Reaction Mechanism of Polar Diels-Alder Reactions between 3-Nitrofuran and different Dienes. A Theoretical Study.

MAURO CAINELLI, CARLA ORMACHEA, PEDRO MANCINI, MARÍA KNEETEMAN*
Área Química Orgánica- Departamento de Química- Facultad de Ingeniería Química, Universidad Nacional
del Litoral. Santiago del Estero 2829. (3000) Santa Fe, Argentina.
FAX: +54-342-4571162. *e-mail: mkneeteman@fiq.unl.edu.ar

Abstract: The reactivity in Polar Diels-Alder reactions of 3-nitrofuran acting as electrophile join to several dienes of different nucleophilicity is analyzed using computational theorical methods based in the DFT theory. Electrophilicity and nucleophilicity indices, based in the energy of frontier molecular orbitals, were the parameter employed. It was observed that the pentaheterocycle suffer the cycloaddition yielding benzofuran derivatives. The regioselectivity was predicted using Fukui function and the reaction mechanism was analyzed. It was observed that there is only one asynchronous transition state when isoprene is the diene involved, and two transition states when 1-methoxy-1,3-butadiene and Danishefsky's diene were used. It is possible to observe two transition states and a consequent reaction intermediate The last observation is not common in this cycloaddition reactions and it would be based in the polar character that increase with the nucleophilicity of the dienes. The benzofuran derivatives were observed in the experimental experiences develop in thermal conditions.

Keywords: Nitrofuran, DFT, Diels-Alder

Introduction

In any carbon-carbon bond constructions, the Diels-Alder (DA) cycloaddition reaction is one of the most useful synthetic strategy when the formation of a six-membered ring is needed. It has place between a compound with two conjugated double bonds (diene) and a simple olefine (dienophile) and provides a fast way to get basis rings that supports a wide variety of functional groups and that could be "economic in atoms".

Previous studies involving aromatic heterocycles such as indoles, benzofurans, pyrroles, furans, and thiophenes in DA reactions demonstrate the viability of these systems as dienophiles when these compounds are properly substituted with electron-withdrawing groups.

According to the mechanisms this reactions can be consider as concert asyncronic processes, that provides to the reaction a polar character *-Polar Diels-Alder reactions (P-DA)-*. Under these conditions, the dienes and dienophiles behavior in DA reactions is not an easy matter of study. A theoretical study trough the Density Functional Theory (DFT) method provides the best analysis of them. With this purpose we try to analyze the reactivity of 3-nitrofuran acting as dienophile in this kind of cycloaddition reactions. Then the aim of the present work is centered in the behavior of the nitrofuran derivative in its reaction with different dienes. More specifically we study the feasibility, regioselectivity and mechanism of each DA reaction.

Methods

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

The first step is to perform a geometrical optimization to get the conformation with the lowest energy. To verify that the structure is an energetic minimum and not a saddle point, frequency calculation was realized.

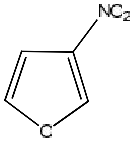
There are some indexes that are used to study the reactivity. The global electrophilicity index, ω, is given by the following simple expression $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta = (\varepsilon_L - \varepsilon_H)$, respectively. Recently an empirical (relative) nucleophilicity index, N, has been introduced. It is 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. For the mechanistic study, from the Potential Energy Surface (PES), the structures of transition states were located. IRC (Intrinsic Reaction Coordinates) calculations verify the transition states (TS).

Results and Discussion

- ***Dienophile***

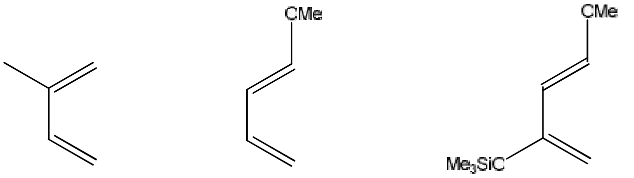
3-nitrofuran (ω = 2.35 eV) is a strong electrophile, its global properties were calculated and the values are showed in Table 1.



