

DFT study of nitrogenated heterocycles of six and seven links

H. Merouani^{1,3}, A. Ounissi^{2,3}, N. Ouddai^{3*}

¹Department of Chemistry, Faculty of Science, University Mohamed Boudiaf M'sila, 28000 M'sila, Algeria.

²Laboratoire de Génie des procédés chimiques, Université Setif-1, Algeria

³Laboratoire de chimie des matériaux et des vivants: Activité, Réactivité, University EL-Hadj Lakhdar Batna, 05000 Batna, Algeria

Received October 30, 2016; Revised December 14, 2016

The 1,3-dipolar cycloadditions (13DC) of the azides were carried out at the B3LYP / 6-31G (d) level. The results obtained show that the aziridinomorpholine formation from the triazoline by removing the di-azote molecule is thermally spontaneous starting from 463.15 K. However, that of seven chains undergoes a cycloreversion at 533.15 K with the R7 reagent (2,4-hexadienyloxypropyl azide), this reaction requires irradiation with ultraviolet light.

Keywords: nitrogenated heterocycles, DFT calculation, molecules reactivity, descriptor dual

INTRODUCTION

The 1,3-dipolar cycloaddition (CD13) reactions are a widespread category of reactions on which numerous studies have been carried out in particular by Huisgen, who has made an exhaustive study of the possible reactions between dipoles and dipolarophiles [1]. Houk et al. Have also contributed to understanding and predicting the reactivity and regioselectivity of (CD13) reactions [2]. These reactions are also used for the synthesis of natural products such as sugar derivatives [3], β -lactams [4], amino acids [5], alkaloids [6] and products of pharmacological interest such as pyrazolines having several biological activities (anti-inflammatory, analgesic, herbicides, etc.) [7]. The 1,3-dipolar cycloadditions are an excellent method for forming 5-membered heterocycles. Thus the use of azide constitutes a good way to synthesise the nitrogenous heterocycles.

The aziridines are three-membered heterocycles comprising nitrogen and two carbons, two methylenes linked to a secondary amine, which is isolatable and even possible to distill [8]. On account of the intrinsic instability of aziridines, these are not abundant in nature, but chemists have nevertheless synthesized some analogues with interesting properties, for example, we can mention the proteins comprising an aziridine in place of a methylene on a glycine [9]. The best example of biologically active molecules comprising an aziridine is certainly the mitomycin family [10], the expulsion of two

nitrogen atoms from the triazoline ring in form of molecular nitrogen "N₂" allows the formation of an aziridine [11,12]. This process can be carried out by irradiation with ultraviolet light or by thermolysis using high temperature heating (scheme 1).

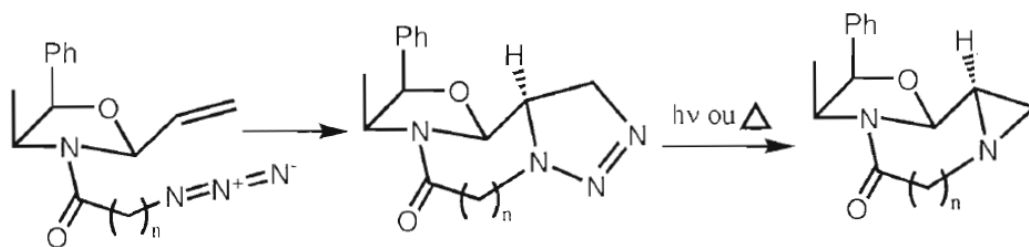
Morpholine skeleton compounds are of great biological interest because of their fungicides, analgesics and antidepressant properties.

Our aim in this research activity is to carry out a theoretical study on the synthesis of six-chain (aziridinomorpholine) and seven-chain nitrogen heterocycles, we will focus on the stereochemical analysis of the 1,3-dipolar cycloaddition and then determine whether the conversion of the cycloadduitriazoline to the corresponding aziridine allows a stereochemical control. The synthesis of aziridinomorpholine from azide (R6) where the presence of a dipolarophilic double bond and the "N₃" group as dipolar species provides adequate conditions for the 1,3-dipolar intramolecular cycloaddition reaction. Heating of the azide (R6) in the refluxing toluene for five days conducted stereospecifically to a single cycloadduit via the intermediate triazoline, The latter having decomposed thermally to give, after removal of N₂, aziridinomorpholine (scheme 2).

