A Theoretical Study of 2-nitrofuran vs 3-nitrofuran as Dienophilic Electrophile in Polar Cycloaddition Reaction: Comparison of the Reactivity and Reaction Mechanism

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Authors’ contributions

This work was carried out in collaboration between four authors. Authors CMO and MC realized the theoretical calculations which appear in this study. Authors MNK and PMEM wrote the protocol and preformed the global analysis related to the Polar Diels-Alder reactions. All authors participated in the analysis of the solvent effect in this type of reactions. Authors MNK and PMEM read and approved the final manuscript.

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ABSTRACT

In this study, we analyzed in a theoretical form the behavior of 2-nitrofuran and 3-nitrofuran acting as dienophilic electrophiles in polar cycloaddition reactions joint to different dienes. The reactivity and regioselectivity was discussed employing global and local reactivity indexes, respectively. The reaction mechanisms of these cycloadditions were compared through the transition state structures and energies calculated.

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1. INTRODUCTION

The Diels-Alder (DA) reaction is a powerful and useful tool in synthetic organic chemistry that allows the construction of a six-membered ring in one step. The process involves the formation of two $\sigma$ bounds and the rupture of two $\pi$ bounds simultaneously between a compound with two conjugated double bonds (diene) and a compound with one double bond (dienophile), producing regioselective and stereospecific products [1,2].

A wide variety of dienes and dienophiles can be used. Previous studies demonstrated that aromatic heterocycles can act as dienophiles in DA reactions [3] when these compounds are properly substituted with electron withdrawing groups such as carbonyl and nitro group [4].

According to the Frontier Molecular Orbital (FMO) theory, in this reaction the bonding formations involve a charge transfer (CT) process between the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) of the reactants [5]. The proper employment of substituents in both, diene and dienophile, decrease the energy gap between these orbitals, resulting in a more favored reactive process [6-7].

The mechanisms of these reactions can be considered, normally, as a concerted synchronous or asynchronous process. In the synchronous process, the rate of rupture and formation of the bonds in the transition state (TS) are the same and the reaction is non-polar, while in the asynchronous process the rates are different and the reaction is known as Polar Diels-Alder reaction (P-DA) [8-10]. The first mechanism is observed when the bonding atoms have similar reactivity, for example when the diene and the dienophile are symmetric, while the second one is observed when the polarities are different, which is the most common situation. A theoretical study, based on the Density Functional Theory (DFT) methods, of the behavior of dienes and dienophiles in DA reactions allows explaining the feasibility of the cycloaddition processes and the type of mechanism observed in each one [11].

Recently a theoretical study was developed to analyze the reaction mechanism of 3-nitrofuran acting as electrophilic dienophile in P-DA reactions with different dienes. It has been demonstrated that 3-nitrofuran reacts efficiently with the selected dienes in normal electron demand P-DA reactions, with the nitro group inducing the formation of a selective product [12]. In this work, we analyze the mechanism of the reaction between 2-nitrofuran and the dienes. Then, we compare the reactivity and reaction mechanisms with those observed in 3-nitrofuran reactions.

2. COMPUTATIONAL METHODS

The theoretical DFT calculations were carried out using the Gaussian 09 [13] program. The hybrid functional method [14] employed was B3LYP [15], together with the standard 6-31G(d) basis set [16].

Geometric structures of reactants and products were optimized using the Berny analytical gradient optimization method [17]. The mechanistic study was realized through the construction of the Potential Energy Surface (PES) for every system. The structures of transition states (TSs) were located, optimized and then verified through IRC (Intrinsic Reaction Coordinates) calculations [18]. The frequency calculations were done to validate the optimized structures. Reactants and cycloadduct (CA) structures were verified by the absence of negative frequencies, and the TSs by the presence of only one imaginary frequency that corresponds to the bond formation.

The reactivity of the systems was studied using some indexes defined in terms of the electronic chemical potential ($\mu$) and the chemical hardness ($\eta$). The chemical potential is 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, $\varepsilon_H$ and $\varepsilon_L$ [19].

