

Theoretical study of the chemo- and regioselectivity toward [3+2] cycloaddition reaction between mesitonitrile oxides and 2-fluoren-9-ylidene-malononitrile

M. El idrissi¹, R. El Ajlaoui³, M. Zoubir¹, S. Abouricha⁴, M. Moumou², N. Ourhriss², A. Zeroual^{1,2*}, A. Benharref², A. El Hajbi¹

¹ Laboratory of Physical Chemistry, Faculty of Science, Chouaib Doukkali University, P.O. Box 20, 24000 El Jadida, Morocco

² Laboratory of Biomolecular Chemistry, Natural Substances and Reactivity, URAC 16, Faculty of Sciences Semlalia, Cadi Ayyad University, P.O. Box 2390, 40000 Marrakech, Morocco

³ Laboratory of Organic and Analytical Chemistry, Faculty of Sciences and Techniques, Sultan Moulay Slimane University, P.O. Box 523, Beni-Mellal, Morocco

⁴ Laboratory of Interdisciplinary Research in Science and Technology, P.O. Box 592, 2300, Poly Disciplinary Faculty, Sultan Moulay Slimane, University, Beni Mellal Morocco.

Received 2 Mar 2017,
Revised 23 May 2017,
Accepted 27 May 2017

Keywords

- ✓ Molecular Electron Density Theory,
- ✓ regioselectivity,
- ✓ chemoselectivity,
- ✓ [3+2] cycloaddition,
- ✓ The electrostatic potential.

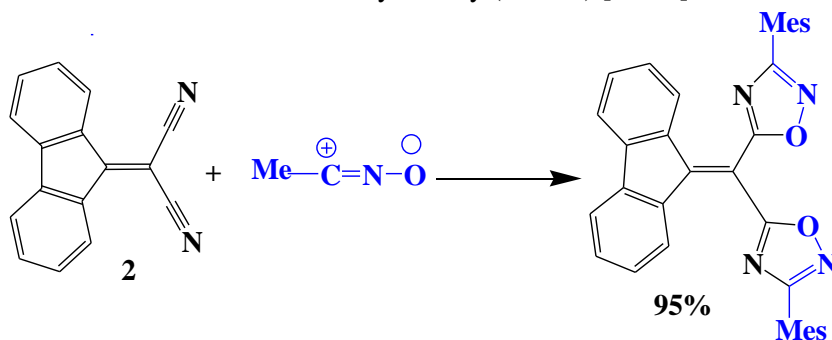
zeroual19@yahoo.fr
Phone: +212667845405

Abstract

The mechanism, the chemo- and regioselectivity toward mesitonitrile oxides and 2-fluoren-9-ylidene-malononitrile in [3+2] cycloaddition reaction, have been theoretically studied using DFT methods at the B3LYP/6-31(d) computational level. The possible chemoselective and ortho/meta regioselective channels were explored and characterized. The free energies analyses associated with the different reaction pathways indicated that the 1,3-DC reaction between mesitonitrile oxides and 2-fluoren-9-ylidene-malononitrile were highly chemo- and regiospecific, in agreement with the experimental outcomes.

1. Introduction

[3+2] cycloaddition reaction shows one of the most successful processes for the synthesis of pentagonal heterocycles [1-4], which are difficult to access by other synthetic pathways. In particular, they provide access to several biologically active substances [5, 6] and pharmaceuticals [7, 8]. In 2008, a distortion/interaction [9, 10] was introduced by Houk [11] to explain the reactivity. This model is analogous of that proposed by Bicklehaupt in 1999 [12, 13]. Houm found that the activation enthalpies correlated very nicely with distortion energies. The partition of the total density of the TS geometry into two separated structures doesn't have any physical sense within density functional DFT [14]. Consequently, the energy of two reagents could not be correlated with the energy of TS because each of them losses the external potential created by the other reagents. The changes in the electron density and not molecular orbital interaction are responsible for the reactivity in organic molecules [15]. Very recently, Domingo proposed a new theory to study the reactivity in organic chemistry named Molecular Electron Density Theory (MEDT) [16-17].



