NITROPYRIDINES AS DIENOPHILES IN POLAR DIELS-ALDER REACTIONS. A DFT THEORETICAL STUDY.

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Abstract: 3-nitropyridine and 4-nitropyridine *N*-oxide were theoretically studied, acting as dienophiles in the Diels-Alder reaction with different dienes. It was observed that both azacycles would suffer the cycloaddition reaching the quinoleine derivatives. Regioselectivity was predicted. The mechanism reaction was also analyzed observing that there is only one asymmetric and asynchronous transition state between the reactants and the primary cycloadduct when isoprene is the diene involved, and two when 1-methoxy-1,3-butadiene and Danishefsky's diene were used.

Keywords: Nitropyridine, DFT, Diels-Alder

Introduction

Every chemical process is primary interesting if it provides a fast way to get basis rings that supports a wide variety of functional groups and that could be “economic in atoms”. Diels-Alder (D-A) reaction is nowadays one of the most useful reactions in any synthetic strategy that needs, at least in one step, the formation of a six-membered ring. D-A reaction has place between a compound with two conjugated double bonds (diene) and a simple olefine (dienophile).

In the last years it has been consider and proved that heterocycles could act as dienophiles in this kind of cycloaddition reactions when these compounds are properly substituted with electron-withdrawing groups. According to the mechanisms this reactions can be consider as concert and asyncronic processes, that provides a polar character *-Polar Diels-Alder reactions (PD-A)-*. Understand the dienes and dienophiles behavior in D-A reactions is not an easy work. A theoretical study trough the Density Functional Theory (DFT) method provides the best analysis of them. With this purpose we pretend to analyze the reactivity of some azaheterocycles acting as dienophiles in this kind of cycloaddition reactions

The aim of the present work is centred in the reactivity of pyridine nitro derivatives with different dienes. More specifically we study the feasibility, regioselectivity and mechanism of each D-A reaction.

Methods

DFT calculations were carried out using the B3LYP exchange-correlation functionals, together with the standard 6-31G* basis set. All calculations were carried out with the Gaussian 09 suite of programs.

First a geometrical optimization was realized to get de conformation with the lowest energy. In all the cases frequency calculation was performed to verify that the structure is an energetic minimum and not a saddle point.

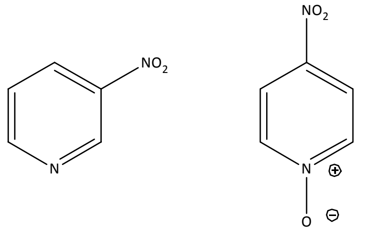
There are some indexes that are used to study the reactivity. The global electrophilicity index, ω, is given by the following simple expression. $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively. Recently, Domingo et al. have introduced an empirical (relative) nucleophilicity index, *N*, based on the HOMO energies obtained within the Kohn-Sham scheme, and defined as $N = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)}$. The nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. Local electrophilicity and nucleophilicity indexes, ω_k and

N_k, were evaluated using the following expressions: $\omega_k=\omega f_k^+$ and $N_k=Nf_k^-$ where f_k^+ and f_k^- are the Fukui functions for a nucleophilic and electrophilic attacks, respectively.

So, once the energetic parameters were get, the value of HOMO and LUMO orbitals were considered to quantify the reactivity indexes. To include the solvent the Polarizable Continium Model (PCM) was used. For the mechanist study, from the Potential Energy Surface (PES), the structures of transition states were located. IRC (Intrinsic Reaction Coordinates) calculations verify that the transition states are minimums.

Results and Discussion

– *Dienophiles*



3-nitropyridine 4-nitropyridine *N*-oxide

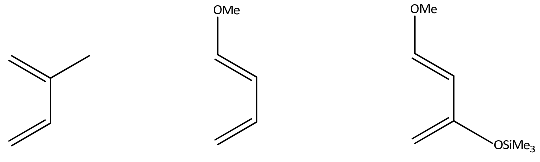
Figure 1

The results showed in Table 1 demonstrate that both pyridine derivatives (dienophiles) are strong electrophiles. The 4-nitropyridine *N*-oxide (ω=3.91 eV) is a stronger electrophile than 3-nitropyridine (ω=3.31 eV).