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

$$\eta = \varepsilon_L - \varepsilon_H$$

The global electrophilicity index, $\omega$, represents the capability of a molecule to accept an electron...
considering the environment saturated 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.

\[ N = \varepsilon_{\text{HOMO}(\text{Nu})} - \varepsilon_{\text{HOMO}(\text{TCE})} \]

The nucleophilicity is referred to tetracyanoethylene (TCE), which presents the lowest HOMO energy in relation to large series of molecules already investigated in the context of polar cycloadditions [20].

Fukui function is a measure of the sensitivity 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].

\[ f(r) = \left( \frac{\partial \rho(r)}{\partial n} \right)_{\nu(r)} = \left( \frac{\partial \mu}{\partial \nu(r)} \right)_{n} \]

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

\[ f_{\mu} = \sum_{\mu \epsilon k} f_{\mu}^{a} \]

\[ f_{\mu}^{a} = \left| c_{\mu \alpha} \right|^2 + \sum_{\nu \neq \mu} c_{\nu \alpha} S_{\mu \nu} \]

\( f_{\mu}^{a} \) and \( f_{\mu}^{e} \) are the Fukui functions for a nucleophilic and electrophilic attack, respectively. Local electrophilicity and nucleophilicity indexes, \( \omega_{k} \) and \( N_{k} \), can be obtained using the following expressions

\[ \omega_{k} = \omega f_{k}^{+} \]

\[ N_{k} = N f_{k}^{-} \]

The optimization structures provide the values of HOMO and LUMO orbitals that are used to quantify the reactivity indexes [22].

3. RESULTS AND DISCUSSION

3.1 Global Properties of Dienophile and Diene

In order to compare the reactivity of 2-nitrofuran (Fig. 1) with 3-nitrofuran, the global properties were calculated (Table 1).

![Fig. 1. Structure of 2-nitrofuran](image)

The global electrophilicity (\( \omega \)) of 2-nitrofuran is 2.51 eV which is a little higher than in case of 3-nitrofuran (2.35 eV).

The dienes used in this study are 2-methyl-1,3-butadiene (Isoprene) (1), 1-methoxy-1,3-butadiene (2) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky’s diene) (3) (Scheme 1). The reactivity is analyzed comparing the differences of global electrophilicity between the dienophile and the different dienes (Table 2).

![Scheme 1. Structure of dienes](image)

| Table 1. Electronic properties of 2-nitrofuran |
|-----------------------------------------------|
| Dienophile | \( \varepsilon_{\text{HOMO}} \) (eV) | \( \varepsilon_{\text{LUMO}} \) (eV) | \( \mu \) (eV) | \( \eta \) (eV) | \( \omega \) (eV) | \( N \) (eV) |
|-----------|---------------------------------|---------------------------------|-------------|-------------|---------------|-------------|
| 2-nitrofuran | -0.26971 | -0.09222 | -0.180965 | 0.17749 | 2.51 | 1.78 |

| Table 2. Electronic properties of dienes |
|-----------------------------------------|
| Diene | \( \varepsilon_{\text{HOMO}} \) (eV) | \( \varepsilon_{\text{LUMO}} \) (eV) | \( \mu \) (eV) | \( \eta \) (eV) | \( \omega \) (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 |
This difference ($\Delta \omega$) presents the highest value for Danishefsky’s diene (2) ($\omega = 0.96$ eV). Then the reactions involving this diene would be more favourable than those in which 1-methoxy-1,3-butadiene (3) ($\omega = 1.07$ eV) or isoprene (4) ($\omega = 1.27$ eV) are employed.

3.2 Local Properties of Dienophile and Diene

The regioselectivity was analyzed using the local properties of the dienophile (Table 3) and dienes (Table 4).

