Moroccan Journal of Chemistry
ISSN: 2351-812X
http://revues.imist.ma/?journal=morjchem&page=login
H. Hazhazi/ Mor. J. Chem. 4N°4 (2016) 1106-1116

Theoretical study of the regio- and stereoselectivity of the 1,3-DC reaction of 2,3,4,5-tetrahydropyridine-l-oxide with methyl crotonate

Halima. Hazhazi[(a)], Youcef. Boumedjane[(a)], Boulanouar. Messaoudi[(b,c)]*

(a) Laboratoire de Chimie Moléculaire et Environnement (LCME), Equipe de Chimie Informatique et Pharmaceutique (ECIP), Faculté des Sciences et Sciences Exacte - Département des sciences de la matière, Université de Biskra, BP 145 RP, 07000 Biskra, Algérie

(b) Laboratoire de Thermodynamique Appliquée et Modélisation Moléculaire, Département de Chimie, Faculté des Sciences, Université A. Belkaid, BP 119, Tlemcen, 13000, Algérie

[(c)] Ecole Préparatoire en Sciences et Techniques Tlemcen, BP 165 RP Bel horizon, 13000 Tlemcen, Algérie

Abstract

A theoretical study of the regio- and stereoselectivities of the 1,3-dipolar cycloaddition reaction between methyl crotonate and 2,3,4,5-tetrahydropyridine-l-oxide has been carried out using density functional theory (DFT) calculations at B3LYP/6-31G(d) level of theory. Analysis of the global reactivity and local electrophilicity indices has been used to explaining the regioselectivity of the titled reaction. Overall, our results show that the studied 1, 3-dipolar cycloaddition reactions favor the formation of the meta-endo cycloadduct in both cases. The bond order and charge transfer at the transition states and activation energies indicate that these reactions proceed via an asynchronous concerted mechanism. Thermodynamic and kinetic quantities for the possible stereoisomeric and regioisomeric pathways have been calculated at gas and solvent phase. Solvent effects do not modify the gas-phase selectivities but slightly increases the reactivity of the reagents. A good concordance is found between the obtained results and the experimental outcomes.

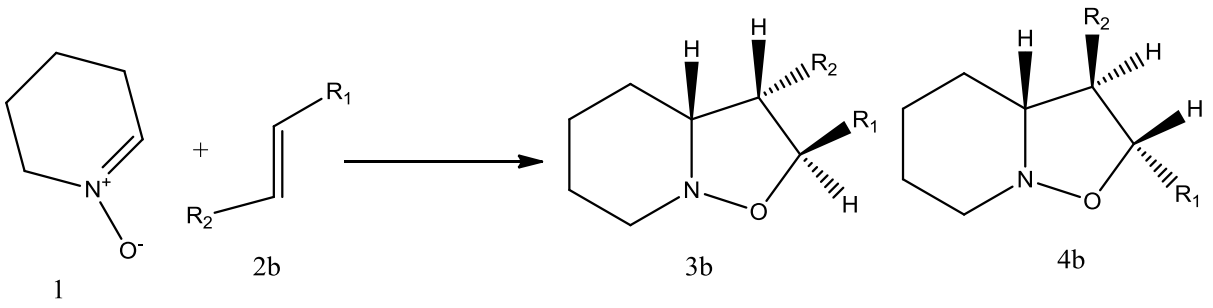
* *Corresponding author:*
messaoudiboulanouar@gmail.com

Received 20 Sept 2016,
Revised 16 Dec 2016,
Accepted 16 Jan 2017

Keywords: 1,3-Dipolar cycloaddition; 2,3,4,5-tetrahydropyridine-l-oxide; Selectivity; DFT calculations.

