Original Research Article

A Theoretical Study of the Diels-Alder Reaction between 3-nitrofuran and different dienes developed in Ionic Liquids.

KEYWORDS: **Nitrofuran, Diels-Alder, theoretical calculations, mechanism**

ABSTRACT.

In this study the reactivity of 3-nitrofuran acting as electrophile in their reactions with different dienes, was analyzed in theoretical form. Specifically, the mechanism of each DA reaction was explored. Moreover, considering the polar character of this type of cycloaddition reaction we have discussed the modification of the dienophile reactivity when the solvent effect is considered by adding molecules of ILs to the dienophile optimizations.

Introduction

The Diels-Alder (DA) reaction allows the simple construction of a six-member ring from a compound with two conjugated double bonds (diene) and a simple olefine (dienophile), being one of the most significant and useful tools in synthetic organic chemistry.[1,2] The process involves the formation of two σ bounds and the rupture of two π bounds simultaneously and a wide variety of dienes and dienophiles can be used.

According to the Frontier Molecular Orbital Theory (FMO) the bonding formations implicate a charge transfer process (CT) from the Highest Occupied Molecular Orbital (HOMO) of one component to the Lowest Unoccupied Molecular Orbital (LUMO) of the other one.[3] Substituents can be used in order to low the energy gap between these orbitals resulting in a more favored reactive process.[4,5]

Previous studies involving aromatic heterocycles such as indoles, 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.[6]

The mechanisms of these reactions can be considered as a concerted asynchronous processes, that provides a polar character to the reaction –Polar Diels-Alder Reactions– (P-DA) being able to experiment solvent effects.[7,8,9] Ionic liquids (ILs) have shown that they can be a good alternative compared to conventional solvents due to their physical properties such as low vapor pressure, reutilization capacity, and less environmental aggressive preparation and degradation ways.[10]

Recently, we analyzed the reactions between 3-nitrofuran and different dienes using protic ionic liquids (PILs) as solvents. In these cases, furan acts as an electrophilic dienophile. The experimental data showed that the presence of an IL as reaction media results in higher reaction yields and in less reaction conditions (temperature and time) than those in which organic solvents are employed. It has been demonstrated that 3-nitrofuran reacts efficiently with the selected dienes in normal electron demand PDA reactions, with the nitro group inducing the formation of a selective product.

The study of the behavior of dienes and dienophiles in DA reactions is not easy. A theoretical analysis based on the Density Functional Theory (DFT) methods has been successful in explaining the feasibility of the cycloaddition process.[11] A theoretical study was developed in order to analyze the reaction mechanism of 3-nitrofuran acting as electrophilic dienophile in PDA reactions involving different dienes. Then, and considering the effect of the PILs on this type of reactions and the polar character of these cycloaddition process, we analyzed the modification of the dienophile reactivity when the solvent effect is considered by adding molecules of PILs to the optimization.[12,13]

Computational Methods

DFT calculations were carried out using the Gaussian 09[14] program, B3LYP[15] hybrid functional[16], together with the standard 6-31G(d) basis set.[17]

The first step is to perform a geometrical optimization to get the conformation with the lowest energy. In order to verify that the structure is an energetic minimum and not a saddle point, frequency calculation was realized.[18]

There are some indexes defined in terms of the electronic chemical potential μ and the chemical hardness η that are used to study the reactivity. The chemical potential is associated with the charge transfer capacity of the system in basal state and the hardness is the resistance to change the chemical potential when the number of electrons variates. 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.[19]

$$\mu = \frac{(\varepsilon_H + \varepsilon_L)}{2}$$

$$\eta = (\varepsilon_H - \varepsilon_L)$$

The global electrophilicity index, ω, represents the capability of a molecule to accept an electron considering the environment satured by them and it's given by the following simple expression

$$\omega = \frac{\mu^2}{2\eta}$$

Recently an empirical (relative) nucleophilicity index, *N*, has been introduced based on the HOMO energies obtained within the Kohn-Sham scheme.

$$N = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)}$$

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.[20]

The Fukui function is a measure of the sensibility of the chemical potential in a particular point when an external perturbation is present and the number of electrons remain constant, or the variation of the electronic density in a point when the number of electron changes and the external potential remains constant.[21]

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N} \right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)} \right)_{N}$$

The resolution of this function can be obtained in terms of the FMO.

