucleophilic attack of C3 carbon atom of TAC on an electrophilic C_α carbon atom of nitroalkene. Therefore, the creation of 1,3,4-triphenyl-5-nitro-Δ^2-pyrazoline, according to channel B, is more probable. Similarly, to presented conclusion, for reactions of nitroalkene with nitryle imines containing an ED group at *para* position of the phenyl ring also the most favourable reaction paths run through channel B leading to 1,3,4-triaryl-5-nitro-Δ^2-pyrazolines. In turn, reactions of nitroalkene with nitryle imines containing an EW group at *para* position of the phenyl ring have the opposite preference and the most favourable reaction paths is channel A leading to 1,3,5-triaryl-4-nitro-Δ^2-pyrazolines.

1. Introduction

Heterocyclic chemistry is currently one of the most dynamically developing branches of science [1-3]. New compounds of this class are still wanted, due to wide application of these compounds, both in medicine as well as in industry[4-9]. Among all five- and six-membered nitrogen-containing heterocycles like 1,2-oxazolidine analogues of nicotine[10], isoxazolines[11,12], and pyrrolidines[13], the pyrazoline system is becoming more and more popular (**Fig. 1**)[14-17].

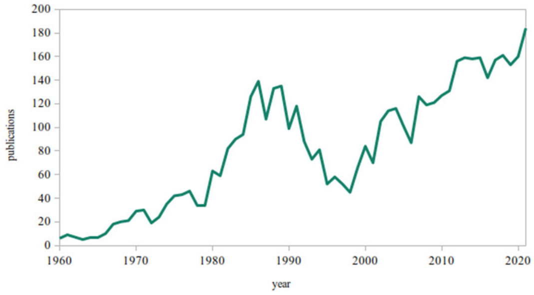


Fig. 1. Publications on pyrazolines indexed by Scopus database[18] since 1960.

---

* Corresponding author.
E-mail address karolina.kula@pk.edu.pl (K. Kula)

doi: 10.5267/j.ccl.2022.11.004

Pyrazolines (dihydropyrazoles) are five-membered heterocyclic organic compounds containing two adjacent nitrogen atoms. The double bond is situated within the heterorganic ring. Depending on the position of the double bond one can distinguish Δ^1-, Δ^2- as well as Δ^3-pyrazolines (**Fig. 2**)[14,15,19].

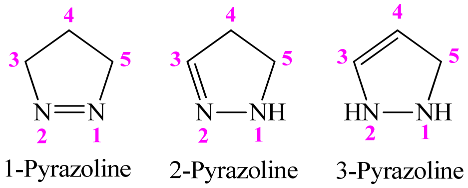


Fig. 2. Structures and atom numeration of pyrazoline ring.

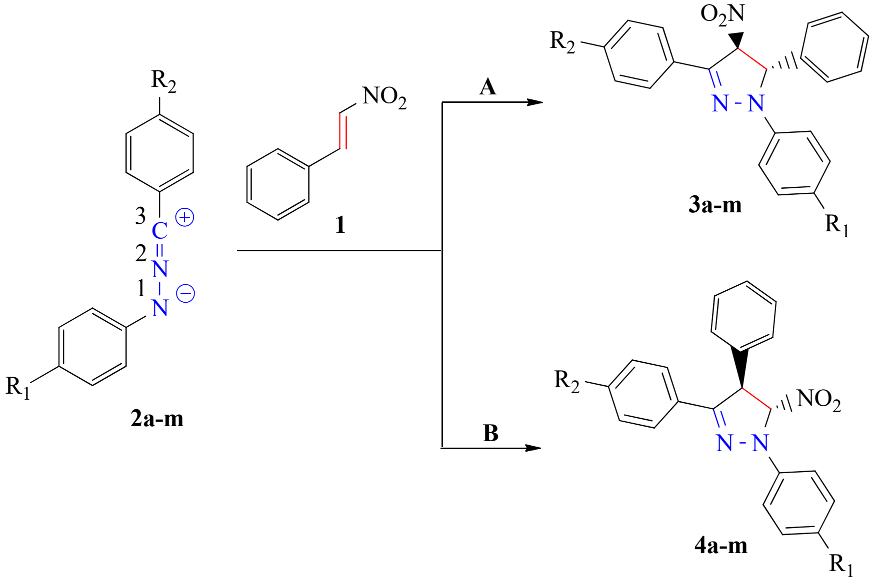
There are several methods of pyrazoline synthesis. The most common include cyclocondensation of α,β-unsaturated carbonyl with hydrazine[20], 1,3-alkylation of hydrazines with 1,3-dihalo-propanes[21], intramolecular cyclization of hydrazones[22] as well as [3+2] cycloaddition (32CA) reaction of alkene with diazocompounds (Δ^1-pyraolines), nitrylimines (Δ^2-pyrazolines) as well as azomethine imines (Δ^3-pyrazolines)[23,24]. Among other synthetic methods, 32CA reactions are the most universal. Depending on the three atom components (TACs)[25] used, it is possible to obtain a pyrazoline containing the double bond in different positions[26,27].

In the framework of this paper, the regioselectivity for synthesis of new nitro substituted analogues of Δ^2-pyrazolines was studied. For this purpose, as the model nitroalkene the *trans*-β-nitrostyrene (**1**) was selected. This nitroalkene can be characterized by high reactivity in organic synthesis, ability to insert both sterically crowded phenyl groups as well as extremely active and easy to convert NO_2 group, which additionally stimulates biological activity of nitroalkenes[28-30]. In turn, in a role of TACs we decided to use a series of C,N-diarylnitryle imines **2a-m**. For such defined addents, reactions can be theoretically realised by two regioisomeric paths, leading to cycloadducts with the nitro group at 4 (**3a-m**) or 5 (**4a-m**) position (**Scheme 1**).

Similar reactions, including 32CAs between 2-aryl-1-cyano-1-nitroethenes and diarylnitryle imines were recently tested by us. The DFT computational study of these reactions shown, that the polar processes of nitryle imines with nitroalkenes are realised through the interaction of C_α carbon atom of nitroalkene with the carbon atom of –N=N=C– nitrile imine fragment. However, the regioselectivity of not all studied 32CA reactions could have been determined due to the non-polar nature of these processes[31].