The azide (R7) is heated to reflux with toluene in order to obtain the corresponding aziridine, the thermolysis is not complete insofar as there was no complete disappearance of the starting material, even at the end Of the twentieth day.

* To whom all correspondence should be sent:

E-mail: Ouddai_nadia@yahoo.fr



Scheme 1. Cycloaddition to chiral triazoline and transformation to aziridine

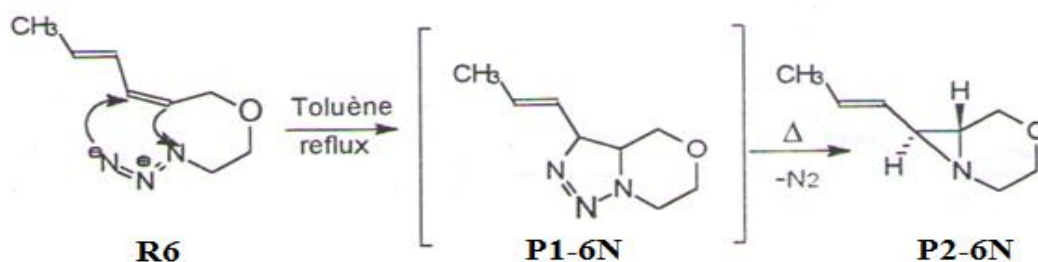
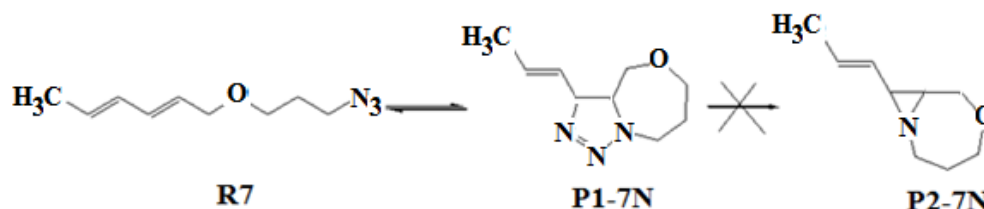


Schéma 2. Synthesis of aziridinomorpholine



Scheme 3. 1,3-dipolar cycloaddition of R7 and cycloreversion

Thermolysis gave the azide as reaction product, the corresponding triazoline underwent a known cycloreversion (variant of a retro Diels-Alder reaction) regenerating the starting product. The non-disappearance of the starting azide would certainly be due to an equilibrium established with the corresponding triazoline (Scheme 3).

CALCULATION METHODOLOGY

The equilibrium geometries were optimized at the B3LYP/6-31G(d) level, using the Gaussian09W program[13]. The corresponding transition states have been located at B3LYP/6-31G(d) [14,15,16], their existence was confirmed by the presence of one and only one imaginary frequency in the Hessian matrix. The enthalpy and free enthalpy of each stationary point were evaluated at $T = 298.15\text{K}$ and $P = 1\text{atm}$, in the approximation of a rigid rotator and a harmonic oscillator for the first step of the reactions (Preparation of triazolin). For the second part "N₂ removal", the free enthalpy was evaluated at different temperatures (from $T = 463.15\text{K}$ to $T = 533.15\text{K}$) and $P = 1\text{atm}$. Finally, in order to reproduce as best as possible the solvent in which the intramolecular dipolar cycloaddition reaction takes

place, I SCRF PCM (polarizable continuum Model) Mode of Tomasi[17] was chosen to model the solvent by a continuum of dielectric constant equal to that of the toluene $\epsilon = 2.38$.