$$f_k^{\alpha} = \sum_{\mu \in k} f_{\mu}^{\alpha}$$

$$f_{\mu}^{\alpha} = |c_{\mu\alpha}|^2 + c_{\mu\alpha} \sum_{\nu \neq \mu} c_{\nu\alpha} S_{\mu\nu}$$

f_k^+ and f_k^- are the Fukui functions for a nucleophilic and electrophilic attacks, respectively. Local electrophilicity and nucleophilicity indexes, ω_k and N_k, can be obtained using the following expressions

$$\omega_k = \omega . f_k^+$$

$$N_k = N . f_k^-$$

So, after the optimization of the system, the value of HOMO and LUMO orbitals were used to quantify the reactivity indexes.[22]

The mechanistic study was realized through the construction of the Potential Energy Surface (PES) for every system. The structures of transition states were located, optimized and then verified through IRC (Intrinsic Reaction Coordinates) calculations.[23]

The solvent effect was studied using an explicit model of solvation, the supermolecular method, which consist on adding molecules of ILs together with the dienophile and then optimize the system. The molecules of ILs were added progressively until a total amount of 4. The effect is analyzed only with the dienophile due to the capacity of this one to form hydrogen bonds. In order to compare the results of this model, we analyze the solvation effect using the *polarizable continuum model* (PCM) where the solute (dienophile) is placed into a cavity and the interaction with the solvents are considered only through their dielectric constants independently of their structure.[24]

Results and Discussion

3.1. Dienophile and diene's properties

3.1.1. Dienophile

For understanding the polar character trend in a series of P-DA reactions a theoretical study was developed using a known method.

The electrophilicity of 3-nitrofuran **(1)** is a high value (2.35 eV). The electronic properties were calculated and the values are showed in Table 1.

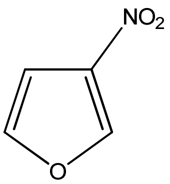


Figure 1

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

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

3.1.2. Dienes

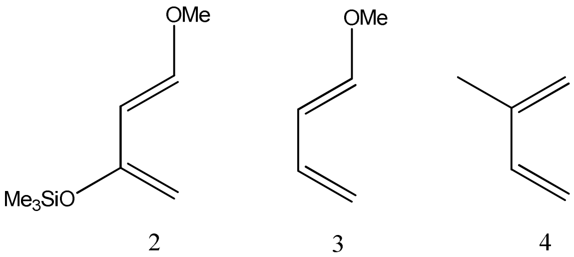


Figure 2

The dienes used in this study are show in the Figure 2. These nucleophiles dienes are poor electrophiles. The diene that presents the highest difference with respect to the dienophile (Δω) is the Danishefsky's diene **(2)** (ω =0.96 eV). Then the polarity of the reactions involving this diene would higher and the results are more favorable than those in which 1-methoxy-1,3-butadiene **(3)** (ω =1.07 eV) and with isoprene **(4)** (ω =1.27eV) are employed. Moreover the reaction using this diene would be regioselective.

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

DIENE		**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**

The dienophile has the highest value of electronic chemical potential (μ), which indicates that the charge transference process derives from the dienes to the first one. In these cases the diene is going to act as a nucleophile and the dienophile as the electrophile.

3.1.3. Local Properties

The local properties are used for the determination of the regiselectivity of the reactions. 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 relative positions, specially the influence of the –OMe group.

Table 3. *Local indexes for dienes*

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

In 3-nitrofuran, C2 presents the highest value of local electrophilicity. In consequence, this atom is expected to react with the most nucleophilic center of the diene (C4 in the case of Danishefsky's diene).

3.2. Mechanism of reaction

It was observed that in cycloaddition reactions such as D-A with nitro-dienophiles, in general, primary adducts retaining the nitro group are not observed. There is an elimination stage of the substituent group as nitrous acid that needs to be considered. This is a domino processes that involve consecutive reactions. If asymmetric dienes such as Danishefsky's diene are used, an extra stage of the elimination of -OMe group and hydrolysis of –$OSiMe_3$ group is also present. In this study we analyze the reaction mechanism considering only the process of the formation of the primary adducts because this is the determinant step of the reaction. It is necessary taken into account that the irreversible character of these reactions is due to the elimination of the nitrous acid and the subsequent aromatization of the products.