DIENOPHILES		ε_{HOMO}(eV)	ε_{LUMO}(eV)	μ (eV)	η (eV)	ω (eV)	*N* (eV)
4-Nitropyridine *N*-oxide	**Gas Phase**	-6.81	-3.02	-4.91	3.80	**3.18**	**2.31**
	Chloroform	-6.71	-2.99	-4.85	3.72	**3.16**	**2.41**
3-Nitropyridine	**Gas Phase**	-7.68	-2.76	-5.22	4.91	**2.77**	**1.44**
	Chloroform	-7.64	-2.79	-5.21	4.85	**2.80**	**1.48**

Table 1. *Global properties calculated using the B3LYP/6-31G(d) method. For the inclusion of chloroform as solvent the PCM method was applied.*

– *Dienes*



Isoprene 1-methoxy-1,3-butadiene Danishefsky's diene

Figure 2

In the other side, the dienes (nucleophiles) are poor electrophiles. Danishefsky's diene (ω=0.96 eV), is the diene with the major difference (Δω) with the diene electrophilicity, so the reactions with this diene would be more polar than the ones with 1-methoxy-1,3-butadiene (ω=1.07 eV) and with isoprene (ω=1.27eV).

DIENOS		ε_{HOMO}(eV)	ε_{LUMO}(eV)	μ (eV)	η (eV)	ω (eV)	*N* (eV)
Isoprene	**Gas Phase**	-6.18	-0.41	-3.30	5.77	**0.94**	**2.93**
	Chloroform	-6.24	-0.50	-3.37	5.74	**0.99**	**2.88**
Danishefsky's diene	**Gas Phase**	-5.56	0.04	-2.76	5.60	**0.68**	**3.56**
	Chloroform	-5.65	-0.07	-2.86	5.58	**0.73**	**3.47**
1-Methoxy-1,3-butadiene	**Gas Phase**	-5.57	-0.14	-2.85	5.43	**0.75**	**3.55**
	Chloroform	-5.63	-0.26	-2.95	5.37	**0.81**	**3.49**

Table 2. *Global properties calculated using the B3LYP/6-31G(d) method. For the inclusion of chloroform as solvent the PCM method was applied.*

The regioselectivity is expected to be higher for the processes that involve Danishefsky's diene due to the electron donor groups (-OMe y –OSiMe$_3$) and its relatives positions.

The electronic chemical potential (μ) presents the highest values for the dienophiles, what indicates that the charge transference is going to take place from the first ones to the aromatic heterocycles. So the diene is going to be a nucleophile and the dienophile would act as electrophile.

Local Properties

Figures 3 and 4 show the values of the local indexes of nucleophilicity (for dienes) and electrophilicity (for the dienophiles).

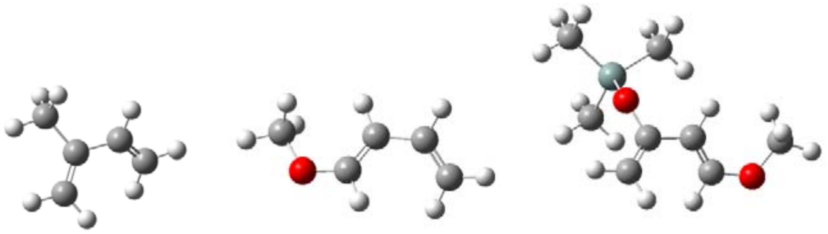


Figure 3- *Local nucleophilicity indexes (N_k) for the dienes – B3LYP/6-31G(d)*

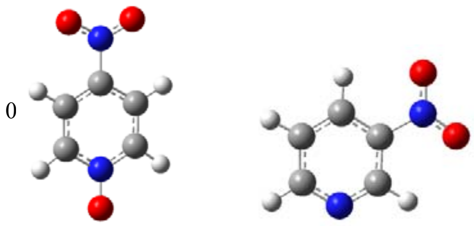


Figure 4- *Local electrophylicity indexes (ω_k) for the dienophiles –B3LYP/6-31G(d)*

- **Predicted results for the reactions of nitropyridine derivatives as dienophiles**

***3-nitropyridine as dienophile*:**

  - *3-nitropyridine + isoprene*

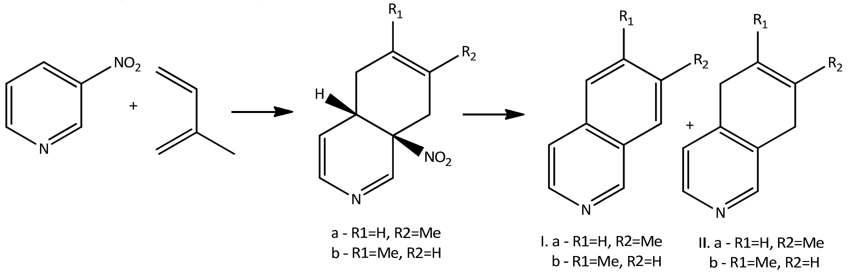


Figure 5

The C_4 of the 3-nitropyridine is the most electrophilic site, so is going to be the one that reacts with the most nucleophilic carbon of the diene. First the $\Delta\omega$ of the reactions was calculated, in this case 1.83 eV. The ΔN_k for isoprene beween C_1 and C_4 is near 0.30 eV, as this difference is not big enough we expected both isomers as products.