1. Introduction

Cycloaddition reactions are among the most powerful tools for synthesis and mechanistic interest in organic chemistry area because of their capacity to construct in region- and /or stereoselectively method[1]. The current understanding of the underlying principles of 1,3- dipolar cycloaddition (1,3-DC) reactions has grown from the interplay between theory and experiment[2]. The 1,3-DC are a versatile manner for obtaining five-membered heterocycles[3]. Several experimental and theoretical studies continued to populate the literature over different manners of the 1,3 dipolar cycloaddition[4]. Reactions between nitrones and alkenes to obtaining isoxazolidines are well-known due to their great importance in construction processes[2-5]. Substituted isoxazolidines are interesting biological active compounds[6] that could be used as enzyme inhibitors[7-8], and applied as synthetic intermediates of a variety of compounds[9]. Many theoretical investigations have been devoted to the study of regio- and stereoselectivities of 13DC reactions of nitrone with alkenes[10]. Recently, reactivity descriptors based on the density functional theory (DFT) have been widely used for the prediction of the regioselectivity[11]. Kumar Das et al[4]. have studied the 1,3-dipolar cycloadditions of both 1-phenylethyl-trans-2-metyl nitrone with styrene and 1-phenylethyl nitrone with allyl alcohol. An analysis of frontier orbitals interaction, electrophilicity difference, Pauling's bond order and Wiberg bond index in the transition state was found to be in good agreement with the experimental data. A few years ago, Cossó et al[12]. have used B3LYP/6-31G(d) level of theory to study the 1,3-dipolar cycloaddition reaction of unsubstituted nitrone with nitroethene. Asynchronicity in the bond formation process for the two regioisomeric approaches was found to be electron-deficient dipolarophile controlled. Liu et al[13]. have performed DFT calculations at B3LYP/6-31G(d) on the 1,3-dipolar cycloaddition reaction of the simplest nitrone to dipolarophiles containing electron-releasing substituents. Another time again, the endo approach is kinetically favoured because of the stabilising secondary orbital interactions. Moreover, Nacerddine et al[14]. have studied the region and stereoselectivities of the 1,3- dipolar cycloaddition of C-diethoxyphophoryl-N- methylnitrone with substituted alkenes. The given analysis of potential energy surface shows that these 1,3-dipolar cycloaddition reactions favour the formation of the ortho-trans cycloadduct in both cases to be in good agreement with experimental findings. Very recently, Marakchi et al[15]. have studied the mechanism of the 1,3-dipolar cycloaddition reaction between nitrone and sulfonylethene chloride using ab initio and DFT methods. HF and DFT calculations predict meta path, in agreement with the experimental results, while MP2 calculations provided the ortho regioselectivity. In another work, Khorief et al[16]. have studied the region and stereoselectivities of the 1,3-dipolar cycloaddition reaction between C-phenyl-N-methylnitrone and Ethylvinylether. The ortho/ endo were produced to be more favorable kinetically and thermodynamically. Later, Chafaa et al[17]. have reported a DFT calculations at B3LYP/6-31+G(d) level of the 1,3-dipolar cycloaddition of C-diethoxyphosphoryl-N-methlnitrone and N-(2-florophenyl)acrylamide. Analysis of the bond order and charge transfer at the transition states indicates a one –step asynchronous mechanism. Experimentally, Asrof et al[18]. have determined the 1,3-DC reaction between 2,3,4,5-tetrahydropyridine-1-oxide **1** and methyl crotonate **2b** to giving a mixture of substituted isoxazolidines (see Scheme 1) **3b** and **4b** with a ratio of 90:10, respectively. The stereochemistry of the major adduct is depicted in **4b** having endo oriented carbomethoxy group which is known to manifest favourable secondary orbital interaction. Our interest in this study is focused on the investigation and interpretation of the regio- and stereoselectivities of the 1,3-DC reactions of 2,3,4,5 tetrahydropyridine1-oxide(dipole) with methyl crotonate (dipolarophile) by using several theoretical frontier molecular orbital (FMO) interactions, conceptual DFT, and the analysis of stationary points.



Scheme 1: 1,3-Dipolar cycloaddition of 2,3,4,5-tetrahydropyridine-l-oxide with methylcrotonate

2/Theory and computational details

The reported quantum chemical calculations were performed at the B3LYP/6-31G(d) level of theory using GAUSSIAN 09 suite of programs[19]. Full geometry optimizations followed by frequency calculations at the same level of theory were carried out for all stationary points. The intrinsic reactions coordinate (IRC)[20] path was calculated in order to check that each TS connects well to the two corresponding minima in the energy profiles of the proposed mechanism. Atomic electronic populations were computed using the natural bond orbital (NBO) method[21]. Bulk solvent effects of Dichloromethane were considered implicitly by performing single point energy calculations on the gas phase stationary structures using the polarisable continuum model (PCM) as developed by Tomasi's group[22] on the basis of the self-consistent reaction field (SCRF) background[23-24]. Values of enthalpy and free energy were obtained by frequency calculations over B3LYP/6-31G(d) geometries.

The global electrophilicity index ω[25], is given by

$$\omega = (\mu^2/2\eta) \qquad (1)$$

where "μ" is the electronic chemical potential and "η" is the chemical hardness[26]. These quantities could be expressed as a function of the frontier molecular orbitals HOMO and LUMO, ε_H and ε_L, as:

$$\mu \approx (\varepsilon_{HOMO} + \varepsilon_{LUMO})/2 \qquad (2)$$

$$\eta \approx (\varepsilon_{LUMO} - \varepsilon_{HOMO}) \qquad (3)$$

A new empirical (relative) nucleophilicity index N[27] has been recently introduced on the basis of the HOMO energies[28]:

$$N = E_{HOMO(nucleophile)} - E_{HOMO(TCE)} \qquad (4)$$

The tetracyanoethylene (TCE) is taken as a reference because of its lower HOMO energy in a large series of molecules [29].