- ***3-nitrofuran + isoprene***

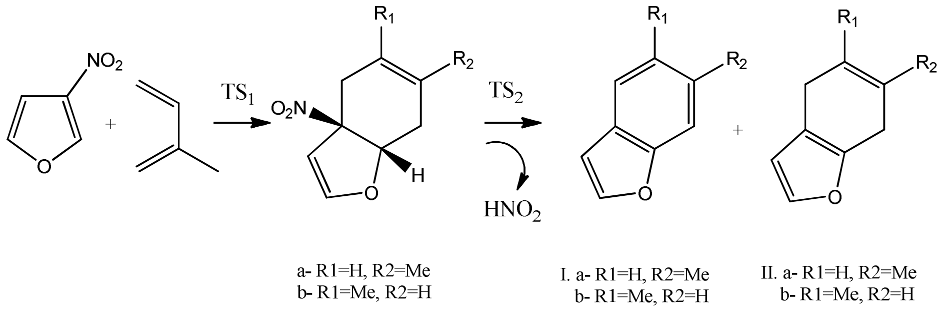


Figure 3

Local indexes indicates that the most electrophilic center of the 3-nitrofuran is C2, so it is going to react with the most nucleophilic atom of isoprene. The ΔN_k between C1 and C4 is near 0.30 eV in this diene, which is not enough to observe regioselectivity and both isomers appear as products.

The Δω of the reaction for this system is 1.41 eV. The structure of TS1 (Figure 4), forming the *para* and *meta* product, showed a concerted cycloaddition process because both formatting bonds vibrate at the same time and in an asymmetric form [(Δr_{para}= 1.23 Å), (Δr_{meta}= 1.37 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 $C3^{dienophile}$ -$C4^{diene}$.

Figure 4

This is due to the fact that the formation of the bond is between the most electrophilic center of the dienophile (C3) and the most nucleophilic center of the diene (C4). The energy barrier of the *meta* isomer is a little higher than the *para* one.

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

Figure 5

The Δω in this reaction reach the 1.60 eV. Then a good yield of the cycloaddition product is expected. Moreover, 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 dihydro compounds (ΔN_k=0.29 eV) subsequent derivates in the same final aromatic product.

Figure 6

For this diene we observed one concerted transition state (TS_1 -Figure 6-) which indicates that is a cycloaddition process. Both forming bonds vibrate at the same time and in an asymmetric form [(Δr_{ortho}=1,24 Å), (Δr_{meta}=0,90 Å), (Δr= (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}. The *meta* isomer energy barrier is a little higher than the *para* one.

- ***3-nitrofuran + Danishefsky's diene***

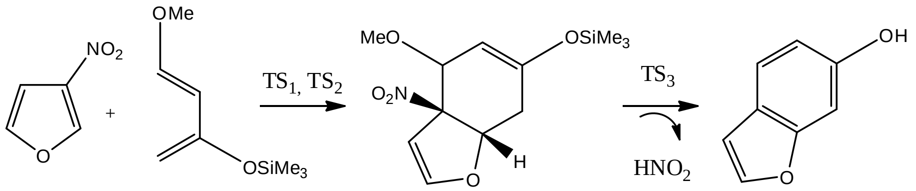


Figure 7

Whit Danishefsky's diene ($\Delta\omega$=1,67), the formation of only one isomer is expected (ΔN_k=0.89 eV). The product derives from the union of C4 of the diene and C2 of the dienophile. The reaction is completely regioselective and the aromatic compound that corresponds to the *para* adduct is observed after the loss of the -NO_2 and –OMe groups.

Finally, with Danishefsky's diene the mechanism is surprising. There are two transition states [(Δr_{TS1}=1,24 Å), (Δr_{TS2}=0,90 Å)] corresponding to each sigma bond formation and an intermediate state, which was not possible to optimize. We are in presence of a *two-step non-intermediate mechanism*. This fact does not agree with the pericyclic reaction concept. In a similar way we detected in a theoretical study that the reaction of 3-nitropyridine as electrophilic dienophile with Danishefsky's diene, presents a comparable mechanism with two step and a detectable an intermediate state.[25]

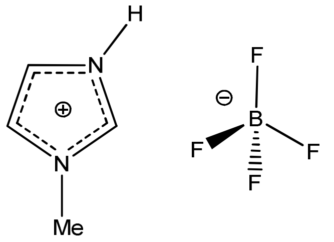
TS_1 ***TS_2***

Figure 8

The primary cycloadduct is not observed in all of these cases because of the relative stability of the nitrate adduct respect to the final product with elimination of nitric acid. The irreversible step of the D-A reaction (impulsive force) is the extrusion of nitrous acid and the stability is related to the aromaticity of the final product.