Table 3. Local electrophilicity of 2-nitrofuran

| Dienophile            | $\omega_k$(eV) |
|-----------------------|----------------|
| 2-nitrofuran          |                |
| C$_2$                 | 0.10           |
| C$_3$                 | 0.38           |

In case of 2-nitrofuran, the local electrophilicity of C$_2$ and C$_3$ are 0.10 eV and 0.38 eV respectively ($\Delta \omega_k = 0.28$ eV), while for 3-nitrofuran are 0.43 eV and 0.06 eV respectively ($\Delta \omega_k = 0.37$ eV). It’s observed that the most electrophilic center is, in both cases, the carbon atom next to the one substituted with the nitro group.

Table 4. Local electrophilicity of dienes

| Diene                          | $N_k$(eV) |
|--------------------------------|-----------|
| Isoprene                       |           |
| C$_1$                          | 1.20      |
| C$_4$                          | 0.92      |
| 1-metoxy-1,3-butadiene         |           |
| C$_1$                          | 0.74      |
| C$_2$                          | 0.94      |
| Danishefsky’s diene            |           |
| C$_1$                          | 0.56      |
| C$_4$                          | 1.46      |

On the other hand, the dienes have a local nucleophilicity in C$_1$ and C$_4$ of 1.20 eV and 0.92 eV ($\Delta N_k = 0.28$ eV) respectively for isoprene, 0.74 eV and 0.94 eV ($\Delta N_k = 0.20$ eV) respectively for 1-methoxy-1,3-butadiene, 0.56 eV and 1.46 eV ($\Delta N_k = 0.90$ eV) respectively for the Danishefsky’s diene. The regioselectivity is expected to be higher for the processes that involve Danishefsky’s diene due to the higher difference in the local nucleophilicity between C$_1$ and C$_4$ which is a consequence of the electron donor groups (-OMe y –OSiMe3) and its relative positions, specially the methoxy group.

It’s expected that atoms of the dienophile with higher values of local electrophilicity (C$_3$ in case of 2-nitrofuran) will react with the atoms with higher values of local nucleophilicity of the diene (C$_4$ in case of the Danishefsky’s diene).

3.3 Reaction Mechanism

The primary adducts of the DA reactions involving nitro-dienophiles are usually not observed experimentally due to the elimination of the nitro group as nitrous acid. This is an irreversible process that involves several reactions which leads to the subsequent aromatization of the products. If asymmetric dienes such as Danishefsky’s diene are used, the process involves the elimination of methoxy group and the hydrolysis of trimethylsilyloxy group.

In this study, it’s analyzed the reaction mechanism of the DA process until the formation of the primary adducts because this is the determinant step of the reaction. The loose of nitro group is irreversible. This step of the process is favored by the aromatic character of the final product.

3.3.1 2-nitrofuran + isoprene

The $\Delta N_k$ between C$_1$ and C$_4$ is not enough to observe regioselectivity and both isomers appears products (Scheme 2). The isomers relation was dihydro/aromatic 1:3. The elimination of the nitro group allows to obtain a mixture of dihydro and aromatic isomers as final products.

The $\Delta \omega$ of the reaction for this system is 1.57 eV. This reaction presents one transition state (TS, Fig. 2) for each, para and meta products.

![Scheme 2. Diels-Alder reaction between 2-nitrofuran and isoprene](image-url)
This process is concerted and asynchronous because both formatting bonds vibrate at the same time and in an asymmetric form \([(\Delta r_{\text{para}}= 0.12 \text{ Å}), (\Delta r_{\text{meta}}= 0.30 \text{ Å})\) where \(\Delta r\) is the difference in length of the forming bonds at TS. The energy barrier of both isomers is similar (24 kcal/mol) which validate the obtention of the two products (Fig. 3a). The energy barrier of this reaction is higher than that in which 3-nitrofuran is employed as dienophile (17.5 kcal/mol) (Fig. 3b).

### 3.3.2 2-nitrofuran+1-methoxy-1,3-butadiene

In this case the methoxy group is eliminated as methanol after the cycloaddition, together with the nitro group. Both isomers reach the same aromatic product (Scheme 3).