The local electrophilicity index, ω_k[30] condensed to atom k is easily obtained by projecting the global quantity onto any atomic center k in the molecule by using the electrophilic Fukui index (i.e. the Fukui function for the nucleophilic attack f_k^+). This gives the following equation:

$$\omega_k = \omega f_k^+ \qquad (5)$$

The local nucleophilicity condensed to atom k (N_k)[31] was then calculated as:

$$N_k = N f_k^- \qquad (6)$$

For an atom k in a molecule, three different types of condensed Fukui function could be considered,[32]

$f^+ = [\rho_k (N + 1) - \rho_k (N)]$ (for nucleophilic attack), (7a)

$f^- = [\rho_k (N) - \rho_k (N - 1)]$ (for electrophilic attack), (7b)

where ρ_k (N), ρ_k (N - 1) and ρ_k (N + 1) are the gross electronic populations of the site k in neutral, cationic, and anionic systems, respectively.

3/Results and discussion

3.1 Regioselectivity study based on DFT reactivity indices

The determination of NED/IED reaction character is necessary for the prediction of regioselectivity. This characterization can be performed by using electronic chemical potential (μ), global electrophilicity (ω), global nucleophilicity N and HOMO–LUMO gap. This latter is calculated by considering the directly involved orbitals in the reaction. Frontier molecular orbitals Fig.1 analysis shows that HOMO and LUMO of the nitrone are π molecular orbitals (MOs).

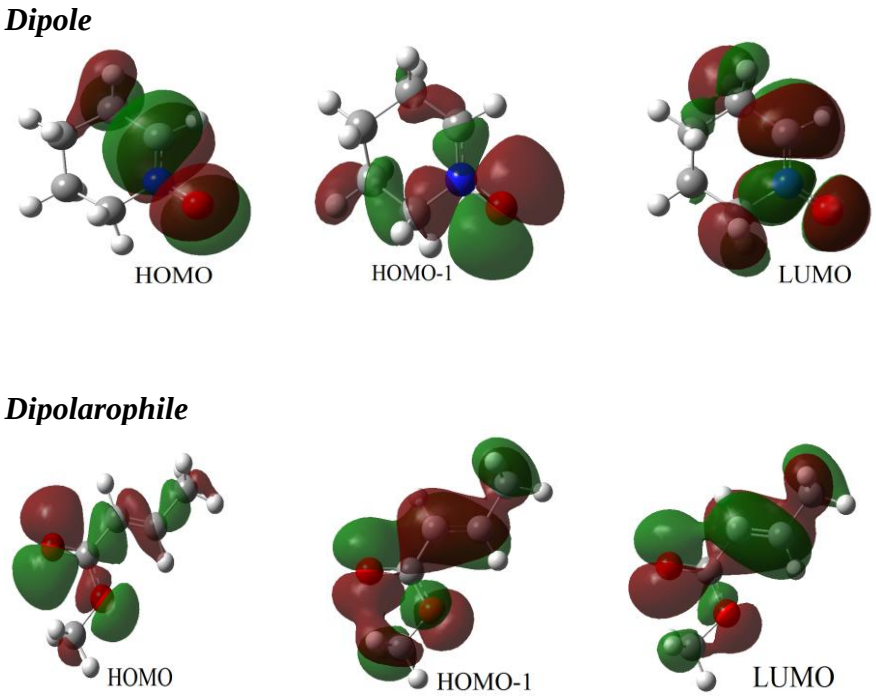


Fig1. Optimized geometries and visualized FMOs for the reactants

On one hand, the HOMO of the methyl crotonate is a nonbonding MO localized essentially on the carbonyl group's oxygen. Consequently, it will not be directly involved in the 1, 3-DC process. On the other hand, the dipolarophile's $HOMO^{-1}$ is a bonding π molecular orbital showing an important contribution of the active sites' atoms Fig.1 The HOMO-1 density (dipolarophile) is more pronounced than the HOMO ones. Thus, the cycloaddition reaction will take place between the LUMO of the dipole and the HOMO-1 of the dipolarophile. In the light of FMO theory, Sustmann[33] classified various types. Type (I) is the FMO interaction between the highest occupied molecular orbital of the 1, 3-dipole ($HOMO_{dipole}$) and the lowest unoccupied molecular orbital of the dipolarophile ($LUMO_{dipolarophile}$) that is corresponding the normal-electron demand (NED) $\Delta E(I) = HOMO_{dipole} - LUMO_{dipolarophile}$ (4.406 eV) a large number of 1,3-DC reactions is classified in. Type (II) interaction between the LUMO of dipole and the $HOMO_{-1}$ of dipolarophile. This type is named as the inverse-electron demand (IED) ΔE (II) = $HOMO_{-1\ dipolarophile}$-$LUMO_{dipole}$ (7.072 eV). These types of interactions are illustrated in Fig 2.