- *3-nitropyridine + 1-methoxy-1,3-butadiene*

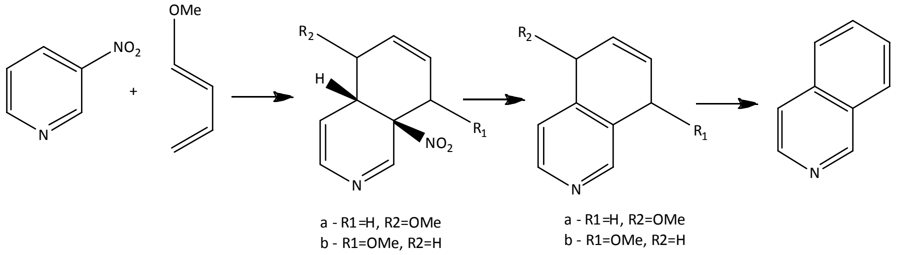


Figure 6

For this diene the $\Delta\omega$ of the reaction reach the 2.02 eV. It is expected a good yield of the cycloaddition product and that the –OMe group is going to be eliminated as MeOH to reach the aromatic final product. In this case the mixture of isomers of the dihidro compounds (ΔN_k=0.29/0.24 eV), which derivate then in the same final aromatic product.

- *3-nitropyridine + Danishefsky's diene*

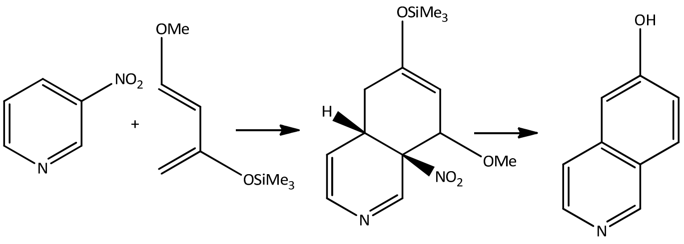


Figure 7

When Danishefsky's diene is used, only the formation of one isomer is expected. This is the one that corresponds to the union of C_1 of the diene and C_4 (ΔN_k=0.89/0.80 eV) of the dienophile. The reaction must be completely regioselective and with loose of the -NO_2 and –OMe groups to form the aromatic compound that corresponds to the *para* adduct.

4-nitropyridine N-oxide as dienophile:

Taking in account that the pyridine nucleus is really hard to nitrate the use of the derivative *N*-oxide allows an alternative analysis considering its higher electrophile power. Making a theoretical study it could be observed that the nitration occurs in position 4 in spite of the position 3 of the pyridine itself. In consequence, using the pyridine *N*-oxide it would be possible to get different isomers that the ones reached with the pyridine when it reacts with asymmetric dienes.
As it can be observed the 4-nitropyridine *N*-oxide has a higher electrophilicity value than the corresponding 3-nitropyridine, which generates higher $\Delta\omega$ facing each diene.

