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Molecular Electron Denstity Study on the [3+2] cycloaddition reaction between diphenylnitrylimine and cinnamaldehyde

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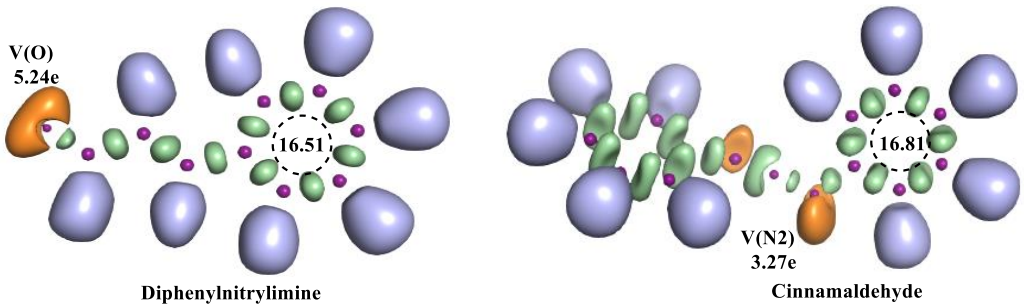

Abstract: The theoretical study of the reaction between cinnamaldehyde and nitrile-imine, conducted using the MEDT/B3LYP/6-311G(d,p) method, clarified the nucleophilic and electrophilic roles of the two components, demonstrating that the dipole acts as a nucleophile, while the dipolarophile acts as an electrophile. Parr functions indicate that the double bond of the dipolarophile is identified as the most reactive site, providing a clear explanation for the chemoselectivity observed in the experiment. Furthermore, the study of interactions reveals that the formation of the first bond involves the most electrophilic carbon. The analysis of the products and transition states reveals that one of the products is thermodynamically favored, while a certain transition state represents the dominant kinetic pathway.

Keywords: Cinnamaldehyde, chemoselectivity, MEDT, B3LYP/6-311G(d,p)

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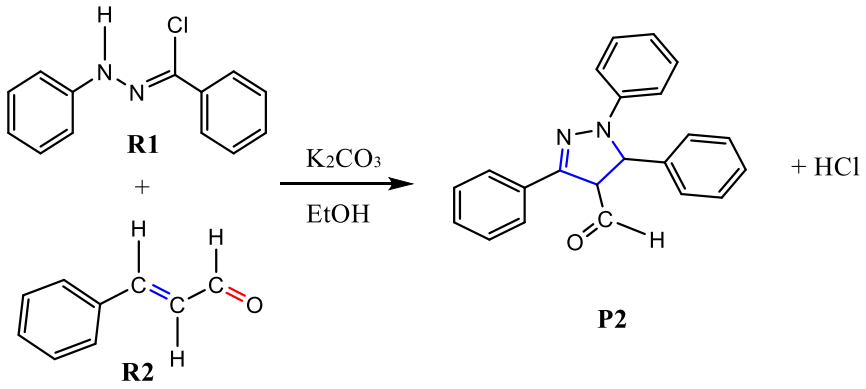
Introduction

Cycloaddition reactions [3+2] are a special type of reaction in which two molecular fragments, each carrying a function that is two folded and other one is three-folded combine to make five-member rings in one synthetic step possibly under specific conditions; these achieve them via heating the mixture, by applying high pressure or making use of some catalysts [1-3]. Such conditions permit the regulation of molecular reactivity, maximize catalyst efficacy and product yield, and enable molecular complexity through processable cycles necessary for materials- and polymer-synthetic chemistries [4]. Within the emerging fields of polymer science, the types of products synthesized by these three dimensional architectural systems endow materials with resists, pliability and characteristics that promote electrical, optical or even bioapplications [5]. In pharmaceutical chemistry, these reactions facilitate the synthesis of bioactive compounds, including anti-cancer, antimicrobial, and anti-inflammatory agents, which exert their effects by specifically inhibiting enzymes or blocking cellular signaling pathways [6]. In addition, products of [3+2] cycloaddition may also serve as promising COX-2 inhibitors for topical treatment of chronic inflammatory diseases [7].
Density Functional Theory (DFT) is an often applied computational method for theoretical chemistry to assess the electronic structure of molecular systems. This approach is based on the idea that the electronic density contains all the information corresponding to a specific set of properties of the system, thus reducing as such many-body problems related to electrons interactions. Instead of "seeing" each electron separately, DFT incorporates electronic density functionals to approximate the energy of the system, therefore being more computationally efficient than older quantum chemistry methods, like the Hartree-Fock method [8-10].