RESULTS AND DISCUSSION

Analysis of geometric structures

The control of stereochemistry in 1,3-dipolar cycloadditions depends on the approach of dipole and dipolarophile orbitals in space. The overlapping is done suprafacially for both species and summarized by the denomination [2 + 4] [18,19]. Concretely, the suprafacial approach indicates that the two groups must overlap with parallel planes. Thus the intramolecular 1,3-dipolar cycloaddition reaction begins with the folding of the azides so that the dipolarophilic and the dipole part are held in proximity, this relation allows a good control of the stereochemistry as for all the suprafacial approaches, which makes it possible to know, in advance, that E di-substituted alkenes will give cycloadduits having a trans orientation. Indeed, the dipolarophiles have a π -bond which makes them linear or plane and the same is true for dipoles. The "R6" and "R7" folded azides are shown in (FIG 1).

In this study, the alkenes used are planar, characterized by the dihedral angle C5-C6-C7-C8 equal to 180 ° and they should orient themselves appropriately with azides which are mainly linear. Thus, without other effects, spatial orientation of a group related to the other is random, since the N3-C6 distance is about (3.6Å) for the two reactants and about (3.4 - 3.7Å) For the N1-C7 distance for R6 and R7, respectively. Analysis of the intramolecular geometric parameters such as the σ : N1-C7 and N3-C6 bonds, formed in the transition state, shows that they have different values, This is quite normal because of the dissymmetry of the dipolarophile. The asynchronicity of the cycloaddition process can be estimated using the difference: $\Delta r = |d(N1-C7) - d(N3-C6)|$. The results obtained for the first step of the reaction are 0.12 Å and 0.24 Å for TS1-P6N and TS1-P7N respectively, this allows us to conclude that the cycloaddition of R7 is more asynchronous.

The bonding order concept can be used to obtain a deeper analysis of the extent of formation/breakdown for the bonds along a reaction path, this theoretical tool is used to study the molecular mechanism of chemical reactions. In order To find the nature of the formation process of "N3-C6", "N1-C7" bonds for the transition states

TS1-6N, TS1-7N and the "N3-C6", "N3-C7" bonds for the transition states TS2-6N, TS2-7N, the Wiberg²⁰ binding index was calculated using the NBO analysis implemented in the Gaussian09 program. The results are illustrated in (Table 1).

The general analysis of the obtained values for bond's orders, relative to all the transition structures, indicates that the TS1-7N is more asynchronous in the bonds formation process, these values [0.0155-0.2684] are in good agreement with asynchronicity analysis, previously discussed for these azide cyclization reactions. On the other hand TS2-7N is more asynchronous in the second part "N2 removal" of triazoline in the process of formation of N3-C6 and N3-C7 bonds. In contrast, in the "N2 removal" reaction, the " N1-N2" Bonding order is close to 3 which implies the formation of a triple bond N1≡N2 and the bonding index "N1-C7" tends towards zero, which means breaking of this bond.

Transition states TS1-P6, TS2-P6, TS1-P7 and TS2-P7 were located at the B3LYP / 6-31G * level. The transition states were confirmed by the presence of one and only one negative eigen value in the matrix of force constants, in other words a single imaginary frequency in the Hessian matrix. The transition states are shown in (Fig. 2)

Table 1. Wiberg binding order at the transition structures corresponding to TS1-6N, TS2-6N, TS1-7N and TS2-7N.

	TS1-6N	TS1-7N	TS2-6N	TS2-7N
N2-N3	1.0913	1.1207	0.1449	0.4427
N1-N2	1.6022	1.5038	2.9790	3.2435
N3-C6	0.1868	0.2684	1.2624	0.5785
N1-C7	0.0155	0.1902	0.0003	0.0006
N3-C7			0.9062	0.1695