Presented research is a continuation of studies of electronic properties of nitroalkenes and different types of TACs, and the studies of selectivity of 32CA reactions including these addents[32]. For this purpose, the Conceptual Density Functional Theory (CDFT) in the framework of Molecular Electron Density Theory (MEDT)[33] was applied.

	R_1	**R_2**
2a	$N(CH_3)_2$	H
2b	OCH_3	H
2c	CH_3	H
2d	Cl	H
2e	CF_3	H
2f	CN	H
2g	**H**	**H**
2h	H	$N(CH_3)_2$
2i	H	OCH_3
2j	H	CH_3
2k	H	Cl
2l	H	CF_3
2m	H	CN



Scheme 1. Theoretically possible 32CA reaction paths between *trans*-β-nitrostyrene (**1**) and C,N-diarylnitryle imines **2a-m**.

CDFT is a branch of density functional theory, developed by American theoretical chemist *Robert Parr* in the end of 20th century. CDFT's approach is to connect well established chemical concepts, like electronic chemical potential μ and chemical hardness η, with electronic structure of a molecule, thus allowing those values to be computed. Based on those, the indication of global electronic properties of substrates can be made. As an effect, it is possible to assign addends to either the role of electrophile or nucleophile in studied reaction (**Table 1**). Furthermore, with application of either *Parr* or *Fukui* functions, not only global, but also local electronic properties of a molecule can be estimated[34] thus allowing to predict reactivity of molecules in the studied reaction, based only on substrates structure[35].

Table 1. Global electrophile and nucleophile scale according to Domingo[34,36].

Electrophile				Nucleophile			
Marginal	Moderate	Strong	Super	Marginal	Moderate	Strong	Super
$\omega < 0.8$	$0.8 < \omega < 1.5$	$1.5 < \omega < 3.0$	$\omega \geq 3.0$	$N < 2.0$	$2.0 < N < 3.0$	$3.0 < N < 4.0$	$N \geq 4.0$

In turn, MEDT is an approach, established by Spanish theoretical chemist *Luis Ramon Domingo*, in an effort to assess reactivity of compound based on electron density distribution $\rho(x,y,z)$ in molecule. MEDT is the next step for rationalisation of chemical reactivity, after valence bond theory and frontier molecular orbital theory. In contrast to previous theories, MEDT is based on electron density instead of wave functions $\Psi(x,y,z)$[27]. Electron density distribution $\rho(x,y,z)$ in contrast to wave functions can be measured, whereas wave functions are solutions of Shrödinger's equation, and are purely mathematical constructs ($\rho(x,y,z) = |\Psi(x,y,z)|^2$). The application of electron density also simplifies computations[37].

2. Results and Discussion

2.1. Global electronic properties

In the first part of our research, we decided to shed light on global electronic properties for *trans*-β-nitrostyrene (**1**) and C,N-diarylnitryle imines **2a-m** in order to investigate the nature of their interactions. All of global reactivity indices, namely electronic chemical potential μ, chemical hardness η, global electrophilicity ω, global nucleophilicity N, were determined via calculations based on B3LYP/6-31G(d) theory level in the gas phase[34,38,39] and are given in **Table 2**.

Table 2. Global electronic properties for the studied addents.

		μ [eV]	η [eV]	ω [eV]	N [eV]
1		-4.79	4.31	**2.66**	2.17
2a	N-position ED group	-2.96	3.39	1.29	**4.47**
2b		-3.14	3.60	1.37	**4.18**
2c		-3.29	3.72	1.45	**3.99**
2d	N-position EW group	-3.58	3.77	1.70	**3.84**
2e		-3.54	3.62	1.73	**3.77**
2f		-3.71	3.54	1.95	**3.64**
2g		-3.37	3.78	1.50	**3.86**
2h	C-position ED group	-2.92	3.97	1.07	**4.21**
2i		-3.16	3.94	1.27	**3.99**
2j		-3.29	3.80	1.43	**3.93**
2k	C-position EW group	-3.57	3.71	1.72	**3.84**
2l		-3.59	3.36	1.91	**3.82**
2m		-3.72	3.33	2.07	**3.70**

Table 2 shows that the electronic chemical potential[34] of *trans*-β-nitrostyrene (**1**), μ = -4.79, is lower when compared to μ of all C,N-diarylnitryle imines **2a-m**. It means that the flux of the electron density will take place from TACs **2a-m** to nitroalkene **1** (**Fig. 3**). Thus, all studied 32CA reactions can be classified as the forward electron density flux (FEDF)[40].

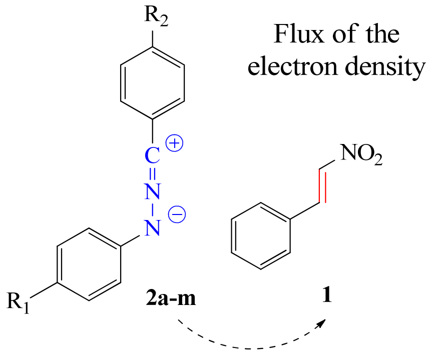


Fig. 3. Flux of the electron density in 32CA reaction paths between *trans*-β-nitrostyrene (**1**) and C,N-diarylnitryle imines **2a-m**.

Polar cycloaddition reactions require the participation of good electrophiles and good nucleophiles. Useful information about the polarity of a reaction may be obtained from the difference in the global electrophilicity between components involved in the reaction $\Delta\omega$. The polarity of the processes can be related with nonpolar reactions, when $\Delta\omega < 1$ eV, or polar reactions, when $\Delta\omega > 1$ eV[41,42]. The global electrophilicity power $\Delta\omega$ for all studied 32CAs were determined and are given in **Table 3**.

Table 3. Global electrophilicity power $\Delta\omega$ of studied reactions.