Scheme 1. [2+3] cycloaddition reaction between mesitonitrile oxides and 2-fluoren-9-ylidene-malononitrile

2. Material and Methods

Theory and computational details

DFT computations were carried out using the B3LYP functional [19], together with the standard 6-31(d) basis set [20]. The optimizations have been realized using the Berny analytical gradient method. All computations have been shown with the Gaussian 09 suite of programs [21]. The global electrophilicity index [22] ω , was given by the following expression: $\omega = \frac{\mu^2}{2\eta}$, in terms of the electronic chemical potential μ and the chemical hardness η . Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L as $\mu = \frac{\varepsilon_H + \varepsilon_L}{2}$ and $\eta = \varepsilon_H - \varepsilon_L$, respectively. The empirical nucleophilicity index N [23, 24], based on the HOMO energies obtained within the Kohn-Sham [25], and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. the nucleophilicity was referred to tetracyanoethylene (TCE). This choice allowed us to handle conveniently a nucleophilicity scale of positive values. Electrophilic P_k^+ and nucleophilic P_k^- Parr functions were obtained through analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents. The local electrophilicity and the local nucleophilicity indices were evaluated using the following expressions: $\omega_k = \omega P_k^+$ and $N_k = N P_k^-$ [26-31]. The stationary points were characterized by frequency computations in order to verify that TSs have only one imaginary frequency. Intrinsic reaction coordinate (IRC) [32] pathways were traced to verify the connectivity between minima and associated TSs. Solvent effects of dichloromethane were taken into account through single point energy calculation using the polarizable continuum model (PCM) developed by Tomasi's group in the framework of the self-consistent reaction field [33].

3. Results and discussion

The present theoretical study has been divided in three parts: (1) an analysis of the conceptual DFT indices of the reagents involved in cycloaddition reaction between mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile. (2) Next, the potential energy surface (PES) associated with the cycloaddition reaction of mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile were explored and characterized, (3) finally a transition states geometries were analyzed

3.1. Understanding the regioselectivity of the 1,3-DC reaction of mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile using Parr functions and electrostatic potential

The global DFT indices, namely the electronic chemical potential μ , chemical hardness η , electrophilicity ω and nucleophilicity N , are summarized in table 1.

Table 1. B3LYP/6-31(d) electronic chemical potential μ , chemical hardness η , electrophilicity ω and nucleophilicity N in eV of the 1,3-DC reaction of mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile.

System	μ	η	N	ω
mesitronitrile oxides (1)	-2.90	7.65	2.80	0.54
2-Fluoren-9-ylidene-malononitrile (2)	-4.89	3.32	2.97	3.60

We can conclude from table 1 that the electronic chemical potentials of mesitronitrile oxides, $\mu = -2.90$ eV, is higher than that of 2-Fluoren-9-ylidene-malononitrile, $\mu = -4.89$ eV. Thus, along a polar reaction, the GDET will take place from mesitronitrile oxides to the 2-Fluoren-9-ylidene-malononitrile

The mesitronitrile oxides present a smaller electrophilicity ω index of 0.54 eV and higher nucleophilicity N index of 3.60 eV, than 2-Fluoren-9-ylidene-malononitrile. Consequently mesitronitrile oxides will be as nucleophile and 2-Fluoren-9-ylidene-malononitrile as electrophiles.

The frontier molecular orbital HOMO and LUMO representations, the nucleophilic Parr function, the electrophilic Parr function and electrostatic potential of the reagents were analyzed in order to characterize the most electrophilic and nucleophilic centers of the species involved in this reaction and thus to explain the chemo- and regioselectivity experimentally observed (fig. 1).

From the figure 1 we can observe that:

The density map of the HOMO orbital of 2-fluoren-9-ylidene-malononitrile is distributed over all atoms except those of double and triple bond, because of this reason, the LUMO orbital of the 2-fluoren-9-ylidene-malononitrile will correlate with HOMO orbital of the mesitronitrile oxides.