Molecular Electron Density Theory (MEDT) is considered a modern theoretical chemistry approach to chemical reactivity based on electron density rather than molecular orbitals [11], which fits perfectly within the framework of DFT. In contrast to classical methods that have traditionally sounded in molecular orbital theory for theoretical underpinnings of reaction mechanisms and alternative explanations, MEDT claims that the nature of chemical reactivity is inherently an electronic density interaction phenomenon between interacting molecules [12-14]. This theory enables the prediction of a molecule's reactive zones by considering the electronic density distribution and localization and identifies both electrophilic and nucleophilic parts of the molecule, rendering them significant in determining the pathway of any given chemical reaction [15-17]. As MEDT allows a profounder insight into reaction mechanisms on an electronic density basis, it has

demonstrated to be a key tool for designing new chemical reactions and optimizing synthetic routes in organic chemistry [18].

In this investigation, MEDT was utilized to analyze the selectivities observed in the [3+2] cycloaddition reaction involving diphenylnitrylimine and cinnamaldehyde, chosen for their well-documented reactivity and synthetic potential in forming heterocyclic compounds [19]. Understanding the mechanism of this reaction provides insights into its regio- and stereoselectivities, enabling better control over product formation.



Scheme. 1.

Computational Approach

At the computational level of B3LYP/6-311G(d,p), every stationary point involved in this [3+2] cycloaddition reaction has been tuned. Berny's analytical gradient optimization method [20,21] was used in the optimization process. Frequency calculations verified the presence of a single distinct imaginary frequency in the transition states. The energetic profiles connecting each transition state to the two associated minima are validated using the intrinsic reaction coordinates (IRC) method. The polarizable continuum model (PCM) and the self-consistent reaction field framework [22-25] developed by Tomasi's group were used to fully optimize the impacts of ethanol solvents into the gas-phase optimized stationary points. The total natural atomic charges (q) of the atoms in each frame (j) within the transition stages (TS) were applied to calculate the global electron density transfer (GEDT) [26].

Global electrophilicity indicator [27] is measured via the formula: $\omega = \mu^2/2\eta$, where μ represents the chemical electron potential and η signifies the chemical hardness, with $\mu = \frac{\varepsilon_{HOMO} + \varepsilon_{LUMO}}{2}$, and $\eta \approx \varepsilon_{LUMO} - \varepsilon_{HOMO}$. [28,29]. To ascertain the nucleophilicity of the reagents, the following formula was used: $N=\varepsilon_{HOMO}(Nu)-\varepsilon_{HOMO}$ (TCE) [30,31].

An electrophilic and nucleophilic Parr function of radical cations or anions were calculated using the Mulliken spin densities [32]. An analysis of the Electron Localization Function (ELF) was conducted using the Topmod software [33].

Results and discussion

Reactivity Indices Study

Table 1 summarizes the values of the electronic chemical potentials μ, hardness η, electrophilicity indices ω, and nucleophilicity indices N for the two reactants in order to predict their electrophilic/nucleophilic character.

Table 1. The chemical potentials, global hardnesses, electrophilicity indices, and nucleophilicity indices of dipoles and dipolarophiles (values are given in eV)

System	μ	η	ω	N
Diphenylnitrylimine	3.38	3.77	1.51	3.85
Cinnamaldehyde	4.34	4.48	2.10	2.53

According to the values of the global indices obtained in the table above, it is noted that the electronic chemical potential of the diphenylnitrylimine (-3.38 eV) is higher than that of the cinnamaldehyde (-4.34 eV), which implies that the electron transfer will occur from the dipole to the cinnamaldehyde. This observation is consistent with the results obtained from the analysis of frontier molecular orbitals. Furthermore, the values of the electrophilicity index ω indicate that the cinnamaldehyde has the highest value (2.10 eV) compared to that of the dipole (1.51eV), thus designating it as the most electrophilic. By comparing the values of the nucleophilicity index N, it is observed that the diphenylnitrylimine has the highest value (3.85 eV) compared to that of the cinnamaldehyde (2.53 eV), which shows that the diphenylnitrylimine is the most nucleophilic. Thus, this comparison allows us to conclude that, in this reaction, the diphenylnitrylimine acts as a nucleophile while the cinnamaldehyde plays the role of an electrophile.