3.3. Influence of neoteric solvents

The IL employed for the solvent effect analysis was tetrafluoroborate of 1-methyllimidazolium -[HMIM][BF$_4$]- (Figure 9). This selection is related to the possibility of hydrogen bonding formation that presents this IL.



[HMIM][BF$_4$]

Figure 9

If the classical interaction between the electrophile and the IL is considered which mean that the IL cation interact via hydrogen bonding with the nitro group of the electrophile the global electrophilicity index is too high (ca. ω=10, for tetrafluoroborate of 1-methyllimidazolium and ethyl ammonium nitrate). These results are not compatible with the experimental data (although the rate of the reaction is higher than those when a molecular solvent is used, the yields and the temperature of the reactions do not change enough), probably because the anion is not considered formally.

For this reason, the supermolecular approach was explored. In this case the anion is considered. When one par *anion-cation* of IL is taken into account the anion interacts only with the cation (electrostatic interactions) without affecting the 3-nitrofuran, enabling planar arrangement of hydrogen bond between the cation and the dienophile (Figure 10).

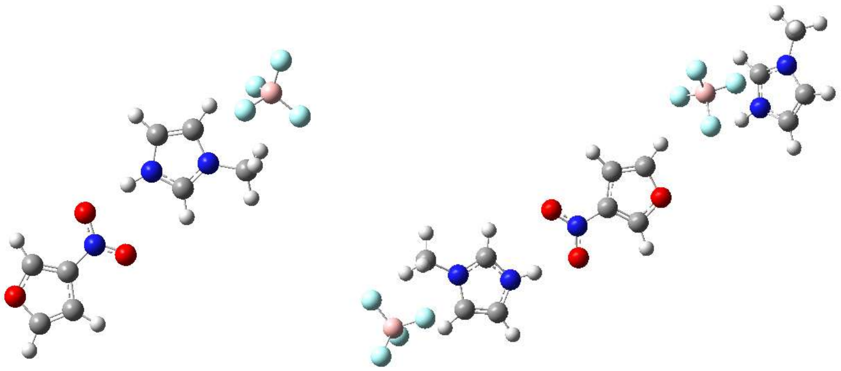


Figure 10

When a second IL par *anion-cation* is added, an additional electrostatic interaction with the dienophile appears and, therefore, the value of ω decreases from 5.01 to 3.78 eV. This trend continues when the 3rd and 4th IL molecules are added, with values of ω of 3.11 and 2.84 eV respectively (Figure 11).

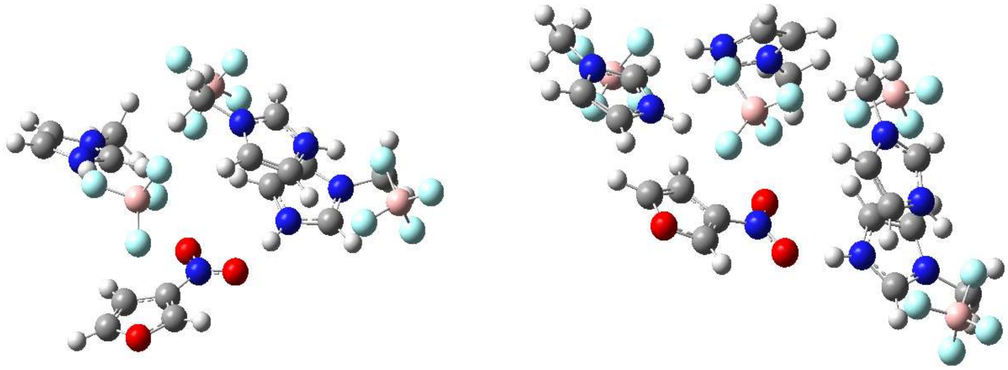


Figure 11

Based on these results, it can be considered that, when predominates a specific interaction of hydrogen bonding on the dienophile, the value of the global electrophilicity increases while when we are also in the presence of electrostatic interactions the effect is counteracted.

Table 4. Global electrophilicity of 3-nitrofuran with different solvents.

Method	**Solvent**	**ω(eV)**
PCM	[HMIM][BF$_4$]	2,49
	Water	2,51
	Benzene	2,41
Supramolecular	[HMIM][BF$_4$]x1	5,01
	[HMIM][BF$_4$]x2	3,78
	[HMIM][BF$_4$]x3	3,11
	[HMIM][BF$_4$]x4	2,84

It is noted that the global electrophilicity of dienophiles increases when the solvent effect is considered respect to the gas phase. Furthermore, the highest values correspond to the influence of the IL.