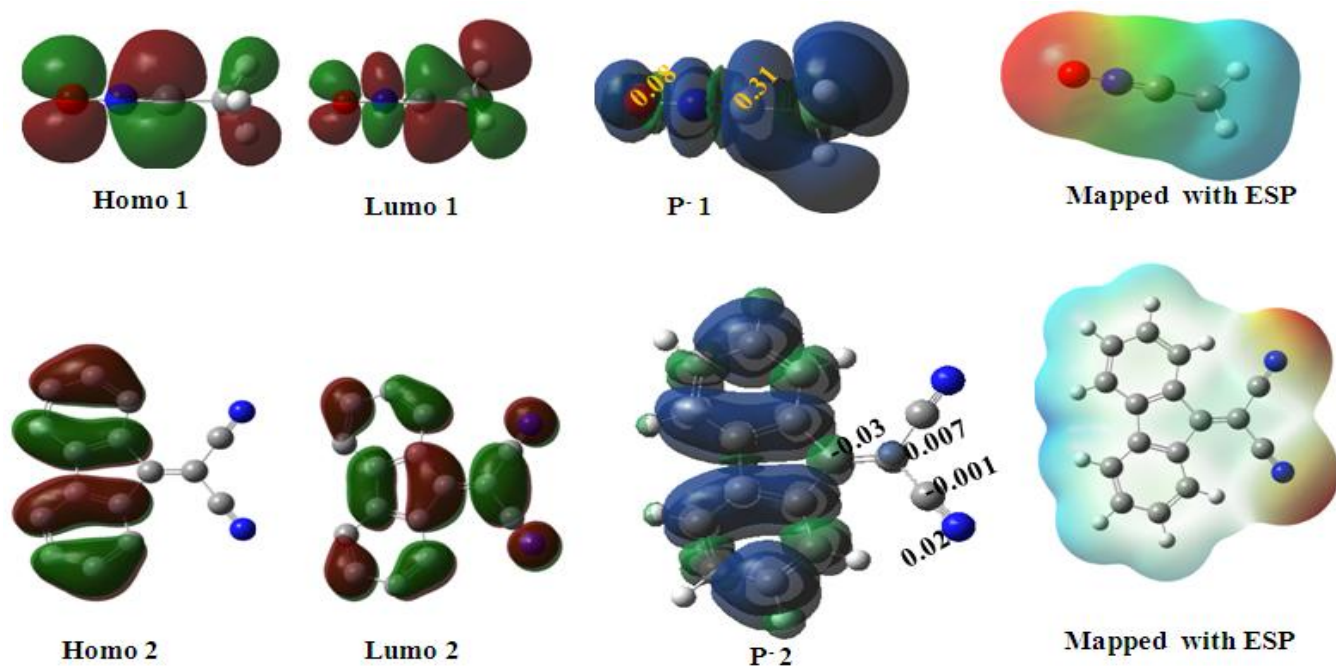


Figure 1. 3D representations of the frontier molecular orbital HOMO and LUMO toward the radical anion and the radical cations as well as the electrophilic and nucleophilic Parr functions and mapped with ESP of the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile.

The ESP map of the reagents indicates that the oxygen atom of the mesitronitrile oxides and the nitrogen atom of the 2-fluoren-9-ylidene-malononitrile have a red color, which shows that these atoms have a negative charge, hence the interaction between these two atoms, was impossible. The most favorable interactions will be between the oxygen of mesitronitrile oxides and the carbon of the cyanide group and the nitrogen of the 2-fluoren-9-ylidene-malononitrile interacts with the carbon of the dipole.

The nucleophilic P_k^- Parr function of mesitronitrile oxides indicates that the carbon atom C is the most nucleophilic center $P_C^- = 0.31$. The electrophilic P_k^+ Parr function of 2-fluoren-9-ylidene-malononitrile indicates that the nitrogen atom is most nucleophilic center $P_N^+ = 0.02$ of this specie. Consequently, in this cycloaddition, the most favorable electrophile and nucleophile interaction will take place between nitrogen N of 2-fluoren-9-ylidene-malononitrile with carbon C1 of the mesitronitrile oxides. In clear agreement with the total regio- and chemoselectivity experimentally observed.