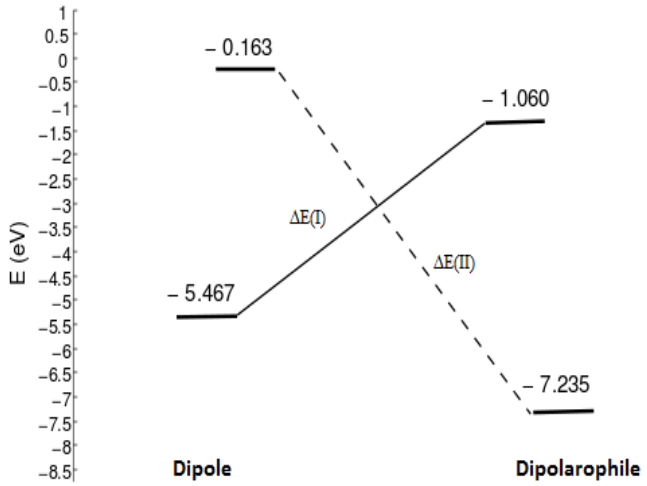


Fig 2. The interactions between HOMO and LUMO orbitals of a 1, 3-dipole/dipolarophile

According to the Houk rule[34], the regioselectivity of 1,3-DC reactions can be explained on the basis of large- large and small- small FMO interactions that are more favoured than large- small and small- large ones. The coefficients of frontier molecular orbitals (FMOs) of the reactants, given in Table 1, show that the most favoured interactions are between O_7 of the dipole and C_1 of the dipolarophile and C_1 of dipole interact with C_2 of dipolarophile leading to the formation of meta regioisomer as the major product. This fact is in agreement with the study of K. Marakchi et al[15] of 1,3-DC between pyrraline -1-oxide and methyl crotonate.

Table 1. FMOs Molecular Coefficients of the dipole and dipolarophile

Dipole				Dipolarophile			
HOMO		LUMO		HOMO-1		LUMO	
C1	O7	C1	O7	C1	C2	C1	C2
-0.3898	0.4677	0.3877	0.3021	0.3449	0.3850	0.4025	-0.2447

In Table 2 are displayed the HOMO and LUMO energies, electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and global nucleophilicity N of the dipole and dipolarophile.

Table 2. FMO energies (a.u), electronic chemical potential (a.u), chemical hardness (a.u), electrophilicity index (eV) and nucleophilicity index (eV)

	HOMO	**LUMO**	μ	η	ω	N^a
Dipole	-0.201	-0.006	-0 .103	0.195	0.740	3.649
Dipolarophile	-0.266	-0.039	-0.152	0.227	1.384	1.881

HOMO energy of tetracyanoethylene is −0.3351 a.u at the same level of theory. Chemical potential, hardness, electrophilicity and nucleophilicity values are associated to the HOMO-1 of dipolarophile.

The electronic chemical potential (μ) of dipole (-0.103 eV) is greater than that of dipolarophile (-0 .152 eV). Consequently, the charge transfer will take place from the 1, 3-dipole to dipolarophile. The Values of electrophilicity indices (ω) of reactants are 1.384 and 0.740 eV for methyl crotonate (dipolarophile) and nitrone (dipole), respectively. As it can be seen, the values of ΔE (HOMO-LUMO gap) for NED character are predicted to be lower than that corresponding to IED. Many studies dealing with cycloaddition reactions are based on the electrophilic (f_k^-) and nucleophilic (f_k^+), Parr functions attacks. Negative values of Fukui functions can be obtained from various population analyses. However, Hirshfeld's population [35] guarantees positive Fukui functions values, thus it is a good means to predict the right regioselectivity[36,37]. Therefore, Fukui functions based on the Hirshfeld's population were calculated for the studied reactants and the corresponding results are given in Table 3. Prediction of regioselectivity can also be performed by using the Chattaraj's polar model where local philicity indices are used[38]. Values of local electrophilicity ω_k and local nucleophilicity N_k are listed in Table 3 and the corresponding most favourable two-centre interaction is shown in Fig 3. In dipolar cycloaddition, the most favourable attack takes place between C1 atom of the dipolarophile (the preferred position for a nucleophilic attack) and O7 of the dipole, leading to the formation of the meta-regioisomer.

Table 3. Local properties of dipole and dipolarophiles calculated at B3LYP/6-31G (d) level of theory

Reactant	*Site*	NPA				Chelpg			
		f^+	f^-	ω	N	f^+	f^-	ω	N
Dipole	O_7	0.189	0.423	0 .140	1 .543	0.211	0.355	0.156	1.295
	C_1	0.298	0.312	0.220	1.138	0.435	0.268	0.180	0.977
Dipolarophile	C_1	0.225	0.246	0.300	0.469	0.234	0.268	0.311	0.511
	C_2	0.116	0.392	0.154	0.747	0.114	0.397	0.151	0.288