DIENOPHILE	ε_{HOMO}(eV)	ε_{LUMO}(eV)	μ (eV)	η (eV)	ω (eV)	*N* (eV)
3-Nitrofuran	-0.26712	-0.08632	-0.1767	0.1808	2.35	1.85

Table 1. *Global properties calculated using the B3LYP/6-31G(d) method.*

- ***Dienes***



1 *isoprene*

2 *1-methoxy-1,3-butadieno*

3 *Danishefsky's diene*

Figure 1

In the other side, the dienes (nucleophiles) are poor electrophiles. Danishefsky's diene (ω =0.94 eV), is the diene with the major difference (Δ ω) related to the electrophilicity of the diene so the reactions with this diene would be more polar than those with 1-methoxy-1,3-butadiene (ω =0.75 eV) and with isoprene (ω = 0.68eV).

DIENE	ε_{HOMO}(eV)	ε_{LUMO}(eV)	μ (eV)	η (eV)	ω (eV)	*N* (eV)
Isoprene	-6.18	-0.41	-3.30	5.77	**0.94**	**2.93**
1-Methoxy-1,3-butadiene	-5.57	-0.14	-2.85	5.43	**0.75**	**3.55**
Danishefsky's diene	-5.56	0.04	-2.76	5.60	**0.68**	**3.56**

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 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

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.

DIENE	Atom	N_k (eV)
Isoprene	C1	1.20
	C4	0.92
1-Methoxy-1,3-butadiene	C1	0.74
	C4	0.94
Danishefsky's diene	C1	0.56
	C4	1.46

***Table 3**. Local indexes for dienes*

The 3-nitrofuran has its major local electrophilicity in position 2. It is expected that the most nucleophilic site of the diene reacts, at first, with the most electrophilic center of the dienophile.

Mechanism

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

Predicted results for the reactions

- *3-nitrofuran + isoprene*

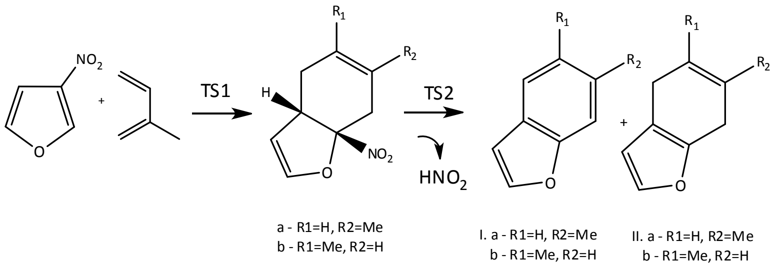


Figure 2

First the Δ ω of the reactions was calculated, in this case 1.41 eV. The C2 of the 3-nitrofuran is the most electrophilic site, so is going to be the one that reacts with the most nucleophilic carbon of the diene. The ΔN_k for isoprene beween C1 and C4 is near 0.30 eV, as this difference is not big enough we expected both isomers as products.

Trough an analysis of the potential energy surface the TS_1 (Figure 3) corresponding to the formation of the *para* product indicates that we are in front of a concerted cycloaddition process because both formatting bonds vibrate at the same time and in an asymmetric form [($\Delta r = 0.92$ Å), ($\Delta r = (r_1 – r_2)$] where r_1 is the distance between $C2^{dienophile}$- $C1^{diene}$ and r_2 is the distance between $C3^{dienophile}$-$C4^{diene}$. 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). The meta isomer was also calculated and its energy barrier is a little higher than the para one.

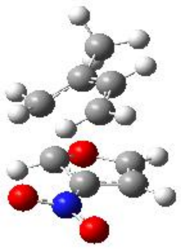


Figure 3

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

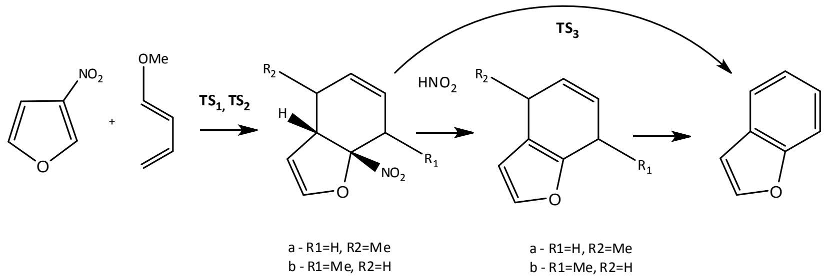


Figure 4

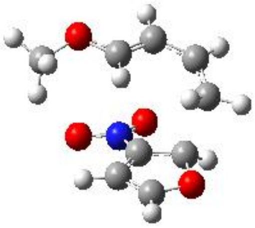


Figure 5
TS$_1$ - formation of the *ortho* product

In this case the $\Delta\omega$ of the reaction reach the 1.60 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=0.20 eV) derivates then in the same final aromatic product.