3.2. Kinetic study of the Diels-Alder 1,3-dipolar cycloaddition reaction of the mesitronitrile oxides with 2-fluoren-9-ylidene-malononitrile

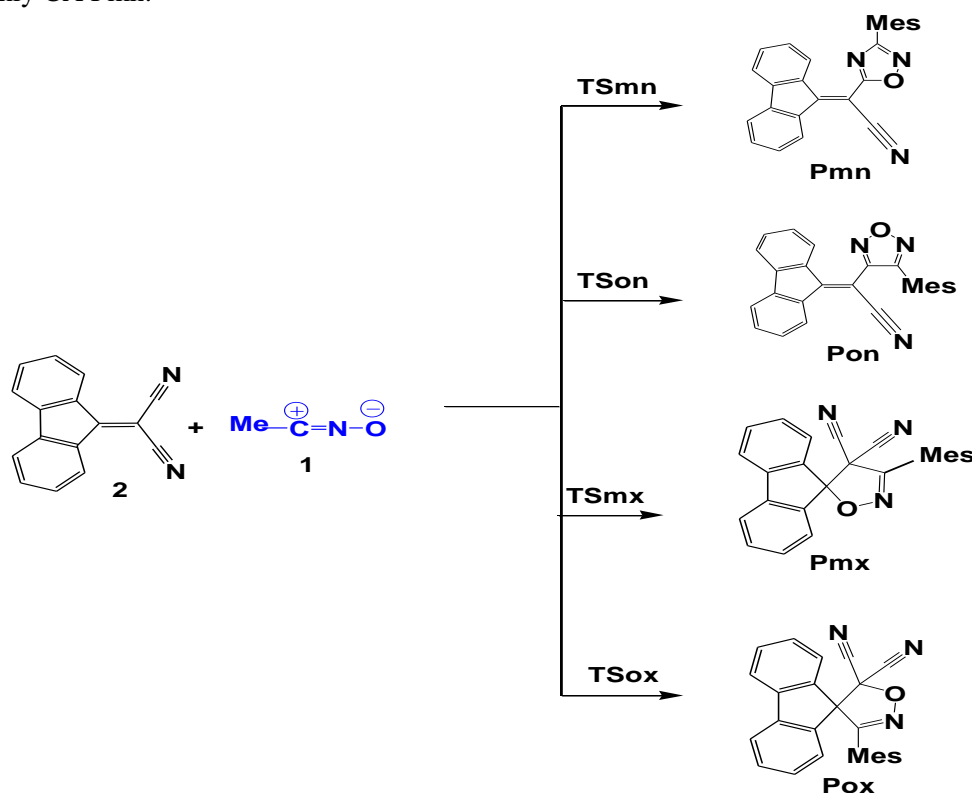
The presence of a non-symmetric dipole and the presence of two functional groups, the 1,3-DC reaction between the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile could take place through four competitive reactive channels, two chemo- and regioisomeric approach modes, namely meta and ortho. (Scheme 2).

The values of the relative enthalpy (ΔH), relative Gibbs free energy (ΔG) and relative entropy (ΔS), of the stationary points involved in the Diels-Alder 1,3-dipolar cycloaddition reaction of the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile are summarized in table 2.

The Gibbs free energy profile of the 1,3-DC reaction of the mesitronitrile oxides and 2-fluoren-9-ylidene are given in figure 2.

The gas phase activation free enthalpies associated with four reactive channels of these 1,3-DC reactions are: 23.62 (TS_{mn}), 35.3 (TS_{on}), 29.11 (TS_{mx}) and 30.56 (TS_{ox}). The reactions could be exothermic by 35.54 (P_{mn}), 9.26 (P_{on}), 1.91 (P_{mx}) and 1.39 kcal/mol (P_{ox}). The exothermic characters of these 1,3-DC reactions make these cycloaddition reactions pathways irreversible in gas phase. The activation energy of the most favorable regio/chemo approach via TS_{mn} (23.62), is 5.49 kcal/mol lower than TS_{mx} (29.11), this high energy difference indicates that the cycloaddition between the mesitronitrile oxides and 2-fluoren-9-ylidene-

malononitrile is highly chemospecific, and comparison between TS_{mn} (23.62) and TS_{on} (35.33), indicates that this reaction is regioselective too, in good agreement with experimental observations. Note that the experimental was obtained only CA Pmn.



Scheme 2. Regio- and chemoisomeric reactive pathways associated with the 1,3-DC reaction between the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile.