- *4-nitropyridine N-oxide + isoprene*

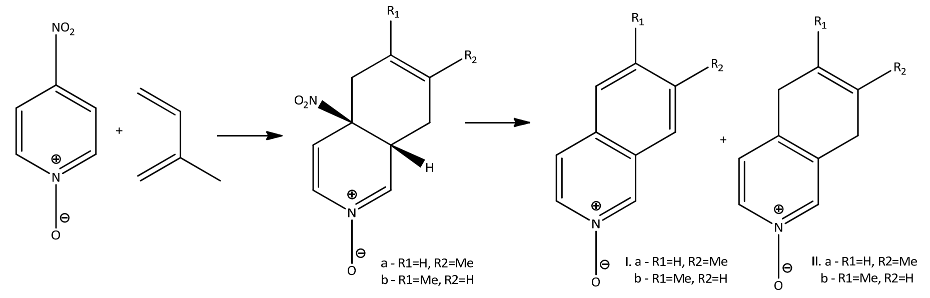


Figura 8- $\Delta\omega$=2,24/2,64 eV $\Delta N_{k(isopreno)}$=0,3/0,37 eV

- *N-óxido de 4-nitropiridina + 1-metoxi-1,3-butadieno*

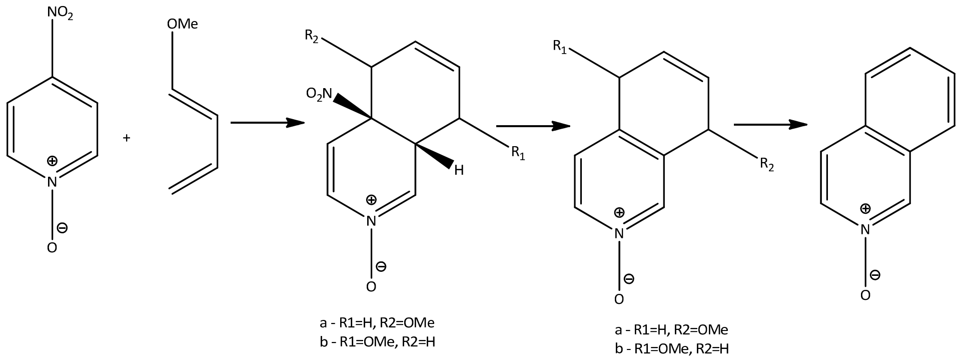


Figure 9 - $\Delta\omega$=2.43/2.84 eV $\Delta N_{k(1\text{-}methoxy\text{-}1,3\text{-}butadiene)}$=0.29/0.24 eV

- *4-nitropyridine N-oxide + Danishefsky’s diene*

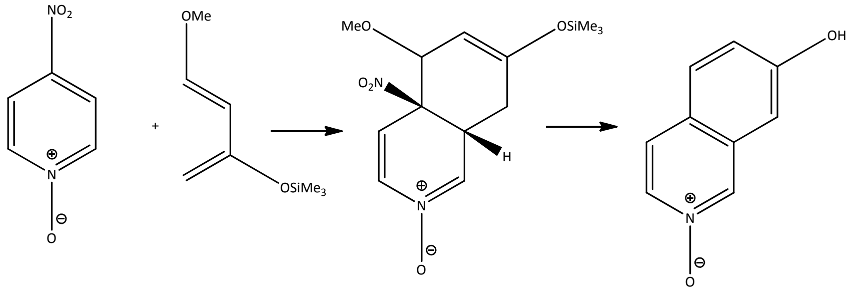


Figure 10- $\Delta\omega$=2.50/2.95 eV $\Delta N_{k(Danishefsky's\ diene)}$=0.89/0.80 eV

Mechanism

The cycloaddition reactions as D-A are domino processes that involve some consecutive reactions. Especially with the nitrate dienophiles it was observed that in almost all of the cases is not possible to get the primary adducts retaining the nitro group, so an elimination stage of it as nitrous acid, is consider. If we add to this behavior the study of systems that include asymmetric dienes as Danishefsky's diene, an extra stage of the -OMe group and hydrolysis of $–OSiMe_3$ is also consider.

- ***System: 3-nitropyridine + isoprene***

Trough an analysis of the potential energy surface the TS$_1$ (Figure 11) corresponding to the formation of the *para* product indicates that we are in front of a synchronic cycloaddition processes because both formatting bonds vibrate at the same time and in an asymmetric form [(Δr= 0.84 Å), ($\Delta r = (r_1 – r_2)$)] where r_1 is the distance between $C_2^{dienophile}$- C_1^{diene} and r_2 is the distance between $C_3^{dienophile}$- C_4^{diene}. This is due to the fact that the formation of the bond between the most electrophilicity center of the dienophile (C_3) and the most nucleophilicity center of the diene (C_4).