Reaction	**1 + 2a**	**1 + 2b**	**1 + 2c**	**1 + 2d**	**1 + 2e**	**1 + 2f**	**1 + 2g**	**1 + 2h**	**1 + 2i**	**1 + 2j**	**1 + 2k**	**1 + 2l**	**1 + 2m**
$\Delta\omega$ [eV]	1.37	1.29	1.21	0.96	0.93	0.71	1.16	1.59	1.39	1.23	0.94	0.75	0.59

The global electrophilicity power $\Delta\omega$[41] index for the 32CA reaction between *trans*-β-nitrostyrene (**1**) and diphenylnitryle imine (**2g**) is 1.16 eV (**Table 3**). For this reason, this 32CA reaction should be classified as polar [36,41,42]. Introduction of an electron donating (ED) group like –$N(CH_3)_2$ (**2a** and **2h**), –OCH_3 (**2b** and **2i**) or –CH_3 (**2c** and **2j**) at *para* position of the phenyl ring in diphenylnitryle imine (**2g**), irrespectively which phenyl ring is substituted, slightly increases the global electrophilicity power $\Delta\omega$ indices for 32CA reactions of these nitrile imines (**2a-c** and **2h-j**) with nitroalkene **1** (**Table 3**). As a consequence, these 32CA reactions should also be classified as of a polar character[36,41,42]. In turn, introduction of electron withdrawing (EW) group like –Cl (**2d** and **2k**), –CF_3 (**2e** and **2l**) or –CH_3 (**2f** and **2m**) at *para* position of the phenyl ring in diphenylnitryle imine (**2g**), irrespectively which phenyl ring is substituted, slightly reduces the global electrophilicity power $\Delta\omega$ indices for 32CA reactions of these nitrile imines (**2d-f** and **2k-m**) with nitroalkene **1** (**Table 3**). Therefore, these 32CA reactions should be classified on the borderline between polar and non-polar processes[36,41,42].

Calculated electrophilicity index ω[38] of *trans*-β-nitrostyrene (**1**) is 2.66 eV and the calculated nucleophilicity [39] N index for this compound **1** is 2.17 eV (**Table 2**). These values give the conclusion that nitroalkene **1** can be classified on the borderline between strong and super-electrophile as well as on the borderline between marginal and moderate nucleophile in a polar reaction within the electrophilicity and nucleophilicity scale[34,36].

Calculated electrophilicity index ω of diphenylnitryle imine (**2g**) is 1.50 eV and the calculated nucleophilicity N index for this compound **2g** is 3.86 eV (**Table 2**). These values give the conclusion that the TAC **2g** can be classified on the borderline between moderate and strong electrophile as well as on the borderline of strong and super-nucleophile in a polar reaction within the electrophilicity and nucleophilicity scale[34,36].

Introduction of an ED group like –$N(CH_3)_2$ (**2a** and **2h**), –OCH_3 (**2b** and **2i**) or –CH_3 (**2c** and **2j**) at *para* position of the phenyl ring in diphenylnitryle imine (**2g**), independently which phenyl ring is substituted, changes global properties of these compounds insensibly. In particular, electrophilicity indices ω of these TACs are slightly reduced, 1.29 (**2a**), 1.37 (**2b**), 1.45 (**2c**), 1.07 (**2h**), 1.27 (**2i**), 1.43 (**2j**) respectively (**Table 2**), as well as their nucleophilicity indices N are slightly increased, 4.47 (**2a**), 4.18 (**2b**), 3.99 (**2c**), 4.21 (**2h**), 3.99 (**2i**), 3.93 (**2j**) respectively (**Table 2**).

In turn, introduction of an EW group like –Cl (**2d** and **2k**), –CF_3 (**2e** and **2l**) or –CH_3 (**2f** and **2m**) at *para* position of the phenyl ring in diphenylnitryle imine (**2g**), independently which phenyl ring is substituted, also changes global properties of these compounds insensibly. In particular, electrophilicity indices ω of these TACs are slightly reduced, 1.70 (**2d**), 1.73 (**2e**), 1.95 (**2f**), 1.72 (**2k**), 1.91 (**2l**), 2.07 (**2m**) respectively (**Table 2**), as well as their nucleophilicity indices N slightly increase, 3.84 (**2d**), 3.77 (**2e**), 3.64 (**2f**), 3.84 (**2k**), 3.82 (**2l**), 3.70 (**2m**) respectively (**Table 2**).

Presented values lead to conclusions that C,N-diarylnitryle imines including ED group **2a-c** and **2h-j** can be classified on the borderline between moderate and strong electrophiles as well as super-nucleophiles in a polar reaction, while C,N-diarylnitryle imines including ED group **2d-f** and **2k-m** can be classified as strong electrophiles and also strong nucleophiles in a polar reaction within the electrophilicity and nucleophilicity scale [28,30]. In summary, **Table 4** illustrates the trend in change of global electrophilicity and nucleophilicity of C,N-diarylnitryle imines **2a-m**.

Table 4. Visualisation of changes of global electronic properties parameters depending on the presence of ED or EW substituent in *para* position of phenyl ring in diphenylnitryle imine (**2g**), together with values of Hammett[43] constant (σ_p).

Substituent	$N(CH_3)_2$	OCH_3	CH_3	H	Cl	CF_3	CN
σ_p	−0.83	−0.27	−0.17	0	+0.23	+0.54	+0.66
ω	→	→	→	→	→	→	→
N	←	←	←	←	←	←	←