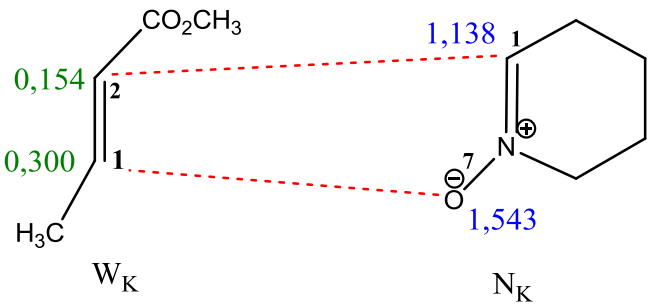
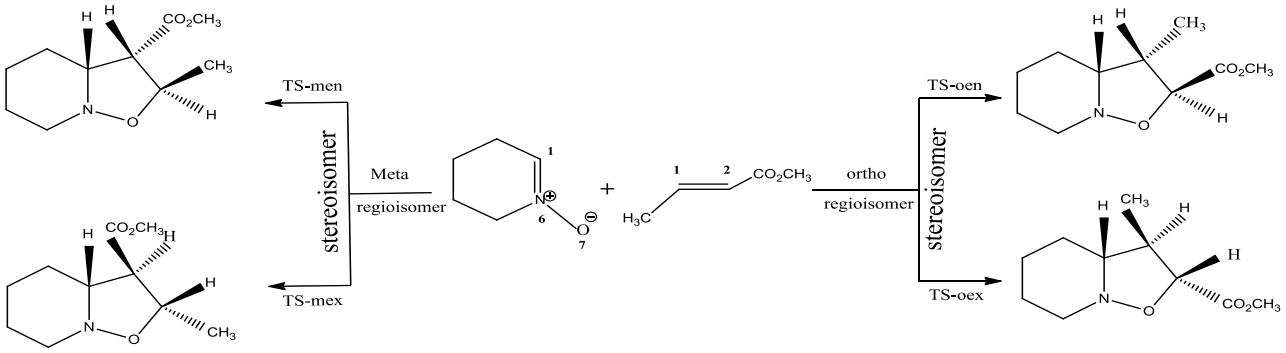


Fig 3. Prediction of the favoured interactions between dipole and dipolarophile using DFT based indices

3.2. Mechanistic study of the cycloaddition reaction based on activation energy

3.2.1. Energies of the Transition Structures

The 1-3 DC reactions of nitrone with dipolarophile can happen along four possible reactive channels corresponding to the endo and exo approach modes in two different regioisomeric channels; the meta and ortho reactions (see Scheme 2). The right pathway corresponds to the O7-C2 and C1-C1 forming bond processes, while the left pathway corresponds to the O7-C1 and C1-C2 ones. Four transition states designated as: TS-men, TS-mex, TS-oen, and TS-oex have been confirmed by frequency calculations. The geometries of the four TSs are represented in Fig 4. The studied energies and relative energies of reactants in both the gas phase and DCM solvent are given in Table 4. The PES schemes, corresponding to the four reactive channels, are given in Fig 5 and 6.



Scheme 2. The exo and endo approaches of tetrahydropyridine -1-oxide to methyl crotonate.

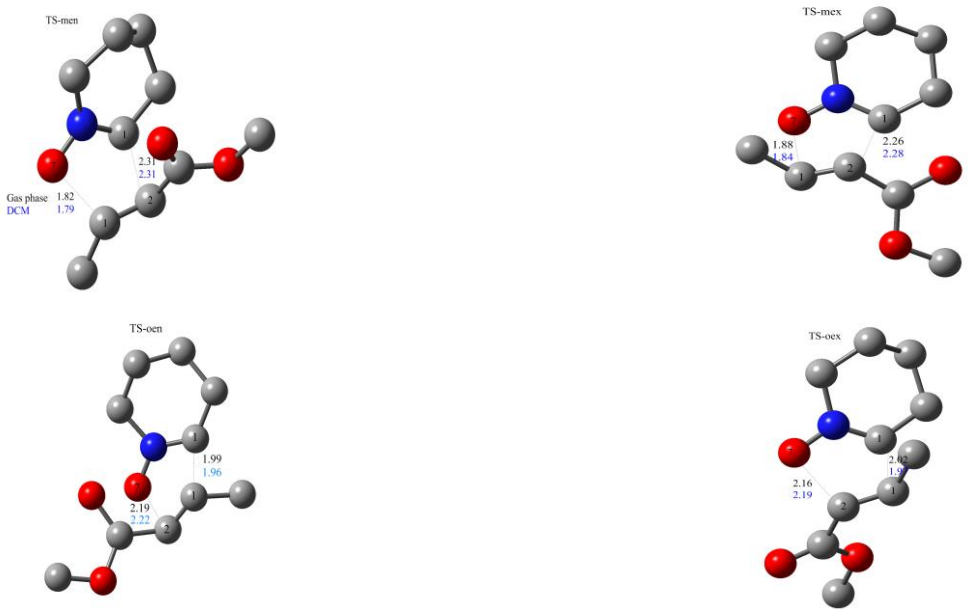


Fig 4. Optimized transition structures of the 1-3 DC reaction between tetrahydropyridine-1-oxide and methyl crotonate

The calculated activation energies and relative electronic energies of the stationary points involved in the 13DC of 2,3,4,5-tetrahydropyridine-l-oxide with methylcrotonate in both cases the gas-phase and dichloromethane solvent are shown in Table 4. The activation energy TS-**men** (6.45 kcal/mol) is lower compared to that of the **TS- mex** (10.91 kcal/mol), **TS-oen** (11.25 kcal/mol) and **TS-oex** (15.47 kcal /mol), In dichloromethane, the reactants are slightly more stabilized than the TSs and this results the activation energies increase respectively **TS-men** (10.45), **TS-mex** (13.80) , **TS-oen** (14.73) and **TS-oex** (17.43) kcal/mol, that is to say, the formation of pathways **P-men** in the gas phase is easier than that in the solvent. We have to note that these 1,3-DC reactions are strongly exothermic. In addition, solvent effects decreased their exothermicity while their corresponding activation energies increased as a consequence of the greater solvation of polar nitrone[39]. The comparison of relative energies with relative free energies given in Table 4 shows that the trends in region- and stereoselectivity are essentially coincident. Finally, we can conclude that the energy results indicate that the **P-men** shows a very high reactivity, both kinetically and thermodynamically.