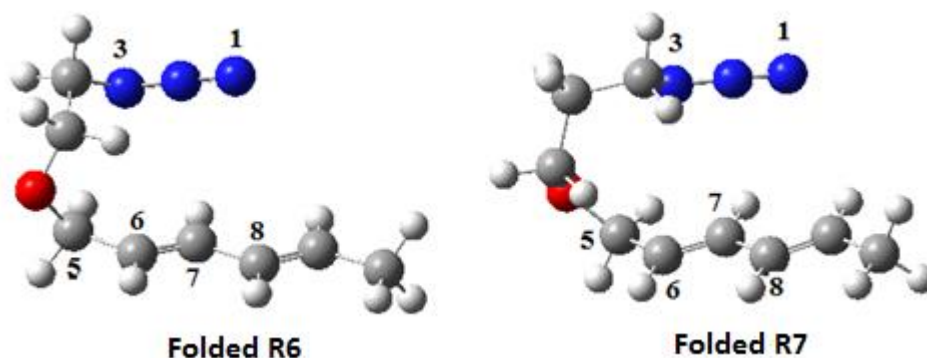


Fig. 1. Optimized geometries (B3LYP / 6-31G (d)) of folded reagents.

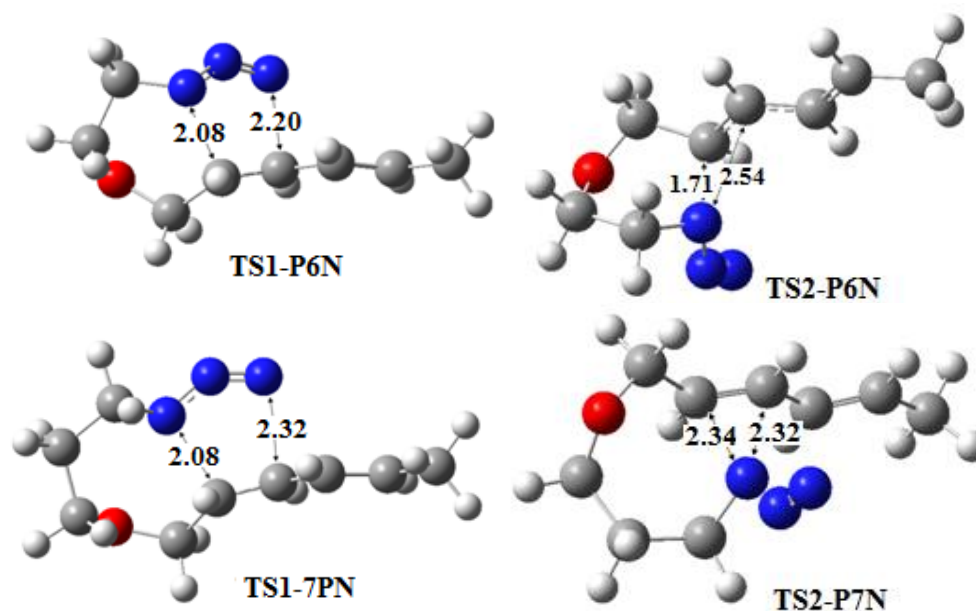


Fig. 2. Optimized geometries (B3LYP / 6-31G (d)) of the transition structures (distance in Å)

Analysis of reactivity by the dual descriptor.

The studies on the molecules reactivity and reaction mechanisms began to be carried out through the analysis of the wave function which defines the quantum state of a molecular system, for example, the Frontier Orbitals[21,22] theory has been very effective in understanding the regioselectivity of organic reactions, through the study of the phase or opposition phase recovery between the highest occupied orbital of the nucleophile and the most vacant base orbital of the electrophile. It was shown that the spin densities of the $N + 1 / N - 1$ systems were good approximations for the Fukui functions, thus the dual descriptor was calculated by the difference between spin densities of the $N + 1 / N - 1$ systems.

In all the representations of the dual descriptor isodensity maps, zones where the values of the descriptors are negative ($\Delta f(r) < 0$) will be colored yellow, while the zones where the descriptor values are positive ($\Delta f(r) > 0$) will be colored red.

The use of the dual descriptor $\Delta f(r)$ allows an unambiguous prediction of the most reactive site with respect to an electrophilic or nucleophilic attack.