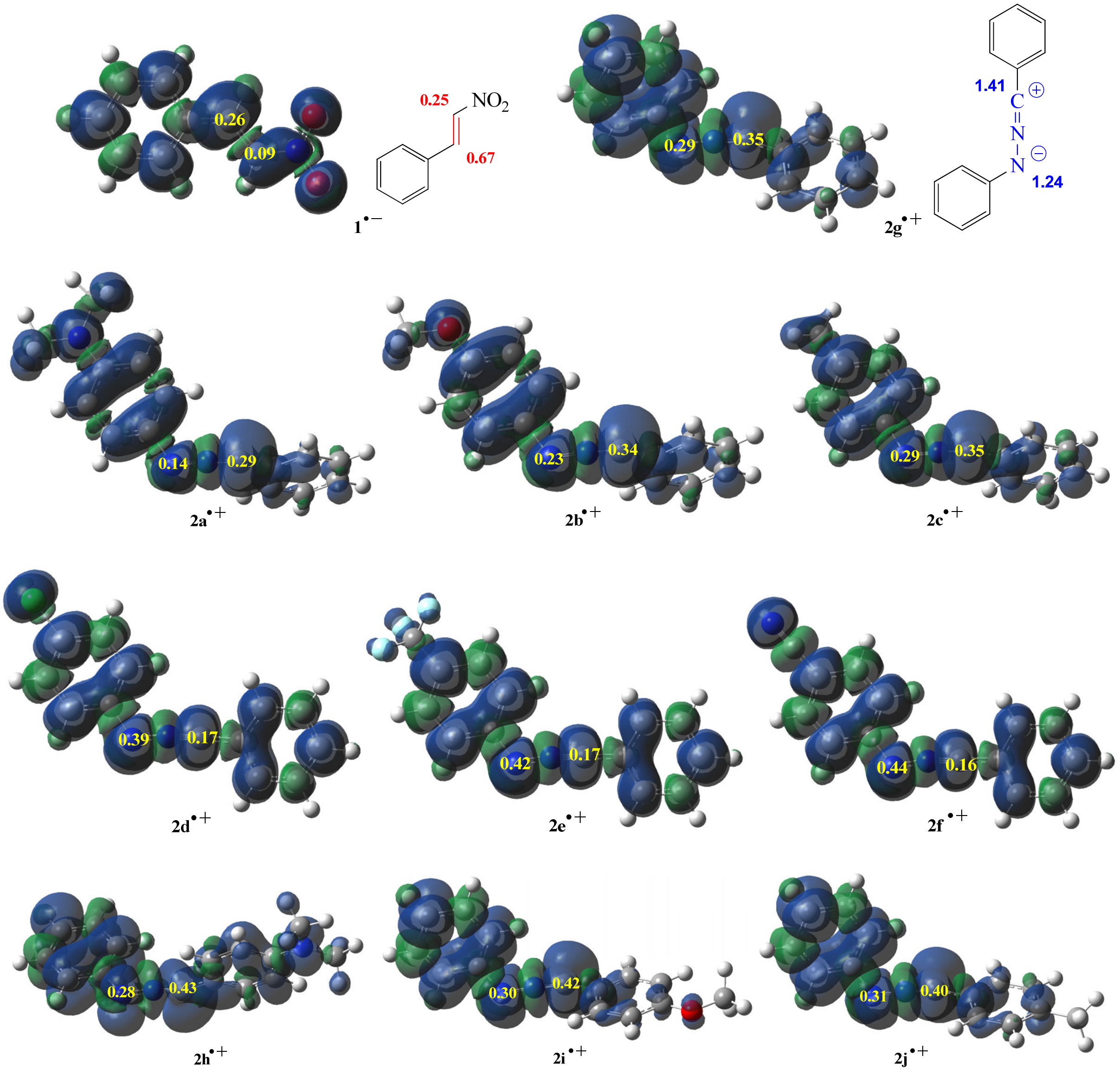
Overall, in all studied 32CA reactions one can assume that *trans*-β-nitrostyrene (**1**) will participate as electrophilic component, while studied C,N-diarylnitryle imines **2a-m** will play a role of nucleophilic substrates. The present information is an important conclusion, as in the cycloaddition reaction the regioselectivity of polar reaction including the participation of non-symmetric reagents can be determined through interaction between the most electrophilic centre of the electrophile and the most nucleophilic centre of the nucleophile[36,38,39].

2.2. Local electronic properties

The studied 32CA reactions between *trans*-β-nitrostyrene (**1**) and C,N-diarylnitryle imines **2a-m** hypothetically can create two regioisomeric products (**Scheme 1**). In order to characterise the most nucleophilic and the most electrophilic centres of the species involved in these 32CA reactions, the electrophilic P_k^+ and nucleophilic P_k^- Parr functions[44] together with local electrophilicity ω_k and local nucleophilicity N_k of *trans*-β-nitrostyrene (**1**) and C,N-diarylnitryle imines **2a-m** were analysed (**Fig. 4**).

Analysis of the electrophilic P_k^+ Parr functions of *trans*-β-nitrostyrene (**1**) indicates that the C_α carbon atom of ethylene fragment is the most electrophilic centre of this species, presenting the maximum value $P_{C\alpha}^+ = 0.26$. At this atom, the value of the local electrophilicity index ω_k is $\omega_{C\alpha} = 0.67$ eV (**Fig. 4**).

Analysis of the nucleophilic P_k^- Parr functions of diphenylnitryle imine (**2g**) indicates that the C3 carbon atom of nitrile imine fragment is the most nucleophilic centre of this species, presenting the maximum value $P_{C3}^- = 0.35$. At this atom, the value of the local nucleophilicity index N_k is $N_{C3} = 1.41$ eV (**Fig. 4**).