For this diene two transition states previous to the formation of the nitrate primary adduct were observed. This TSs have similar energy then we do not noted the presence of an intermediate of reaction. In the ortho isomer, for TS1 r_1= 2.01 Å - the distance between C2^{dienophile}- C4^{diene} - and r_2= 3.12 - the distance between C3^{dienophile}- C1^{diene} - and for TS2 r_1= 1.45 Å (formed bond) and r_2= 2.10 Å. The meta isomer is also showed and its energy barrier is a little higher than the para one.

- *3-nitrofuran + Danishefsky's diene*

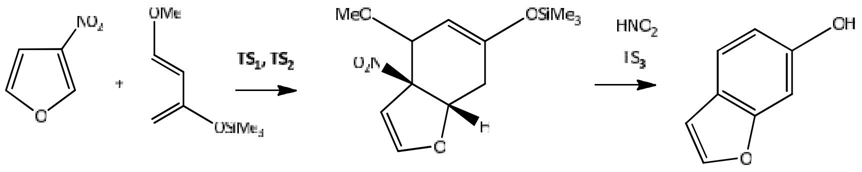


Figure 6

When Danishefsky's diene ($\Delta\omega$=1.60 eV) is used, only the formation of one isomer is expected (ΔN_k=0.89 eV). This isomer corresponds to the union of C4 of the diene and C2 of the dienophile (TS1 in Figure 7). 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.

Finally, with Danishefsky's diene the mechanism is surprisingly. There are 2 transition states corresponding to each sigma bond formation and an intermediate state.

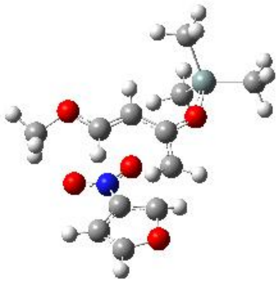


Figure7

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

3-Nitrofuran has enough electrophilicity character to act as dienophile in P-DA reactions. The analysis of the reaction mechanism in this P-DA processes show that when isoprene is used as diene only one transition state is observed. On the other hand when 1-methoxy-1,3-butadiene and Danishesfky's diene is possible observed two transition states and in one case the consequent reaction intermediate. The mechanism corresponding to the last reactions could be considered as stage mechanisms. The 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 of the reaction regioselectivity.

Acknowledgments

This research was supported by CAI+D 2012 –Nº 66,501 201101 00478 LI at Universidad Nacional del Litoral, Santa Fe, Argentina.

References and notes

- Becke, A. D.; *J. Chem.Phys.* **1993**, , 98, 5648.
- Becke, A. D.; *Phys. Rev.* **1988**, *38*, 3098.
- Biolatto, B.; Kneeteman, M.; Mancini, P.M.E.; *Tetrahedron Lett.,* **1999**, 40, 3343-3346.
- Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, P.M.E.; *J. Org. Chem., 66,* **2001**, 3906-3912.
- Della Rosa, C.; Kneeteman, M.; Mancini, P.M.E.; *Tetrahedron Lett.,* **2007**, 48, 1435-1438.
- Domingo, L. R.; Aurell, M. J.; Kneeteman, M. N.; Mancini, P. M. E.; *Teochem*, **2008**, 853, 68-76.
- Domingo, L. R., Aurell, M. J.; Perez, P.; Contreras, R.; *Tetrahedon,* **2002**, 58, 4417.
- Domingo, L. R.; Saez, J. A.; *Org. Biomol. Chem.,* **2009**, 7, 3576-3583.
- Domingo, L.; Aurell, M. J.; Perez, P.; Contreras, R.; *Tetrahedron,* **2002**, 58, 4417.
- Fringuelli, F.; Taticchi, A.; The Diels-Alder Reaction: Selected Practical Methods; Wiley, New York, **2002**.
- Gaussian 09, Revision A.1
- Lee, C.; Yang, W.; Parr, R. G.; *Phys. Rev. B,* **1988**, *37*, 785.
- Parr, R. G.; Yang, W.; *J. Am. Chem. Soc.,* **1984**, 106, 4049.