Table 4. Total energies (a.u), Relative energies ΔE (in kcal/mol), relative free energies ΔG (in kcal/mol) and enthalpies ΔH (in kcal/mol) in gas phase and in DCM, of the stationary points involved in the 1, 3-DC reaction between 2,3,4,5-tetrahydropyridine-1-oxide and methyl crotonate

Stationary point	Gas phase				Dichloromethane solvent			
	ΔG	ΔH	ΔE^*	E_T	ΔG	ΔH	ΔE^*	E_T
Dipole				-325.8570278				-325.8656038
Dipolarophile				-345.7852858				-345.7903845
TS-men	21. 75	8. 05	6. 45	-671.6320213	24. 98	11. 88	10. 45	-671.6393249
TS-mex	25. 71	12. 38	10. 91	-671.6249129	28. 56	15. 27	13. 80	-671.6339965
P-men	-6. 16	-20. 20	-23. 62	-671.6742828	-1. 80	-15. 70	-19. 04	-671.6813970
P-mex	-2. 72	-16. 07	-19. 56	-671.6734902	1. 17	-12. 20	-15. 75	-671.6810906
TS-oex	30. 52	16. 97	15. 47	-671.6176606	32. 56	19. 00	17. 43	-671.6282077
TS-oen	26. 25	12. 76	11. 25	-671.6243785	29. 81	16. 28	14. 73	-671.6325104
P-oen	-3. 87	-17. 80	-15. 56	-671.6671208	0.47	-13. 70	-12. 07	-671.6752383
P-oex	-2. 69	-16. 60	-13. 77	-671.6642700	1. 10	-12. 70	-10. 90	-671.6733701

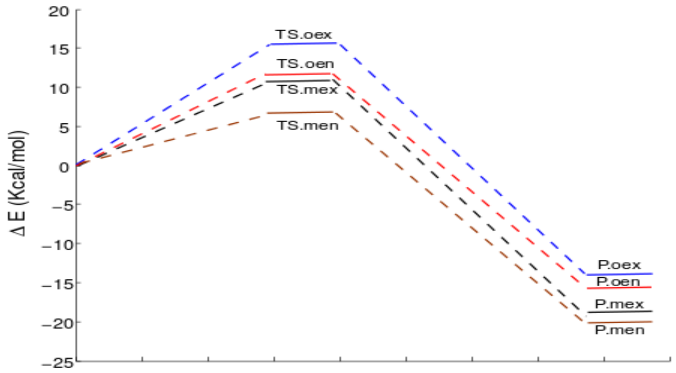


Fig 5. Energy profiles, in kcal/mol, for the 1,3-DC reactions of stationary point in gas phase

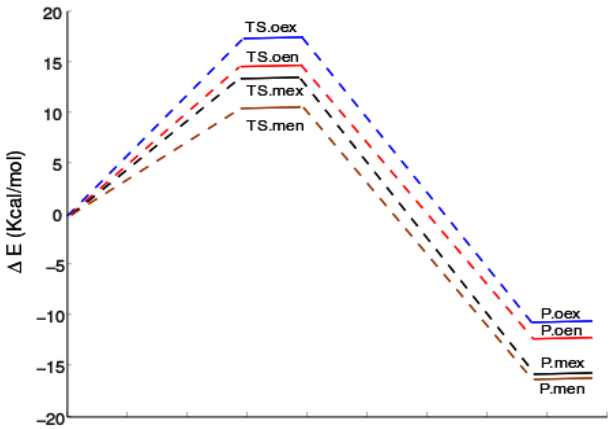


Fig 6. Energy profiles, in kcal/mol, for the 1,3-DC reactions of stationary point in solvent phase

3.2.2. Geometry analysis

Table 5. Values of |Δ*d*| in TS-men, TS-mex, TS-oen and TS-oex of the 1, 3-DC reaction of dipolarophile with dipole in the gas phase and solvent DCM

	Gas phase			**DCM**		
	Meta channels			**Meta channels**		
	$d(O_7–C_1)$	$d(C_1-C_2)$	Δd	$d(O_7–C_1)$	$d(C_1-C_2)$	Δd
TS-men	1.82	2.31	0.48	1.79	2.31	0.52
TS-mex	1.88	2.26	0.37	1.84	2.28	0.44
	Ortho channels			**Ortho channels**		
	$d(O_7-C_2)$	$d(C_1-C_1)$	Δd	$d(O_7-C_2)$	$d(C_1-C_1)$	Δd
TS-oen	2.19	1.99	0.20	2.22	1.96	0.26
TS-oex	2.16	2.02	0.14	2.19	1.97	0.40