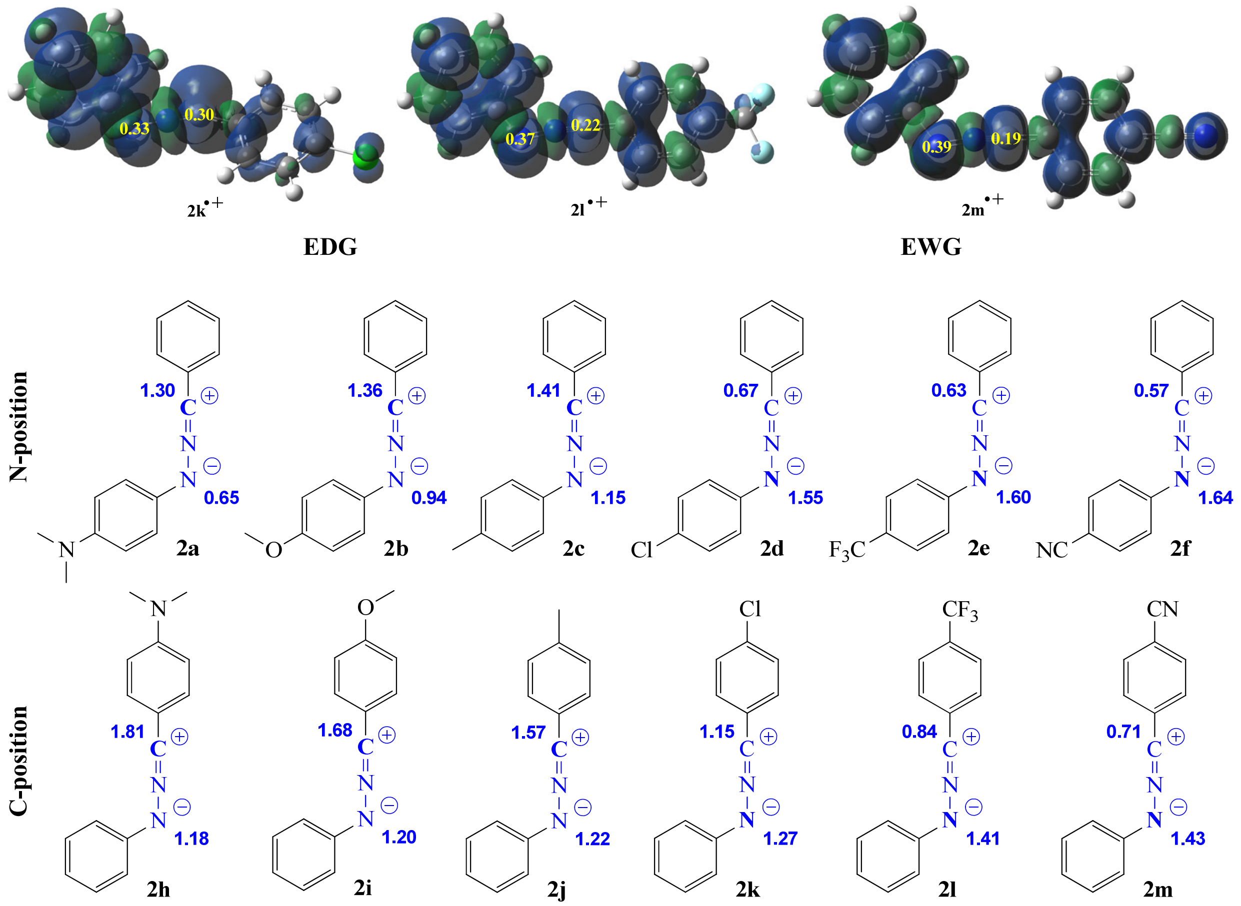


Fig. 4. The local electronic properties of substrates **1** and **2a-m** presented as three-dimensional representations (3D) of Mulliken atomic spin densities for the nitroalkene $\mathbf{1}^{\cdot-}$ radical anions and C,N-diarylnitryle imines $\mathbf{2a\text{-}m}^{\cdot+}$ radical cations, together with the electrophilic P_k^+ Parr functions of **1** and the nucleophilic P_k^- Parr functions of **2a-m**, given in yellow, as well as the indexes of the local electrophilicity ω_k of **1**, given in red, and the local nucleophilicity N_k of **2a-m**, given in blue.

Introduction of an ED group at *para* position of the phenyl ring in diphenylnitryle imine (**2g**), independently which phenyl ring is substituted, does not change the position of the most nucleophilic center in nitrile imine fragment. Invariably, the C3 carbon atom presents the maximum value $P_{C3}^- = 0.29$ (**2a**); 0.34 (**2b**); 0.35 (**2c**); 0.43 (**2h**); 0.42 (**2i**) and 0.40 (**2j**). At this atom, the values of the local nucleophilicity index are $N_{C3} = 1.30$ (**2a**); 1.36 (**2b**); 1.41 (**2c**); 1.81 (**2h**); 1.68 (**2i**) and 1.57 (**2j**) eV (**Fig. 4**).

In turn, introduction of an EW group at *para* position of the phenyl ring in diphenylnitryle imine (**2g**), independently of which phenyl ring is substituted, changes the position of the most nucleophilic centre in the nitrile imine fragment. For these species, the nitrogen N1 atom presents the maximum value $P_{N1}^- = 0.39$ (**2d**); 0.42 (**2e**); 0.44 (**2f**); 0.35 (**2k**); 0.37 (**2l**) and 0.39 (**2m**). At this atom, the values of the local nucleophilicity index N_k are $N_{N1} = 1.55$ (**2d**); 1.60 (**2e**); 1.64 (**2f**); 1.27 (**2k**); 1.41 (**2l**) and 1.43 (**2m**) eV (**Fig. 4**).

In summary, based on CDFT theory for the reaction of *trans*-β-nitrostyrene (**1**) with diphenylnitryle imine (**2g**) the most favourable reaction path is determined by the nucleophilic attack of C3 carbon atom of TAC **2g** on electrophilic C_α carbon atom of nitroalkene **1**. Therefore, the creation of 1,3,4-triphenyl-5-nitro-Δ^2-pyrazoline (**4g**), according to channel B, as the most favoured regioisomer is more probable. Similarly, to presented conclusion, for reactions of *trans*-β-nitrostyrene (**1**) with nitryle imines **2a-c** and **2h-j** including an ED group at *para* position of the phenyl ring in diphenylnitryle imine (**2g**) (independently which phenyl ring is substituted) also the most favourable reaction path is determined by the nucleophilic attack of C3 carbon atom of TACs **2a-c** and **2h-j** on the electrophilic C_α carbon atom of nitroalkene **1**. Consequently, the creation of 1,3,4-triaryl-5-nitro-Δ^2-pyrazolines **4a-c** and **4h-j**, according to channel B, as the most favoured regioisomers is more probable. In turn, for reactions of *trans*-β-nitrostyrene (**1**) with nitryle imines **2d-f** and **2k-m** containing an EW group at *para* position of the phenyl ring in diphenylnitryle imine (**2g**) (independently which phenyl ring is substituted) the most favourable reaction path is determined by the nucleophilic attack of N1 nitrogen atom of TACs

2d-f and **2k-m** on the electrophilic C_α carbon atom of nitroalkene **1**. Consequently, the creation of 1,3,5-triaryl-4-nitro-Δ^2-pyrazolines **3d-f** and **3k-m**, according to channel A, as the most favoured regioisomer is more probable.

3. Computational Details

All calculations were performed using the GAUSSIAN 09 D.01 package[45] at the Prometheus computer cluster of the CYFRONET regional computer centre in Cracow. The global reactivity descriptors of the addends, namely electronic potential μ, chemical hardness η as well as global electrophilicity ω and global nucleophilicity N, were approximated according to the equations recommended by Parr[38] and Domingo[34,36,39]. In the calculation we used the correlation-exchange functional B3LYP together with the basis level set of 6-31G(d) in the gas phase[34,39,46,47]. This theory level as well as phase are standard for the study of intermolecular interactions of addents in cycloaddition processes[48-51].