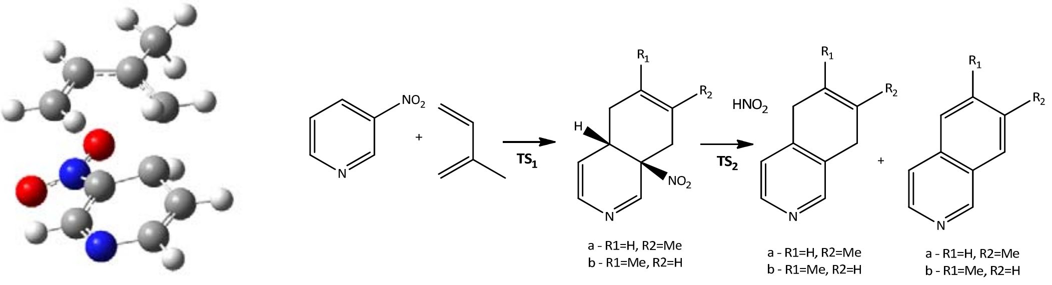


Figure 11

- ***System: 3-nitropyridine + 1-mehtoxy-1,3-butadiene***

In this case 2 transition states (previous to the formation of the nitrate primary adduct). The first one (TS$_1$ – Figure 13) corresponds to the formation of the bond between C_4 of the nitropyridine (most electrophilicc) and the most nucleophilicity atom of the diene. Once this bond is formed another transition state appears (TS2 – Figure 13), which corresponds to the formation of the second sigma bond of the D-A reaction..

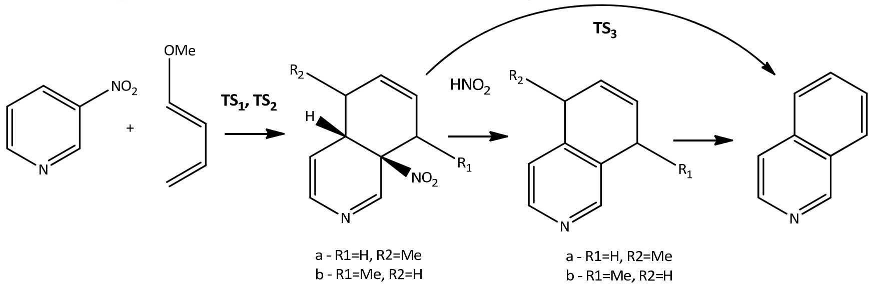


Figure 12

TS$_1$ ***TS$_2$***

Figure 13

– ***System: 3-nitropyridine + Danishefsky's diene***

Finally, with Danishefsky's diene the mechanism is going to be similar to the previous case. There are 2 transition states corresponding to each sigma bond formation. In no case of the mechanism in stage could be possible to get a reaction intermediate between both TSs. These kinds of processes were described by Houk y col. and called *"two-step non-intermediate mechanism"*.

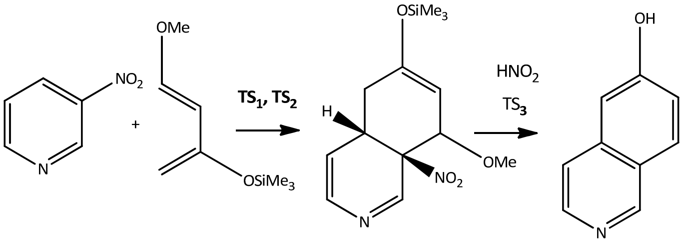
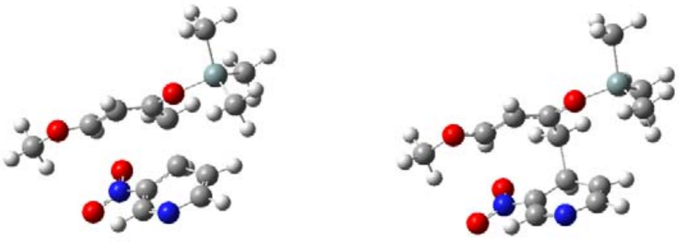


Figure 14



TS$_1$ ***TS***$_2$

Figure 15

In all the cases it is observed that the relative stability of the nitrate adduct respect to the final product with elimination of nitric acid is considerably lower. It is because of this fact that the primary cycloadduct is not observed. The extrusion of nitrous acid is the irreversible step of the D-A reaction (impulsive force) and the aromaticity of the final product explained the stability.

Conclusions

- Nitropyridine derivatives have electrophilicity character enough to act in polar D-A reactions.
- Reactivity indexes are a good tool to explain and predict the behavior of the involved molecules in a cycloaddition reaction. It can be established, from the chemical potential values, which of the molecules are going to act as dienes or dienophiles and how polar the reaction could be ($\Delta\omega$).
- Local indexes result representatives at the moment of analyze the reaction regioselectivity.
- The analysis of the reaction mechanism show that when isoprene is used as diene only one transition state previous to the formation of the primary cycloadduct is observed. On the other hand, when 1-methoxy-1,3-butadiene and Danishesfky's diene is possible observed 2 transition states previous to the formation of the primary adduct. These mechanisms can be considered as stage mechanisms

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Acknowledgments

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