There is a second ω value that is related to the structure where a same anion is interacting with both, the dienophile and the cation, which reduces the effect of the hydrogen bonding interaction due to the rotation in the plane (Figure 12).

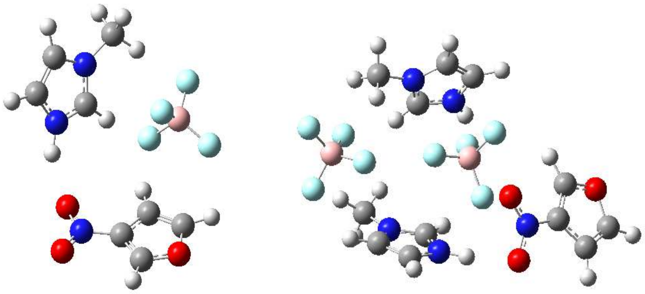


Figure 12

In this case, ω values are lower, 3-nitrofuran+[HMIM][BF_4]x1 (2.91 eV) - 3-nitrofuran+[HMIM][BF_4]x2 (2.92 eV), 3-nitrofuran+[HMIM][BF_4]x3 (2.75 eV), 3-nitrofuran+[HMIM][BF_4]x4 (2.74 eV). This seems to be due to the diminution of the interaction between the orbital of both, the dienophile and the solvent that results as a consequence of the non-planar arrangement

Moreover, incorporating other IL molecules, the number of electrostatic interactions increases, including new solvent-solvent interactions (Figure 12). The ω values fluctuate around 2.80 eV due to the different relation between electrostatic effects and hydrogen bonds.

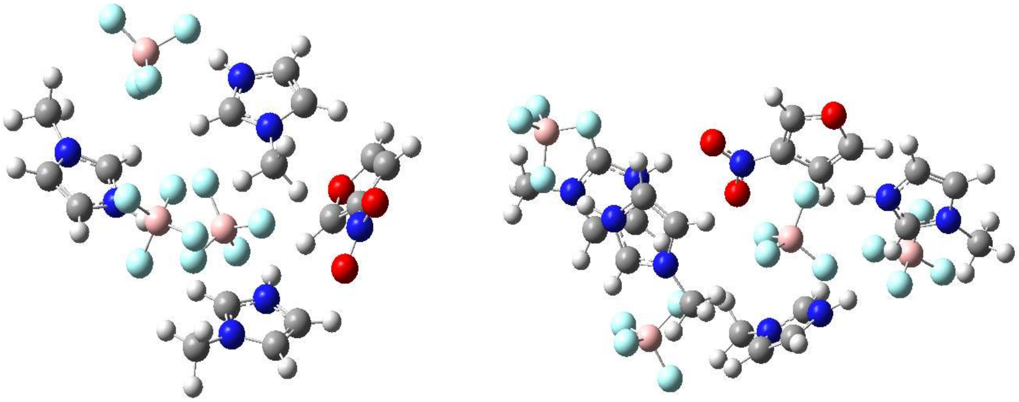


Figure 13

Additionally, the global electrophilicity value of 3-nitrofuran in the presence of IL using the PCM method is lower than the one obtained using the explicit method, its value is in fact similar to water, because it is a polar solvent and, with this method, those solvents having similar dielectric constant values will provide similar results regardless of their structures.

Global electrophilicity values obtained by the second situation provide more consistent results with experience, where the reaction yields are slightly higher and the reaction conditions, time and temperature, decrease.

Conclusions

The theoretical calculations are consistent with the experimental results observed for these reactions in relation with the selectivity and products obtained. The analysis of the reaction mechanism in this P-DA process shows that when isoprene and 1-methoxy-1,3-butadiene are used as diene, only one transition state is observed. On the other hand when

Danishesfky's diene is employed, it is possible to observe two transition states without a classic intermediate state. The mechanism that involves Danishefsky's diene could be considered as stage mechanisms. The behavior of the involved molecules in a cycloaddition reaction could be well described by the reactivity indexes. The chemical potential values are good descriptors to know which of the molecules will act as dienes or dienophiles and how polar the reaction could be (Δω). Local indexes result representatives of the reaction regioselectivity.

The global electrophilicity of the dienophile increase when IL is employed as a reaction media. The PCM is not adequate to explain this effect because it does not consider the solute-solvent specific interactions. On the other hand, the supermolecular approach considers the hydrogen bonding interaction and is more consistent with the experimental results obtained when 3-nitrofuran is used as an electrophile in D-A reactions using ILs as solvents.

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