The electronic chemical potentials (μ) and chemical hardness (η) were evaluated in terms of one-electron energies of FMO (E_{HOMO} and E_{LUMO}) using the following equations[34,38,52]:

$$\boldsymbol{\mu \approx \tfrac{1}{2} \cdot (E_{HOMO} + E_{LUMO})} \tag{1}$$

$$\boldsymbol{\eta \approx E_{HOMO} - E_{LUMO}} \tag{2}$$

where E_{HOMO} and E_{LUMO} may be approached in terms of the one-electron energies of the frontier MOs respectively HOMO and LUMO. Next, values of μ and η were used to calculate a global electrophilicity (ω) according to the formula[34,39]:

$$\boldsymbol{\omega = \mu^2 / 2 \cdot \eta} \tag{3}$$

In turn, the global nucleophilicity (N) can be presented as follow[33]:

$$\mathbf{N = E_{HOMO} - E_{HOMO\,(TCE)}} \tag{4}$$

where $E_{HOMO\,(TCE)}$; the HOMO energy for tetracyanoethylene (TCE); is the reference, because it presents the lowest HOMO ($E_{HOMO\,(TCE)} = -9.368$ eV[39]).

Lastly, the local electrophilicity (ω_k) and the local nucleophilicity (N_k) concentrated on an atom k was calculated based on global properties and the Parr function (P_k^+ or P_k^-). according to the formulas[44]:

$$\boldsymbol{\omega_k = P_k^+ \cdot \omega} \tag{5}$$

$$\mathbf{N_k = P_k^- \cdot N} \tag{6}$$

GaussView program[53] was used to visualize molecular geometries of all the systems as well as to show 3D representations of the Mulliken spin densities for radical anion and the radical cations.

4. Conclusions

The regioselectivity of the [3+2] cycloaddition reactions between *trans*-β-nitrostyrene and C,N-diarylnitryle imine analogues as three atom components has been studied with the use of Conceptual Density Functional Theory in the framework of Molecular Electron density Theory. For this purpose, global and local reactivity indices were determined.

The analysis of the electronic chemical potential shows that the flux of the electron density will take place from TACs to nitroalkene and processes can be classified as FEDF. The global electrophilicity power indices exhibit that in case of reactions between *trans*-β-nitrostyrene and diphenylnitryle imine as well as its analogues including an ED substituent at *para* position of phenyl ring should be classified as polar cycloaddition, while reactions with diphenylnitryle imine analogues containing an EW substituent at *para* position of phenyl ring should be classified on the borderline between polar and non-polar processes.

In summary, based on CDFT, in all presented 32CA reactions, the nitroalkene will participate as electrophilic component, while studied C,N-diarylnitryle imines will pay a role of nucleophilic substrates. For 32CA reaction of *trans*-β-nitrostyrene with diphenylnitryle imine as well as its analogues including an ED substituent at *para* position of phenyl ring, the most favourable reaction path is determined by the nucleophilic attack of C3 carbon atom of TACs on the electrophilic C_α carbon atom of the nitroalkene. Therefore, the creation of 1,3,4-triaryl-5-nitro-Δ^2-pyrazolines as the most favoured regioisomer is more probable. In turn, for 32CA reaction of *trans*-β-nitrostyrene with diphenylnitryle imine analogues containing an EW substituent at *para* position of phenyl ring, the most favourable reaction path is determined by the nucleophilic attack of the N1 nitrogen atom of TACs on the electrophilic C_α carbon atom of the nitroalkene. Consequently, the creation of 1,3,5-triaryl-4-nitro-Δ^2-pyrazolines as the most favoured regioisomer is more probable.

Dedication

The manuscript is dedicated to Professor Luis Ramon Domingo and Professor Mar Ríos-Gutiérrez.

Acknowledgements

This research was supported in part by PLGrid Infrastructure. All calculations reported in this paper were performed on “Prometheus” supercomputer cluster in the CYFRONET computational center in Cracow.

References

1 Ram V. J., Sethi A., Nath M., and Pratap R. (**2019**) *The Chemistry of Heterocycles: Nomenclature and Chemistry of Three to Five Membered Heterocycles*. 1st Ed, Elsevier, Netherlands.

2 Siadati S. A. (**2016**) Beyond the alternatives that switch the mechanism of the 1,3-dipolar cycloadditions from concerted to stepwise or vice versa: a literature review. *Prog. React. Kinet. Mech.*, 41 (4) 331-344.

3 Baranowski M., Dyksik M., and Płochocka P. (**2022**) 2D Metal Halide Perovskites: A New Fascinating Playground for Exciton Fine Structure Investigations. *Sci. Rad.,* 1 3-25.

4 Kula K., Dresler E., Demchuk O. M., and Jasiński R. (**2015**) New aldimine N-oxides as precursors for preparation of heterocycles with potential biological activity. *Przem. Chem.*, 94, 1385-1387.

5 Veerapur B., Netravati L., Naveenakumari H., and Basavaraja K. (**2023**) Design, synthesis, molecular docking and biological evaluation of some pyridinone bearing scaffold benzofuran as antimicrobial and antioxidant activity. *Curr. Chem. Lett.*, 12 (1) 167-174.

6 Pandey G., Sharma P., Geedkar D., and Kumar A. (**2023**). One-pot strategy to synthesize seven–membered 1, 4-diazepine heterocyclic scaffolds assisted by zinc oxide nanoparticles as heterogeneous catalytic support system. *Curr. Chem. Lett.*, 12 (1) 79-90.

7 Jasiński R., Mirosław B., Demchuk O. M., Babyuk D., and Łapczuk-Krygier A. (**2016**) In the search for experimental and quantumchemical evidence for zwitterionic nature of (2E)-3-[4-(dimethylamino) phenyl]-2-nitroprop-2-enenitrile - an extreme example of donor–π–acceptor push–pull molecule. *J. Mol. Struct.*, 1108, 689-697.

8 Abdelhamid A., Elsaghiera A., Aref S., Gad M., Ahmed N., and Abdel-Raheem S. (**2021**) Preparation and biological activity evaluation of some benzoylthiourea and benzoylurea compounds. *Curr. Chem. Lett.*, 10 (4) 371-376.