Table 2 Relative enthalpy (ΔH kcalmol⁻¹), relative Gibbs free energy (ΔG kcalmol⁻¹) and relative entropy (ΔS calmol⁻¹K⁻¹), computed in gas and chloroform, for the stationary points involved in the 1,3-DC reaction between the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile.

	gas			in chloroform		
	ΔH	ΔG	ΔS	ΔH	ΔG	ΔS
TS _{mn}	12.51	23.62	-37.242	14.67	25.74	-37.11
TS _{on}	23.78	35.33	-38.735	25.39	37.13	-39.39
Pmn	-48.95	-35.54	-44.962	-46.50	-33.14	-44.82
Pon	-22.82	-9.26	-45.442	-19.77	-6.41	-44.78
TS _{mx}	16.78	29.11	-41.342	18.55	30.85	-41.24
TS _{ox}	18.19	30.56	-41.479	19.29	31.74	-41.75
Pmx	-15.84	-1.91	-46.812	-13.78	0.13	-46.71
Pox	-15.52	-1.39	-47.377	-13.41	0.59	-46.90

Relative to 1+2,

Inclusion of solvent effects of the chloroform increases the gas phase activation energies by 2.12 (TS_{mn}), 1.80 (TS_{on}), 1.74 (TS_{mx}) and 1.12 kcal/mol (TS_{ox}), and change the exothermic to the endothermic character by 0.13 (Pmx) and 0.59 (Pox), and slightly decreases the exothermic character of the reaction by 2.49 (Pmn) and 2.85 (Pon), consequently the solvent effects support the regio- and chemospecificity.

Additions of the entropic activation are: -37.27 (TS_{mn}), -38.75 (TS_{on}), -41.34 (TS_{mx}) and -41.47 cal mol⁻¹K⁻¹ (TS_{ox}) indicate that the formation of the product Pmn is very favorable, in good agreement with experimental outcomes. The geometries, density map and PES of the TSs involved in the 1,3-DC reaction between the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile are depicted in figure 3.

The distances between the C atom of the mesitronitrile oxides and other atom of the 2-Fluoren-9-ylidene-malononitrile in TS_{mn}, TS_{mo}, TS_{ox} and TS_{nx} are 2.00, 2.01, 2.05 and 2.15, respectively. These distances clearly indicate that the formation of the product Pmn is favorable.

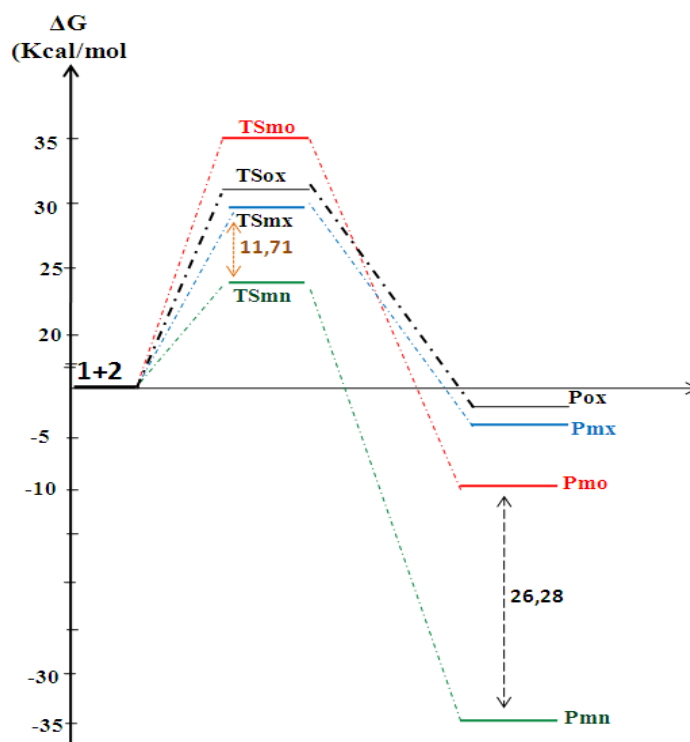


Figure 2 Gibbs free energy profile of the 1,3-DC reaction between the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile.