(Fig.3) shows the isodensity map of the dual descriptor for the azides "R 6" and "R 7", on which it can be observed that the nitrogens possess nucleophilic characters ($\Delta f(r) < 0$, colored in yellow), and will thus react preferentially with the electrophiles, such as the C6 and C7 carbons of the alkene. The discrimination between the electrophilic and nucleophilic properties of the nitrogen and carbon of the double bond is thus clearly established

by the use of the dual descriptor. Same meanings, when studying the "N2 removal" reactions of the triazoline, the dual descriptors of the transition states which lead to the product P2-6N and P2-7N are presented in (Fig.3).

Finally, we conclude that the formation of the two six- and seven-membered heterocycles is under orbital control.

On the other hand, the stability of the products can be studied by the LUMO-HOMO energy gap, (Fig. 4) illustrates this energy gap for the products P1-6N, P1-7N, P2-6N and P2-7N.

Analysis of the potential energy surface and prediction of the reaction mechanism

An exhaustive exploration of the potential energy surface allowed us to determine the different transition structures. The values of the relative enthalpies of the stationary points, entropies, and free energies associated with these intramolecular 1,3-dipolar cycloadditions of the azide and the "N2 removal" of the triazoline were also calculated. The energy results are presented in Table 2. The inclusion of zero-point energy (ZPE) and thermal contributions to barriers does not significantly modify the activation enthalpies for TSs. Indeed, the free enthalpy is inaccessible in solvent because the PCM model includes entropy effects of solvation in the determination of the energy of the system. The evolution of the free enthalpy can be followed in a medium of dielectric constant $\epsilon = 1$ and in a medium of dielectric constant $\epsilon = 2.38$, which makes it possible to analyze, in part, the influence of the solvent.

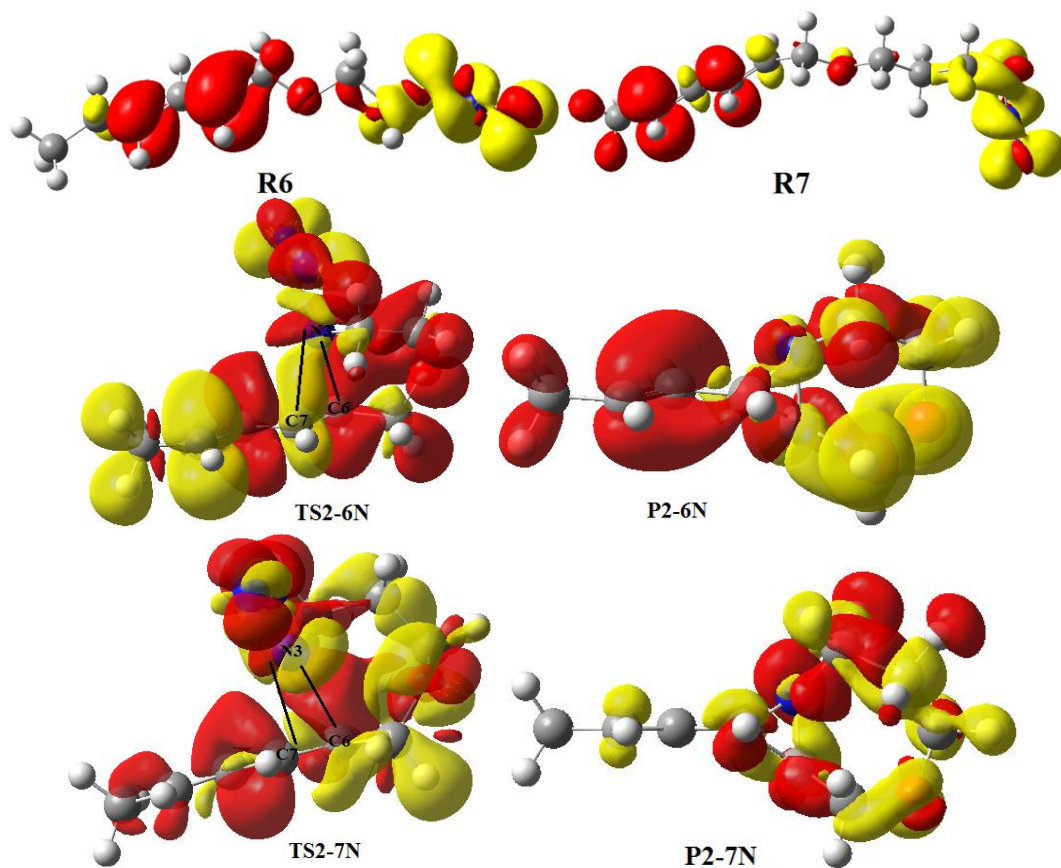


Fig. 3. Isodensity map of the dual descriptor of the azides R6, R7, TS2-6N, P2-6N, TS2-7N and P2-7N