9 Abdel-Raheem S., El-Dean A., Abd-Ella A., Al-Taifi E., Hassanien R., El-Sayed M., Mohamed S., Zawam S., and Bakhit, E. (**2021**) A concise review on some synthetic routes and applications of pyridine scaffold compounds. *Curr. Chem. Lett.*, 10 (4) 337-362.

10 Fryźlewicz A., Łapczuk-Krygier A., Kula K., Demchuk O. M., Dresler E., and Jasiński R. (**2020**) Regio- and stereoselective synthesis of nitrofunctionalized 1,2-oxazolidine analogs of nicotine. *Chem. Heterocycl. Compd.*, 56 (1) 120-122.

11 Zawadzińska K., Ríos-Gutiérrez M., Kula K., Woliński P., Mirosław B., Krawczyk T., and Jasiński R. (**2021**) The participation of 3,3,3-trichloro-1-nitroprop-1-ene in the [3+2] cycloaddition reaction with selected nitrile N-oxides in the light of the experimental and MEDT quantum chemical study. *Molecules*, 26 (22) 6774.

12 Siadati S. A. (**2015**) An example of a stepwise mechanism for the catalyst-free 1,3-dipolar cycloaddition between a nitrile oxide and an electron rich alkene. *Tetrahedron Lett.*, 56 (34) 4857-4863.

13 Żmigrodzka M., Sadowski M., Kras J., Dresler E., Demchuk O. M., and Kula K. (**2022**) Polar [3+2] cycloaddition between N-methyl azomethine ylide and trans-3,3,3-trichloro-1-nitroprop-1-ene. *Sci. Rad.,* 1 26-35.

14 Abd-Ella A., Metwally S., El-Ossaily Y., Elrazek F., Aref S., Naffea Y., and Abdel-Raheem S. (**2022**) A review on recent advances for the synthesis of bioactive pyrazolinone and pyrazolidinedione derivatives. *Curr. Chem. Lett.*, 11 (2) 157-172.

15 Dhaduk M., and Joshi H. (**2022**) Synthesis, characterization and biological study of some new N-acetyl pyrazole derivatives. *Curr. Chem. Lett.*, 11 (2) 199-206.

16 Kula K., Dobosz J., Jasiński R., Kącka-Zych A., Łapczuk-Krygier A., Mirosław B., and Demchuk O. M. (**2020**) [3+2] Cycloaddition of diaryldiazomethanes with (E)-3,3,3-trichloro-1-nitroprop-1-ene: An experimental, theoretical and structural study. *J. Mol. Struct.*, 1203 127473.

17 Kula K., Kącka-Zych A., Łapczuk-Krygier A., Wzorek Z., Nowak A. K., and Jasiński R. (**2021**) Experimental and theoretical mechanistic study on the thermal decomposition of 3,3-diphenyl-4-(trichloromethyl)-5-nitropyrazoline. *Molecules*, 26 (5) 1364.

18 Scopus. Scopus preview. <https://www.scopus.com/>; [Accessed 10.11.2022].

19 Prabhudeva M., Renuka N., and Kumar K. (**2018**) Synthesis of thiophene-pyrazole conjugates as potent antimicrobial and radical scavengers. *Curr. Chem. Lett.*, 7 (3) 73-80.

20 Gupta S. L., Saini S., Saini P., Dandia A., Ameta K. L., and Parewa V. (**2022**) Pyrazoles, Indazoles and Pyrazolines: Recent Developments and Their Properties, in: Ameta K. L., Kant R., Penoni A., Maspero A., Scapinello L. (Eds) *N-Heterocycles*. Springer, Singapore, 415-441.

21 Faisal M., Saeed A., Hussain S., Dar P., and Larik F. A. (**2019**) Recent developments in synthetic chemistry and biological activities of pyrazole derivatives. *J. Chem. Sci.*, 131 (8) 1-30.

22 Lv Y., Meng J., Li C., Wang X., Ye Y., and Sun K. (**2021**) Update on the Synthesis of N-Heterocycles via Cyclization of Hydrazones (2017–2021). *Adv. Synth. Catal.*, 363 (23) 5235-5265.

23 Łapczuk-Krygier A., Kącka-Zych A., and Kula K. (**2019**) Recent progress in the field of cycloaddition reactions

involving conjugated nitroalkenes. *Curr. Chem. Lett.*, 8 (1) 13-38.

24 Jasiński R. (**2015**) On the question of zwitterionic intermediates in 1,3-dipolar cycloadditions between hexafluoroacetone and sterically crowded diazocompounds. *J. Fluor. Chem.*, *176*, 35-39.

25 Ríos-Gutiérrez M., and Domingo L. R. (**2019**) Unravelling the mysteries of the [3+ 2] cycloaddition reactions. *Eur. J. Org. Chem.*, 2 267-282.

26 Siadati S. A., and Rezazadeh S. (**2022**) The extraordinary gravity of three atom 4π-components and 1,3-dienes to C20-nXn fullerenes; a new gate to the future of Nanotechnology. *Sci. Rad.,* 1 46-68.

27 Jasiński R. (**2020**) On the question of the molecular mechanism of N-nitropyrazoles rearrangement. *Chem. Heterocycl. Compd.*, 56 (9) 1210-1212.

28 Ono N. (**2001**) *The nitro group in organic synthesis*, 1st Ed, Wiley-VCH, Germany.

29 Jasiński R., Kula K., Kącka A. and Mirosław B. (**2017**) Unexpected course of reaction between (E)-2-aryl-1-cyano-1-nitroethenes and diazafluorene: why is there no 1,3-dipolar cycloaddition? *Monats. Chem.*, 148 (5) 909-915.

30 Boguszewska-Czubara A., Kula K., Wnorowski A., Biernasiuk A., Popiołek Ł., Miodowski D., Demchuk O. M., and Jasiński R. (**2019**) Novel functionalized β-nitrostyrenes: Promising candidates for new antibacterial drugs. *Saudi Pharm. J.*, 27 (4) 593-601.

31 Fryźlewicz A., Olszewska A., Zawadzińska K., Woliński P., Kula K., Kącka-Zych A., Łapczuk-Krygier A., and Jasiński R. (**2022**) On the Mechanism of the Synthesis of Nitrofunctionalised Δ^2-Pyrazolines via [3+2] Cycloaddition Reactions between α-EWG-Activated Nitroethenes and Nitrylimine TAC Systems. *Organics*, 3 (1) 59-76.