Comparison of the most relevant geometrical parameters of the four TSs involved in gas phase and in solvent 13DCs of the 2,3,4,5-tetrahydropyridine-1-oxide with methyl crotonate is presented in Figure 4. The corresponding selected geometric parameters are given in Table 5. The lengths of the bonds of the C1-C2 are: (2.31 – 2.62) Å and O7-C1 (1.82 – 1.88) Å at the **TS-men** and **TS-mex**, respectively, while at the **TS- men** and **TS-mex** involved in the DCM are: C1-C2 (2.31-2.28) Å and O7-C1 (1.79 – 1.84) Å. These values indicate that they correspond to asynchronous bond formation processes where the lengths of the O-C are shorter than the C-C bonds. However, in the **TS- oen** and **TS-oex**, O–C forming bonds (2.19 and 2.16 Å) are longer than C–C forming bonds (1.99 and 2.02 Å); the lengths of the bonds in the solvent are the same as in the gas phase i.e. O-C is longer than C-C. This shows a change of the dissymmetry on the bond formation process for the two regioisomeric pathways.

The degree of asynchronicity of bond formation at the TSs is determined by considering the difference between the lengths of the two new σ forming bonds such as Δd = [d1 - d2] for four pathways. Values of Δd for the **TS-men** are high asynchronous and more favorable stereoisomeric with respect to the other channels.

Conclusion:

In this work, the 13DC reaction of 2,3,4,5-tetrahydropyridine-l-oxide with methyl crotonate, the regio- and stereoselectivities have been thoroughly probed using DFT methods at the B3LYP/6-31G(d) theoretical level. The ortho/meta regioisomeric pathways along with the endo and exo stereoisomeric channels have been studied on the basis of both kinetic and thermodynamic controls. The regioselectivity has been analyzed and confirmed through DFT based indices. The calculated electrophilic, f_k^+, and nucleophilic, f_k^-, indices prove clearly that the meta channels are the major and most favourable regioisomeric paths. In all the studied cases, the reaction pathways leading to the endo/meta are the most favourable. These 13DCs have basically asynchronous concerted mechanisms and not one presents a stepwise mechanism as a consequence there was no intermediate localization along the present study. The solvent slightly affects the activation energies due to the better solvation of the reactants. All in all, the obtained results using the present theoretical approaches are in good agreement with experimental data.

Acknowledgements

The Ministry of Higher Education and Scientific Research of the Algerian Government (project CNEPRU F01420130050) is gratefully acknowledged for its support.

Supplementary material

The Cartesian coordinates of the important optimized stationary geometries (reactants, intermediates, TSs and products) along the 13DC reaction of 2,3,4,5-tetrahydropyridine-l-oxide with methyl crotonate at B3LYP/6-31 G(d) level of theory are given in supplementary material.

References

[1]. W. Carruthers. In *Some Modern Methods of organic Synthesis*; 2nd ed.; Cambridge University Press: Cambridge, 1978; W. Carruthers. In *Cycloaddition Reactions in Organic Synthesis*; ed.; J.E. Baldawin and P.D. Magnus; Pergamon: Oxford, 1990.

[2]. A. Padwa, In *Comprehensive Organic Chemistry*; Pergamon Press: Oxford, 1991; pp 1069-1109.

[3]. (a) A. Padwa, In *1,3-Dipolar Cycloaddition Chemistry*; Wiley interscience: New York, (1984) pp 1-2; (b) K.V. Gothelf, K. A. Jorgenson, *Chem Rev*., 98 (1998) 863-910.

[4]. T. K. Das, S. Salampuria, M. Banerjee, *J. Mol. Struct. Theochem*., 959 (2010) 22-29.

[5]. (a) A. Padwa, Y. Tomioka, M. K. Venkatramanan, *Tetrahedron Lett*., 28 (1987) 755-758; (b) E. Breuer, H. G. Aurich, In *Nielsen Nitrones, nitronates and nitroxides*; New York: Wiley, 1989; (c) K. B. G. Torssell, In *Nitrile oxides, nitrones and nitronates in organic synthesis*; New York: VCH, 1998; (d) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev*., 98 (1998) 863-910; (e) S. Majumder, P. Bhuyan, J. *Tetrahedron Lett*., 53 (2012) 762-764.

[6]. A. R. Minter, B. B. Brennan, A. K. Mapp, *J. Am. Chem. Soc*., 126 (2004) 10504-10505.

[7]. P. Ding, M. Miller, Y. Chen, P. Helquist, A. J. Oliver, O. Wiest, *Org. Lett*., 6 (2004) 1805-1808.