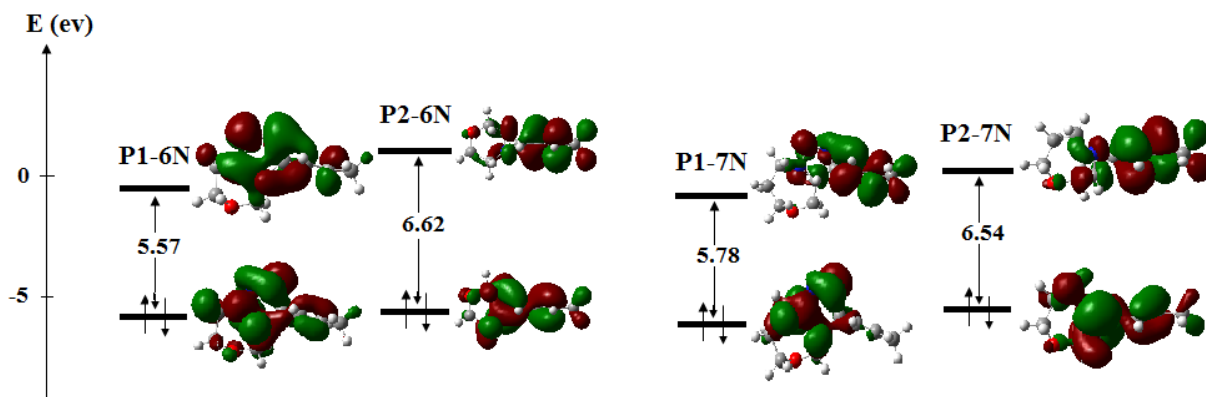


Fig. 4. The energy differences in (ev) for the products P1-6N, P1-7N, P2-6N and P2-7N

Table 2. Relative enthalpy in vacuum ($\Delta H_{\epsilon=1} = 1$, kJ / mol), free relative enthalpy in vacuum ($\Delta G_{\epsilon=1} = 1$, kJ / mol), entropies ($\Delta S_{\epsilon=1} = 1$, J / mol), free relative enthalpy in Toluene ($\Delta G_{\epsilon=2.38} = 2.38$, kJ / mol), for the stationary points of the reaction mechanism studied, calculated at 298.15K and 1atm.

	$\Delta H_{\epsilon=1}$	$\Delta G_{\epsilon=1}$	$\Delta S_{\epsilon=1}$	$\Delta G_{\epsilon=2.38}$
P1-6N	-29.69	-7.23	-75.31	-13.53
TS1-P6N	107.72	128.89	-71.01	128.15
P2-6N+N ₂	204.67	170.80	113.60	
TS2-P6N	156.14	176.08	-66.85	
P1-7N	-48.70	-23.94	-83.05	-27.17
TS1-P7N	113.44	135.19	-72.94	135.05
P2-7N+N ₂	229.69	195.14	100.58	
TS2-P7N	215.34	224.76	-31.59	

Relative to reagents R6 and R7

Table 2 shows that in the intramolecular 1,3 dipolar cycloaddition of the azides R6 and R7, the thermodynamic step is decisive, with an enthalpy ($\Delta H_{\epsilon} = 1 = -29.69$ kJ / mol) for "P1-6N" and ($\Delta H_{\epsilon} = 1 = -48.70$ kJ / mol) for "P1-7N", while the free enthalpy ($\Delta G_{\epsilon} = 1 = -7.23$ kJ / mol) for "P1-6N" and ($\Delta G_{\epsilon} = 1 = -23.94$ kJ / mol) for "P1-7N". The solvation does not have a great influence on the energy barrier to cross to achieve this stage.