32 Kula K., and Zawadzińska K. (**2021**) Local nucleophile-electrophile interactions in [3+2] cycloaddition reactions between benzonitrile N-oxide and selected conjugated nitroalkenes in the light of MEDT computational study. *Curr. Chem. Lett.*, 10 (1) 9-16.

33 Domingo L. R. (**2016**) Molecular Electron Density Theory: A Modern View of Reactivity in Organic Chemistry. *Molecules*, 21 (10) 1319.

34 Domingo L. R., Ríos-Gutiérrez M., and Pérez P. (**2016**) Applications of the Conceptual Density Functional Theory Indices to Organic Chemistry Reactivity. *Molecules*, 21 (6) 748.

35 Domingo L. R., Ríos-Gutiérrez M., and Castellanos-Soriano J. (**2020**) Understanding the Origin of the Regioselectivity in Non-Polar [3+2] Cycloaddition Reactions through the Molecular Electron Density Theory. *Organics*, 1 19-35.

36 Domingo L.R., and Ríos-Gutiérrez M., (**2022**) Application of Reactivity Indices in the Study of Polar Diels-Alder Reactions, in: Liu S. (Ed) *Conceptual Density Functional Theory: Towards a New Chemical Reactivity Theory.* Wiley-VCH, Germany, 481-502.

37 Lewars E. G. (**2016**) Computational Chemistry Introduction to the Theory and Applications of Molecular and Quantum Mechanics, 3rd Ed, Springer, Netherlands.

38 Parr R. G., Szentpály L., and Liu S. (**1999**) Electrophilicity Index. *J. Am. Chem. Soc.*, 121 1922-1924.

39 Pérez P., Domingo L. R., Duque-Noreña M., and Chamorro E. (**2009**) A condensed-to-atom nucleophilicity index. An application to the director effects on the electrophilic aromatic substitutions. *J. Mol. Struct. (THEOCHEM)*, 895 (1-3) 86-91.

40 Domingo L. R., Kula K., Rios-Gutierrez M., and Jasinski R. (**2021**) Understanding the Participation of Fluorinated Azomethine Ylides in Carbenoid-Type [3+ 2] Cycloaddition Reactions with Ynal Systems: A Molecular Electron Density Theory Study. *J. Org. Chem.,* 86 (18) 12644-12653.

41 Aurell M. J., Domingo L. R. Pérez P., and Contreras R. (**2004**) A theoretical study on the regioselectivity of 1,3-dipolar cycloadditions using DFT-based reactivity indexes. *Tetrahedron*, 60 11503-11509.

42 Kula K., Kącka-Zych A., Łapczuk-Krygier A., and Jasiński R. (**2021**) Analysis of the possibility and molecular mechanism of carbon dioxide consumption in the Diels-Alder processes. *Pure Appl. Chem.*, 93 (4) 427-446.

43 Hansch C., Leo A., and Taft R. W. (**1991**) A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.*, 91 (2) 165-195.

44 Domingo L. R., Perez P., and Saez J. A. (**2013**) Understanding the local reactivity in polar organic reactions through electrophilic and nucleophilic Parr functions. *RSC Adv.*, 3 (5) 1486-1494.

45 Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Montgomery J. A., Vreven T. J., Kudin K. N., Burant J. C., Millam J. M., Iyengar S. S., Tomasi J., Barone V., Mennucci B., Cossi M., Scalmani G., Rega N., Petersson G. A., Nakatsuji H., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima Y., Honda O., Kitao O., Nakai H., Klene M., Li X., Knox J. E., Hratchian H. P., Cross J. B., Adamo C., Jaramillo J., Gomperts R., Stratmann R. E., Yazyev O., Austin A. J., Cammi R., Pomelli C., Ochterski J. W., Ayala P. Y., Morokuma K., Voth G. A., Salvador P., Dannenberg J. J., Zakrzewski V. G., Dapprich S., Daniels A. D., Strain M. C., Farkas M. C., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Ortiz J. V., Cui Q., Baboul A. G., Clifford S., Cioslowski J., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Gonzalez C., and Pople J. A. (**2009**) Gaussian 09 rev A.1 Gaussian Inc. Wallingford CT, USA.

46 Greelings P., De Proft F., and Langenaeker W. (**2003**) Conceptual Density Functional Theory. *Chem. Rev.*, 103 (5) 1793-1874.

47 Zawadzińska K., and Kula K. (**2021**) Application of β-phosphorylated nitroethenes in [3+2] cycloaddition reactions involving benzonitrile N-oxide in the light of DFT computational study. *Organics*, 2 (1) 26-37.

48 Mlostoń G., Kula K., and Jasiński R. (**2021**) A DFT study on the molecular mechanism of additions of electrophilic and nucleophilic carbenes to non-enolizable cycloaliphatic thioketones. *Molecules*, 26 (18) 5562.

49 Kula K., and Łapczuk-Krygier A. (**2018**) A DFT computational study on the [3+2] cycloaddition between parent thionitrone and nitroethene. *Curr. Chem. Lett.*, 7 (1) 27-34.

50 Demchuk O. M., Jasinski R., Strzelecka D., Dziuba K., Kula K., Chrzanowski J., and Krasowska, D. (**2018**) A clean and simple method for deprotection of phosphines from borane complexes. *Pure Appl. Chem.*, 90 (1) 49-62.

51 Mlostoń G., Jasiński R., Kula K., and Heimgartner H. (**2020**) A DFT study on the Barton–Kellogg reaction–The molecular mechanism of the formation of thiiranes in the reaction between diphenyl-diazomethane and diaryl thioketones. *Eur. J. Org. Chem.*, 2 176-182.

52 Perez P., Domingo L. R., Aurell M. J., and Contreras R. (**2003**) Quantitative characterization of the global electrophilicity pattern of some reagents involved in 1,3-dipolar cycloaddition reactions. *Tetrahedron*, 59 (17) 3117-3125.

53 Dennington R., Keith T. A., and Millam. J. M. (**2016**) GaussView Version 6., Semichem Inc.: Shawnee Mission, KS, USA.