[8]. G. Wess, W. Kramer, G. Schuber, A. Enhsen, K. H. Baringhaus, H. Globmik, S. Müller, K. Bock, H. Klein, M. John, G. Neckermann, A. Hoffmann, *Tetrahedron Lett*., 34 (1993) 819.

[9]. K. Marakchi, R. Ghailane, O. Kabbaj, N. Komiha, J. *Chem. Sci*., 126 (2014) 283–292.

[10]. S. Bouacha, A. H. Djerourou, I. Chemo, *J. Sci* ., 4 (2013) 1941-3955.

[11]. R. G. Parr, R.G. Pearson, *J. Am. Chem. Soc*., 105 (1983) 7512-7516.

[12]. F. P. Cossío, I. Marao, H. Jiao, P. V. R. Schleyer, *J. Am. Chem. Soc*., 121 (1999) 6737-6746.

[13]. J. Liu, S. Niwayama, Y. You, K. N. Houk, *J. Org. Chem*., 63 (1998) 1064-1073.

[14]. A. K. Nacereddine, W. Yahia, S. Bouacha, A. Djerourou, *Tetrahedron Lett*., 51 (2010) 2617- 2621.

[15]. K. Marakchi, O. Kabbaj, N. Komiha, R. Jalal, M. Esseffar, *J. Mol. Struct. Theochem*., 620 (2003) 271-281.

[16]. A. K. Nacereddi, W. Yahia, C. Sobhi, H. Layeb, Z. Lechtar, A. Djerourou, J. *Appl. Biopharm. Pharmacokinet*., 1 (2013) 18-23.

[17]. F. Chafaa, D. Hellel, A. K. Nacereddine, A. Djerourou, *Mol. Phy*., 114 (2015) 663-670.

[18]. Sk. A. Ali, J. H. Khan, M. I. M. Wazeer, P. H. Perzanowski. *Tetrahedron*., 45 (1989) 5979-5986.

[19]. Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B.Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, F. J. B. Farkas, J. V. Ortiz, J. Cioslowski, D. Fox, J. Wallingford, CT, 2009.

[20]. K. Fukui, *J. Phys. Chem*., 74 (1970) 4161–4163.
[21]. A. E. Reed, F. Weinhold, *J. Chem. Phys*., 78 (1983) 4066-4073.
[22]. J. Tomasi, M. Persico, *Chem. Rev*., 94 (1994) 2017–2094.
[23]. E. Cances, B. Mennucci, J. Tomasi, *J. Chem. Phys*., 107 (1997) 3032–3041.
[24]. M. Cossi, V. Barone, R. Cammi, J. Tomasi, *Chem. Phys. Lett*., 255 (1996**)** 327–335.
[25]. R. G. Parr, L. von Szentpaly, S. Liu, *J. Am. Chem. Soc*., 121 (1999) 1922-1924.
[26]. (a) R. G. Parr, R. G. Pearson, *J. Am. Chem. Soc*., 105 (1983) 7512-7514; (b) R. G. Parr, W. Yang, In *Density Functional Theory of Atoms and Molecules*; Oxford University: New York., (1989).
[27]. (a) L. R. Domingo, E. Chamorro, P. Pérez, *J. Org. Chem*., 73 (2008) 4615-4624; (b) L. R. Domingo, P. Pérez, *Org. Biomol. Chem*., 9 (2011) 7168-7175.
[28]. W. Kohn, L. Sham, *J. Phys. Rev*., 140 (1965) 1133-1138.
[29]. (a) L. R. Domingo, E. Chamorro, P. Pérez, *J. Org. Chem*., 73(12) (2008) 4615-4624. (b) P. Jaramillo, L. R. Domingo, E. Chamorro, P. Pérez, *J. Mol. Struct. Theochem*., 865(2008**)** 68-72.
[30]. L. R . Domingo, M. J. Aurell, P. Pérez, R. Contreras, *J. Phys. Chem. A*., 106 (2002) 6871.
[31]. P .Pérez, L. R. Domingo, M. Duque-Norna, E. Chamorro, *J. Mol. Struct. Theochem*., 895 (2009) 86.
[32]. W. Yang, W. J. Mortier, *J. Am. Chem. Soc*., 108 (1986) 5708.
[33]. R. Sustmann, R. Shubert, *Tetrahedron Lett*., 13 (1972) 4271.
[34]. K.N. Houk, Accounts Chem Res., 8(11) (1975) 361-69.
[35]. F.L. Hirshfeld, *Theor .Chem. Acc*., *44* (1977) 129-38.
[36]. J. Padmanabhan, R. Parthasarathi, U. Sarkar, V. Subramanian, P.K. Chattaraj, *Chem. Phys. Lett*., 383 (2004) 122.
[37]. R. K. Roy, S. Pal, K. Hirao, *J. Chem. Phys*., 110 (1999) 8236.
[38]. R.G. Parr, L. Von Szentpaly, S. Liu, *J. Am. Chem. Soc*., 121 (1999) 1922.
[39]. K. Marakchi, R. Ghailane, O. Kabbaj, N. Komiha, *J. Chem. Sci*., 126 (2014) 283–292.