The calculations show that the step of removing a nitrogen molecule from P1-6N and P1-7N is thermodynamically non-spontaneous at 298.15K. The formation of the aziridine P2-6N and P2-7N can be carried out by irradiation with ultraviolet light or by thermolysis by means of heating at elevated temperature, it is for this reason that we have recalculated the energies for the geometries of the second stage of the reaction at different temperatures of 463.15K up to 533.15K, the corresponding free enthalpies are summarized in (Table 3)

Table 3. Free relative enthalpy ΔG (kJ / mol) to aziridine formation.

	P2-6N	P2-7N	R7
	ΔG	ΔG	ΔG_R
463.15K	-215.89	185.78	6.88
473.15K	-217.87	183.74	5.95
483.15K	-219.84	181.71	5.01
493.15K	-221.82	179.67	4.07
503.15K	-223.80	177.64	3.12
513.15K	-225.78	173.09	2.18
523.15K	-227.76	173.56	1.23
533.15K	-229.74	171.52	0.28

Relative to reagents P1-6N and P1-7N.

The theoretical study of the triazoline P1-6N thermolysis for the nitrogen molecule removal is spontaneous from 463.15K. For P1-7N, the reaction is impossible whatever the temperature, the reaction is directed towards photolysis. However, the free enthalpy $\Delta G_R = 0.28$ kJ / mol at temperature $T = 533.15$ K when the thermolysis gave the azide R7 as the reaction product (Scheme 3), We find that an equilibrium between triazoline P1-7N and azide R7 has been established, The corresponding triazoline thus underwent a known cycloreversion (variant of a retro-Diels-Alder reaction). These results are in good agreement with the experimental part.

CONCLUSION

The intramolecular 1,3-dipolar cycloaddition reaction mechanism of the azides for the six- and seven-membered heterocycles were studied using the DFT method at the B3LYP / 6-31G (d) level. The analysis of the results proposed by the dual descriptor implies that the nitrogen possess

nucleophilic characteristics. The activation energies calculation, the potential energy surface analysis (SEP) and the calculation IRC show that these cycloadditions follow asynchronous concerted mechanisms and that the solvation does not have a great influence on the energy barrier. The formation of aziridinemorpholine from the removal of a dinitrogen molecule from the triazoline cycle is spontaneous at 463.15K, while that of seven links is impossible under the same conditions, Nevertheless an equilibrium is obtained at 533.15 K between the triazoline and the azide R7. We conclude that it is probably a photolysis that can be carried out by irradiation with ultraviolet light.

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DFT-ИЗСЛЕДВАНЕ НА НИТРИРАНИ ХЕТЕРОЦИКЛЕНИ СЪЕДИНЕНИЯ С ШЕСТ И СЕДЕМ ВРЪЗКИ

Х. Меруани^{1,3}, А. Униси^{2,3}, Н. Улдаи^{3*}

¹Департамент по химия, Научен факултет, Университет „Мохамед Будиаф М'сила“, 28000 М'сила, Алжир.

²Лаборатория по химично инженерство, Университет « Сетиф-1 », Алжир

³Лаборатория по химия на материалите и живата материя: активност, реактивоспособност, Университет „Ел-Хадж Лахдар Батна“, 05000 Батна, Алжир

Получена на 30 октомври, 2016 г.; коригирана на 14 декември 2016 г.

(Резюме)

1,3-диполярното циклично присъединяване (13DC) на азиди е извършено на ниво B3LYP / 6-31G (d). Получените резултати показват, че образуването на азидин-морфолин от триазолин чрез отстраняването на азотна молекула става спонтанно при нагряване до 463,15 К. Обаче правите вериги от седем атома претърпяват обратно циклизиране при 533,15 К с реагента R7 (2,4-хексадиенил-оксипропил азид). Тази реакция изисква облъчване с ултравиолетова светлина.