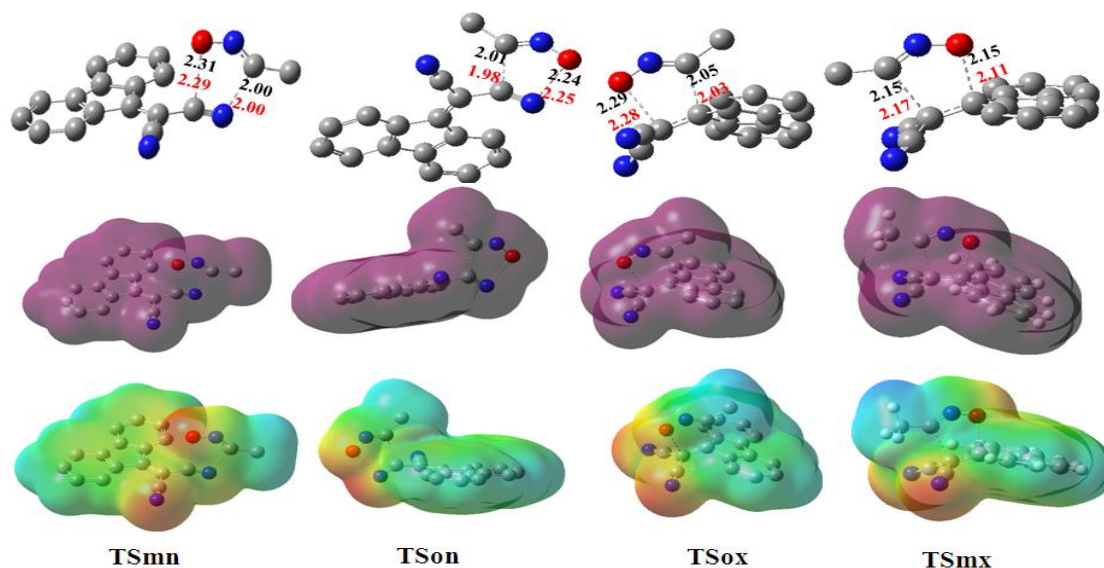


Figure 3. DFT/6-31(d) optimized density map, ESP and structures of the TSs of 1,3-DC reaction between the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile. Lengths are given in angstroms.

Conclusion

The 1,3-dipolar cycloaddition reaction of the mesitronitrile oxides and 2-fluoren-9-ylidene-malononitrile has been studied within the MEDT through DFT calculation at the B3LYP/6-31(d) computational level. The obtained results are supported by the combination of the analysis of the reactivity indices at the good state of the reagents, derived from the conceptual DFT, the exploration of the PES associated with this 1,3-DC reaction.

The analysis of the nucleophilic P_k^- Parr functions allows characterizing the C1 carbon atom as the most nucleophilic center of the mesitronitrile oxides. An exploration of the PES associated with this 1,3-DC reaction indicates that it takes place through a one-step mechanism. In gas phase, the exothermic character of these 1,3-DC reactions makes the formation of the four products Pmn, Pon, Pmx and Pox irreversible. Inclusion of solvent the products Pmx and Pox had endothermic character, and finally and in solvent the CA Pmn is thermodynamically and kinetically very favored in good agreement experimental outcomes.