Analysis of local indices

The formation of the first bond results from the interaction between the most electrophilic site of the dipolarophile, characterized by a high value of the local electrophilicity index ωk, and the most nucleophilic site, characterized by the highest value of the local nucleophilicity index Nk. It is important to note that predicting this first formed bond is sufficient to anticipate the most favored attack. To highlight the preferential regioselectivity of the reaction, we have thus calculated the Parr indices. Representation of

Mulliken atomic spin densities for the two reactants, accompanied by their Parr functions are given in figure 1.

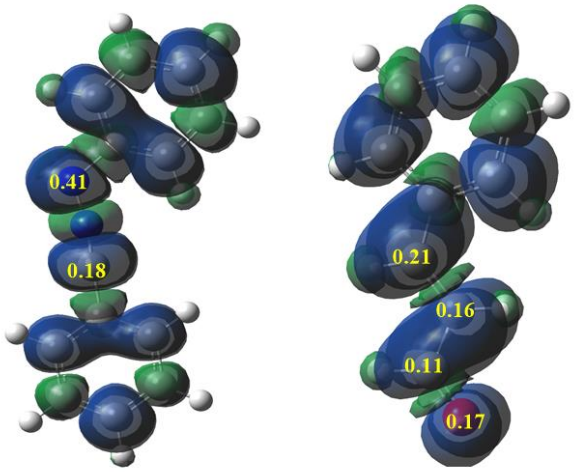


Fig. 1. Representation of the Mulliken atomic spin densities of the two reactants (diphenylnitrylimine and cinnamaldehyde) with their Parr functions.

The Figure 1 show that the Mulliken spin densities of the cinnamaldehyde are mainly concentrated at the C1-C2 double bond. They are also somewhat clustered around the C-O double bond regions, but they are weak. These results indicate that the most reactive fragment of the cinnamaldehyde is the C1-C2 double bond, and this explains the chemoselectivity observed experimentally [19]. Moreover, for this most reactive double bond, the Parr P+ functions of carbons C1 and C2 are 0.21 and 0.16 respectively, indicating that the formation of the first single bond involves the more electrophilic carbon C1.

Exploitation of ELF reagents

The electron localization function (ELF) is a powerful tool for visualizing and interpreting the electronic distribution in molecules, identifying areas where electrons are localized, such as chemical bonds and non-bonding electron pairs. The figure 2 illustrates the different localization domains, particularly the monosynaptic and disynaptic pools, associated with the two reagents. Monosynaptic basins correspond to regions where electrons are localized in isolation around a single atom, often representing non-bonding electron pairs. On the other hand, disynaptic basins show regions of electronic localization shared between two atoms, corresponding to covalent bonds. These localization domains allow for the analysis of the nature of interactions between the reactants and the prediction of the area's most likely to participate in the formation of new bonds during the reaction. By visualizing the electronic basins, one can thus anticipate the nucleophilic and electrophilic sites, which is essential for understanding the reactivity and regioselectivity of the reaction.