References

1. Arrieta A., Otaegui D., Zubia A., Cossío F. P., Díaz-Ortiz A., De la Hoz A., Herrero M. A., Prieto P., Foces-Foces C., Pizarro J. L., Arriortua M. I., *J. Org. Chem.* 72 (2007) 4313-4313.
2. Aucagne V., Berna J., Crowley J. D., Goldup S. M., Hänni K. D., Leigh D. A., Lusby P. J., Ronaldson V. E., Slawin A. M. Z., Viterisi A., Walker D. B., *J. AM. CHEM. SOC.* 129 (2007) 11950–11963.
3. Wang L., Peng S., Danence L. J. T., Gao Y., Wang J., *Chem. Eur. J.* 18(2012) 6088-6093.
4. Zaki M., Oukhrib A., Akssira M., Berteina-Raboin S., *RSC Adv.* 7 (2017) 6523-6529.
5. Velazquez S., Alvarez R., Perez C., Gago F., De C., Balzarini J., Camarasa M., *J. Antivir. Chem. Chemother.* 9 (1998) 481-489.
6. Alvarez R., Velazquez S., San F., Aquaro S., C.De, Perno C. F., Karlsson A., Balzarini J., Camarasa M. J. *J. Med. Chem.* 37 (1994) 4185-4189.
7. Genin M. J., Allwine D. A., Anderson D. J., Barbachyn M. R., Emmert D. E., Garmon S. A., Graber D. R., Grega K. C., Hester J. B., Hutchinson D. K., Morris J., Reischer R. J., Ford C. W., Zurenko G. E., Hamel J. C., Schaadt R. D., Stapert D., Yagi B. H., *J. Med. Chem.* 43 (2000) 953-970.
8. Brockunier L. L., Parmee E. R., Ok H. O., andelore C M. R., Cascieri M. A., Colwell L. F., Deng L, Feeney W. P., Forrest M. J., Hom G. J., MacIntyre D. E., Tota L., Wyvratt M. J., Fisher M. H., Weber A. E., *Med. Chem. Lett.* 10 (2000) 2111-2114.
9. EssD. H. Houk K. N., *J. Am. Chem. Soc.* 129 (2007) 10646-10647.
10. Osuna S., Houk K. N., *Chem. Eur. J.* 15 (2009) 13219- 13231.
11. Ess D. H., Houk K. N., *J. Am. Chem. Soc.* 130 (2008) 10187 –10198.
12. Bickelhaupt F. M., *J. Comput. Chem.* 20 (1999) 114 –128.
13. Fernández I., Bickelhaup F. M., *Chem. Soc. Rev.* 43 (2014) 4953 -4967.
14. Hohenberg P., Kohn W., *Phys Rev B*, 136 (1964) 864-871.
15. Domingo L. R., *RSC Adv*, 4 (2014) 32415 -32428.
16. Ríos-Gutiérrez M., Darù A., Tejero T., Domingo L. R., Merino P., *Organic & Biomolecular Chemistry* (2017).
17. Domingo L. R., Ríos-Gutiérrez M., Pérez P., *Molecules*, 21 (2016) 748.
18. Lianis P. S., Rodios N. A., Alexandrou N. E., *Journal of Heterocyclic Chemistry*, 25 (1988) 1099 –1102.
19. Yanai T., Tew D. P., Handy N. C., *Chemical Physics Letters*, 393 (2004) 51 –57.
20. Francl M. M., Pietro W. J., Hehre W. J., *J. Chem. Phys.* 77 (1982) 3654-3665.
21. Gaussian 09, Revision A.02, M. J. Frisch et al.
22. Parr R. G., Szentpaly L. V., Liu S., *J Am Chem Soc*, 121 (1999) 1922-1924.
23. Domingo L. R., Chamorro E., Pérez P., *J. Org. Chem.* 73 (2008) 4615-4624.
24. Domingo L. R., Pérez P., *Org. Biomol. Chem.* 9 (2011) 7168-7175.
25. Kohn W., Sham L., *J. Phys. Rev A.* 140 (1965) 1133-1138.
26. Zeroual A., Benharref A., El Hajbi A., *J Mol Model.* 21 (2015) 2594-2599.
27. El Idrissi M., El Haib A., Zoubir M., Hammal R., Zeroual A., EL Hajbi A., *Journal of Computational Methods in Molecular Design*, 6 (2016) 75-79.
28. Zeroual A., Hammal R., Benharref A., El Hajbi A., Mazoir N., *Mor. J. Chem.* 4 (4) (2016) 938 -944.
29. Zoubir M., Zeroual A., El Idrissi M., El Haib A., Moumou M., Hammal R., Mazoir N., Benharref A., El Hajbi A., *Journal of Materials and Environmental Sciences*, 8 (2017) 990-996.
30. El Idrissi M., Zoubir M., Zeroual A., El Ajlaoui R., El Haib A., Benharref A., Elhajbi A., *J. MAR. CHIM. HETEROCYCL*, 15 (2016) 145- 151.
31. Ourhriss N., Zeroual A., Ait Elhad M., Mazoir N., Abourriche A., Gadhi C. A., Benharref A., El Hajbi A., *Journal of Materials and Environmental Sciences*, 8, (2017) 1385-1390.
32. Fukui K., *J. Phys. Chem.*, 74 (1970) 4161-4163.
33. Tomasi J., Persico M., *Chem. Rev.* 94 (1994) 2027–2094.

(2017) ; <http://www.jmaterenvironsci.com>