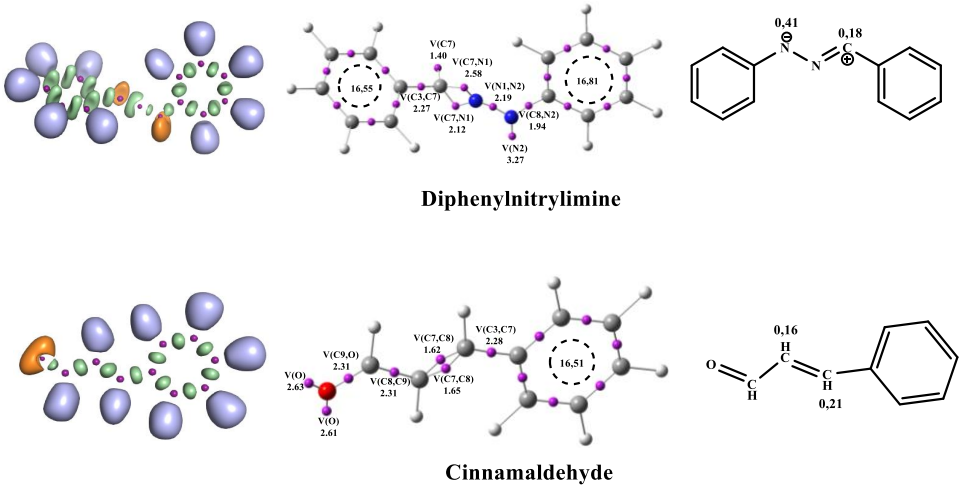
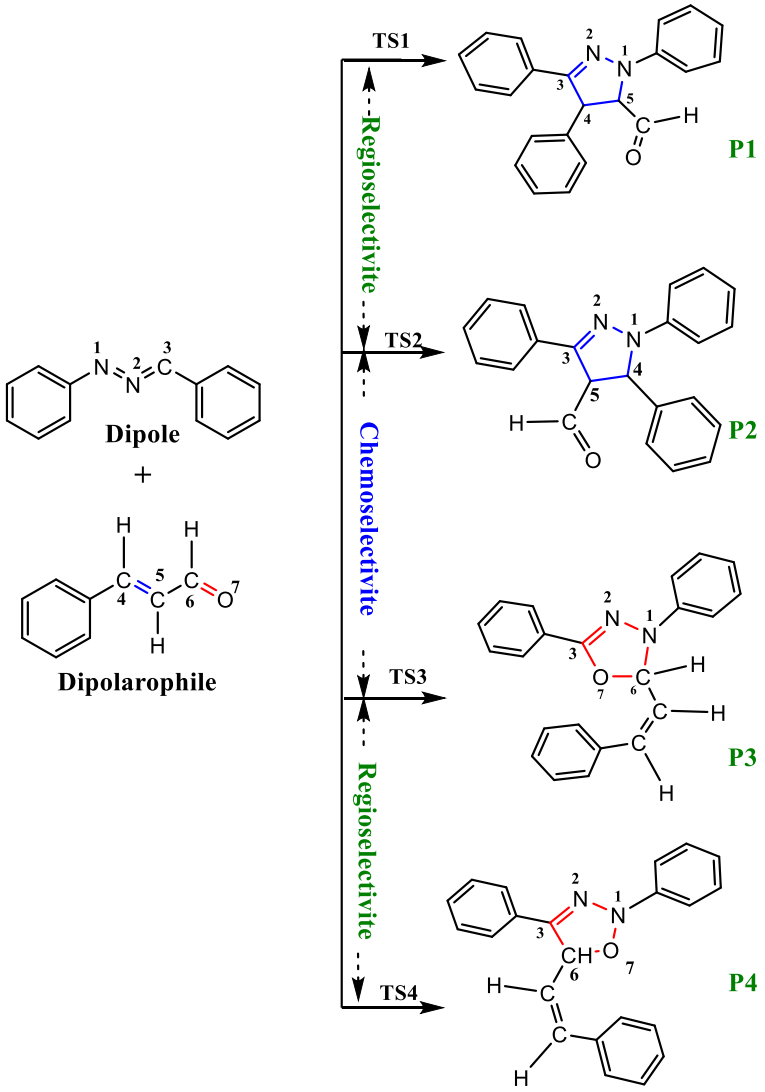


Fig. 2. The electronic localization functions for the two reactants.

The topological analysis of the electron localization function (ELF) of the diphenylnitrylimine reveals the presence of a disynaptic basin (C3, C7) with a population of 2.27 e, a monosynaptic basin V(C7) with a population of 1.40 e, two disynaptic basins V(C7, N1) and V'(C7, N1) with a total population of 4.7 e, a disynaptic basin V(N1, N2) with a population of 2.19 e, a monosynaptic basin V(N2) with a population of 3.27 e, and a disynaptic basin (C8, N2) with a population of 1.94 e. Moreover, six basins are observed in the aromatic cycle related to N2 with a total population of 16.81 e and six basins in the aromatic cycle related to C7 with a total population of 16.55 e. The topological analysis of the electron localization function (ELF) of the cinnamaldehyde shows the presence of two monosynaptic basins V(O) and V'(O) with a total population of 5.24 e, a disynaptic basin V(C9, O) with a population of 2.31 e, a disynaptic basin V(C8, C9) containing 2.31 e, and two disynaptic basins V(C7, C8) and V'(C7, C8) with a total population of 3.27 e. Finally, there are six basins in the aromatic cycle linked to C7, with a total population of 16.51 e.

Energy study of the reaction

A reaction is said to be regioselective if it favors a specific position among several possible positions. In the case of our reaction, the cinnamaldehyde has two double bonds, each of which can lead to two regioisomers, resulting in a total of four possible positions. Scheme 2 illustrates the potential pathways of the studied 1,3-dipolar cycloaddition reaction. While the relative energies are given in table 2.



Scheme. 2 Potential pathways of the studied [3+2] cycloaddition reaction between diphenylnitrylimine and cinnamaldehyde

This table presents the relative energies (ΔG, ΔH) and entropies (ΔS) of several products (P1, P2, P3, P4) and transition states (TS1, TS2, TS3, TS4) of the studied 1,3-dipolar cycloaddition reaction. The products P1, P2, and P3 show negative values of ΔG and ΔH, indicating that they are thermodynamically favorable and exergonic, meaning that their formation is spontaneous and releases energy, while P4, with positive values of ΔG (22.7 kcal/mol) and ΔH (7.6 kcal/mol), is thermodynamically unfavorable. The product P2, possessing the most negative ΔG value (-19.2 kcal/mol), seems to be the most thermodynamically stable and could therefore be predominant under thermodynamic control conditions. Regarding the transition states, the positive values of ΔG and ΔH indicate that each step requires an energy input, with TS4 having the highest free energy (ΔG = 37.9 kcal/mol) and therefore being the least favorable step, while TS2, with ΔG of 27.2 kcal/mol, could be the most energetically accessible pathway. The negative values of ΔS in all cases

suggest a decrease in entropy, probably due to a restriction of molecular movements, although this does not seem to be the determining factor of stability. In conclusion, P2 is thermodynamically the most favorable product, while TS2, having the lowest energy barrier, could represent the dominant kinetic pathway, which points towards optimal conditions for selectively obtaining the desired product.

Table 2. Relative energies of the products and transition states of the [3+2] cycloaddition reaction in ethanol diphenylnitrylimine and cinnamaldehyde, (ΔG, ΔH are in kcal/mol; ΔS are in cal/mol·K)

	ΔG	ΔH	ΔS
P1	-17.7	-33.1	-51,5
P2	-19.2	-35.0	-52.8
P3	-10.6	-26.0	-51.6
P4	22.7	7.6	-50.5
TS1	35.0	20.8	-47.6
TS2	27.2	13.1	-47.5
TS3	30.7	17.7	-43.6
TS4	37.9	23.6	-47.7

Conclusions

In conclusion, the computational study of the reaction between cinnamaldehyde and nitrile-imine, conducted using the MEDT/B3LYP/6-311G(d,p) method, clarified the nucleophilic and electrophilic roles of the reactants, showing that the dipole acts as a nucleophile, while the dipolarophile plays the role of an electrophile. The chemoselectivity observed in the experiment can be clearly explained by the Parr functions, which indicate that the double bond of the dipolarophile is the most reactive site. Moreover, the analysis of the interactions reveals that the formation of the first bond involves the most electrophilic carbon. The evaluation of products and transition states shows that one of the products is thermodynamically favored, while a particular transition state constitutes the dominant kinetic pathway. This theoretical approach provides valuable information for identifying the optimal conditions to selectively obtain the desired product, thereby validating the computational approach employed.

References

[1] Jasiński, R.; Dresler, E. On the Question of Zwitterionic Intermediates in the [3+2] Cycloaddition Reactions: A Critical Review. *Organics* **2020**, 1, 49-69. DOI: 10.3390/org1010005

[2] Domingo, L.R; Ríos-Gutiérrez M.; Emamian, S. Understanding the domino reaction between 1-diazopropan-2-one and 1,1-dinitroethylene. A molecular electron density

theory study of the [3 + 2] cycloaddition reactions of diazoalkanes with electron-deficient ethylenes. *RSC Adv*. **2017**, 7(25). DOI: 10.1039/C7RA00544J

[3] Ouled, Aitouna, A.; Barhoumi, A.; El Alaoui El Abdallaoui, H. et al. Explaining the selectivities and the mechanism of [3+2] cycloloaddition reaction between isoalantolactone and diazocyclopropane. *J. Mol. Model.* **2023**, 29, 280. DOI: 10.1007/s00894-023-05688-0

[4] Matthew, R.; Aronoff, Brian Gold; Ronald, T. Raines; 1,3-Dipolar Cycloadditions of Diazo Compounds in the Presence of Azides, *Org. Lett*. **2016**, 18, 7, 1538–1541. DOI: 10.1021/acs.orglett.6b00278

[5] Fathi-karkan, S.; Shamsabadipour, A.; Moradi, A; et al. Four-Dimensional Printing Techniques: A Comprehensive Review of Biomedical and Tissue Engineering Developments. *BioNanoSci*. **2024** 14, 4189–4218. DOI: 10.1007/s12668-024-01596-6

[6] Salah, M.; BelghitI, M.E.; Aitouna, A.O.; et al. MEDT study of the 1,3-DC reaction of diazomethane with Psilostachyin and investigation about the interactions of some pyrazoline derivatives with protease (Mpro) of nCoV-2. *J. Mol. Graph. Model*. **2021**, 102. DOI: 10.1016/j.jmgm.2020.107763

[7] Mai, I. Abo-Elmagd; Rasha, M. Hassan; Mona, E. Aboutabl; Kamilia, M. Amin; Aida, A. El-Azzouny; Mohamed, N. Aboul-Enein; Design, synthesis and anti-inflammatory assessment of certain substituted 1,2,4-triazoles bearing tetrahydroisoquinoline scaffold as COX 1/2-inhibitors, *Bioorg. Chem.* **2024**, 150, 107577. DOI: 10.1016/j.bioorg.2024.107577

[8] Mardirossian, N.; Head-Gordon, M.;. Thirty years of density functional theory in computational chemistry: an overview and extensive assessment of 200 density functionals. *Mol. Physi.***2 017** 115(19), 2315–2372. DOI: 10.1080/00268976.2017.1333644

[9] Bader, R. F. W; Atoms in Molecules: A Quantum Theory, Oxford University Press. 1990:438. https://global.oup.com/academic/product/atoms-in-molecules-9780198558651. Accessed April 28, **2023**.

[10] Casida, M.E.; Time-Dependent Density Functional Response Theory of Molecular Systems: Theory, Computational Methods, and Functionals, *Theoretical and Computational Chemistry,* **1996**, 4, 391-439. DOI: 10.1016/S1380-7323(96)80093-8

[11] Domingo, L.R.; Molecular electron density theory: A modern view of reactivity in organic chemistry. *Molecules*, **2016**; 21(10). DOI: 10.3390/molecules21101319

[12] Domingo, L.R; Ríos-Gutiérrez, M.; Pérez, P.; Applications of the Conceptual Density Functional Theory Indices to Organic Chemistry Reactivity. *Molecules* **2016**, 21, 748. DOI: 10.3390/MOLECULES21060748

[13] Johnson, E.R; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen A.J.; Yang, W.; Revealing noncovalent interactions. *J. Am. Chem. Soc*. **2010**, 132(18). DOI: 10.1021/ja100936w

[14] Domingo, L.R.; Emamian, S.R.; Understanding the mechanisms of [3+2] cycloaddition reactions. the pseudoradical versus the zwitterionic mechanism. *Tetrahedron*, **2014**, 70(6). DOI: 10.1016/j.tet.2013.12.059

[15] Domingo, L.R.; Ríos-Gutiérrez, M. A.; Molecular Electron Density Theory study of the reactivity of azomethine imine in [3+2] cycloaddition reactions. *Molecules*. **2017**, 22(5). DOI: 10.3390/molecules22050750

[16] Domingo, L.R.; Ríos-Gutiérrez, M.; Pérez, P. A.; New model for C-C bond formation processes derived from the Molecular Electron Density Theory in the study of the mechanism of [3+2] cycloaddition reactions of carbenoid nitrile ylides with electron-deficient ethylenes. *Tetrahedron*. **2016**, 72(12). DOI: 10.1016/j.tet.2016.01.061

[17] Aizikovich, A.Y.; Korotaev, V.Y.; Kodess, M.I.; Barkov, A.Y.; Study of regioselectivity and stereoselectivity of 1,3-dipolar cycloaddition of 2-diazo-3-nitro-1,1,1-trifluoropropane to electrophile alkenes. *Ж. Орг. Хим.* **1998**, 34(3), 383-387.

[18] Chai, J. Da; Head-Gordon, M.; Long-range corrected hybrid density functionals with damped atom–atom dispersion corrections. *Chem. Phys*. **2008**, 10(44), 6615-6620. DOI: 10.1039/B810189B

[19] Bertuzzi, G.; Fochi, M.; Franchini, M.C.; Regiocontrolled 1,3-dipolar cycloadditions of nitrile imines with acetylenes and α,β-unsaturated systems: synthesis of polysubstituted and ring fused pyrazoles with pharmaceutical activity. *Targets in Het. Systems* **2017**, 337-364. DOI: 10.17374/targets.2017.20.337

[20] Schlegel, H.B.; Optimization of equilibrium geometries and transition structures. *J Comput Chem*. **1982**, 3(2), 214-218. DOI: 10.1002/JCC.540030212

[21] Yarkony, D.R.; Modern Electronic Structure Theory. **1995**, 2. DOI: 10.1142/1957

[22] Cancès, E.; Mennucci, B.; Tomasi, J.; A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics. *J. Chem. Phys*. **1997**, 107(8), 3032-3041. DOI: 10.1063/1.474659

[23] Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J.; Ab initio study of solvated molecules: a new implementation of the polarizable continuum model. *Chem. Phys. Lett*. **1996**, 255(4-6), 327-335. DOI: 10.1016/0009-2614(96)00349-1

[24] Barone, V.; Cossi, M.; Tomasi, J.; Geometry optimization of molecular structures in solution by the polarizable continuum model. *J. Comput. Chem*. **1998**, 19(4). DOI: 10.1002/(SICI)1096-987X(199803)19:4<404::AID-JCC3>3.0.CO;2-W

[25] Tomasi, J.; Persico, M.; Molecular Interactions in Solution: An Overview of Methods Based on Continuous Distributions of the Solvent. *Chem. Rev*. **1994**, 94(7), 2027-2094. DOI: 10.1021/CR00031A013/ASSET/CR00031A013.FP.PNG_V03

[26] Domingo, L.R.; RSC Advances quantum chemical topology of electron density. *RSC Adv*. **2014**, 4, 32415-32428. DOI: 10.1039/C4RA04280H

[27] Parr, R.G.; Szentpály, L. V.; Liu, S.; Electrophilicity Index. *J. Am. Chem. Soc*. **1999**, 121(9), 1922-1924. DOI: 10.1021/JA983494X

[28] Parr, R.G.; Pearson, R.G.; Absolute Hardness: Companion Parameter to Absolute Electronegativity. *J. Am. Chem. Soc*. **1983**, 105(26), 7512-7516. DOI: 10.1021/JA00364A005/ASSET/JA00364A005.FP.PNG_V03

[29] Parr, R.G.; Weitao, Y.; Density-Functional Theory of Atoms and Molecules. Density-Functional Theory Atoms Mol. Springer **1995**. DOI: 10.1093/OSO/9780195092769.001.0001

[30] Domingo, L.R.; Chamorro, E.; Pérez, P.; Understanding the reactivity of captodative ethylenes in polar cycloaddition reactions. A theoretical study. *J Org Chem*. **2008**, 73(12), 4615-4624 DOI: 10.1021/JO800572A/SUPPL_FILE/JO800572A-FILE003.PDF

[31] Domingo, L.R.; Pérez, P.; The nucleophilicity N index in organic chemistry. *Org. Biomol. Chem*. **2011**, 9(20), 7168-7175. DOI: 10.1039/C1OB05856H

[32] Domingo, L.R.; Pérez, P.; Sáez, J.A.; Understanding the local reactivity in polar organic reactions through electrophilic and nucleophilic Parr functions. *RSC Adv*. **2013**, 3(5), 1486-1494. DOI: 10.1039/C2RA22886F

[33] Becke, A.D.; Edgecombe, K.E.; A simple measure of electron localization in atomic and molecular systems. *J. Chem. Phys.* **1990**, 92(9). DOI: 10.1063/1.458517