The \(\Delta \omega\) of the reaction for this system is 1.76 eV. This reaction presents one transition state (TS, Fig. 4) for each, ortho and meta products.

This process is concerted and asynchronous because both formatting bonds vibrate at the same time and in an asymmetric form \([(\Delta r_{\text{para}}= 0.95 \text{ Å}), (\Delta r_{\text{meta}}= 0.76 \text{ Å})\). The energy barrier of the ortho isomers is 22.5 kcal/mol and the energy of the para isomer is slightly higher \((\Delta E_a = 2.52 \text{ kcal/mol})\) (Fig. 5a). The energy barrier of the ortho cycloadduct is higher than those in which 3-nitrofuran is employed as dienophile (13.37 kcal/mol). Moreover, the energy difference between both isomers in this case is higher \((\Delta E_a = 14.81 \text{ kcal/mol})\) (Fig. 5b).

### 3.3.3 2-nitrofuran + Danishefsky’s diene

The \(\Delta N_e\) between C1 and C4 in this diene is high enough to observe the formation of only one isomer (Scheme 4). In this case the methoxy group is also eliminated as methanol and the trimethylsilyloxy group is hydrolyzated together with the elimination of the nitro group to reach the final hydroxylated aromatic product.

The \(\Delta \omega\) of the reaction for this system is 1.83 eV. The product is the para one, which derives from the bond between the most electrophilic atom of

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**Scheme 3. Diels-Alder reaction between 2-nitrofuran and 1-methoxy-1,3-butadiene**
the dienophile (C₃) and the most nucleophilic atom of the diene (C₄). This reaction is highly asynchronous and presents two transition states (TS₁ and TS₂, Fig. 6). The TS₁ is associated with the bonding formation between these two reactive atoms (ΔrTS₁=1.24 Å) and the TS₂ corresponds to the bonding formation between the C₂ of the dienophile and the C₁ of the diene (ΔrTS₂=0.90 Å).

The energy barrier of the TS₁ is 18.95 kcal/mol and the energy of the TS₂ is 16.83 kcal/mol (Fig. 6). The energy barrier of the para cycloadduct is higher than those in which 3-nitrofuran is employed as dienophile (11.31 kcal/mol and 6.55 kcal/mol for TS₁ and TS₂ respectively, (Fig. 7b). Moreover, the energy of the TS₁ is the determinant step of the reaction because it is higher than the one of the TS₂.

![Fig. 5. Reaction path of 2-nitrofuran (a) and 3-nitrofuran (b) with 1-methoxy-1,3-butadiene](image1)

![Scheme 4. Diels-Alder reaction between 2-nitrofuran and Danishefsky’s diene](image2)

![Fig. 6. Transition states for the para cycloadduct](image3)

![Fig. 7. Reaction path of 2-nitrofuran (a) and 3-nitrofuran (b) with Danishefsky’s diene](image4)
4. CONCLUSION

The global electrophilicity (ω) of 2-nitrofuran is a little higher than the one of 3-nitrofuran. However, the difference of local electrophilicity (∆ωk) between C_2 and C_3 is higher in the case of 3-nitrofuran, which leads to higher asynchronous TS, that can be observed in higher values of ∆r.

The mechanism of these reactions is concerted and asynchronous. When isoprene and 1-methoxy-1,3-butadiene are employed, only one TS is observed. However, when Danishefsky’s diene is employed, two TSs are noted corresponding with each bonding formation. This is due to the higher difference of local nucleophilicity (∆Nk) between C_1 and C_4 of this diene, which leads to a higher asynchronous TSs.

When isoprene is employed, the activation energies of the reactions are similar and the obtention of both isomers is equally possible. Moreover, when 1-metoxy-1,3-butadiene is employed, the mechanism suggests a preference for the ortho cycloadduct, which is more notable in case of 3-nitrofuran. However the final product is the same and the experimental determination is not possible. Finally, the reactions involving the Danishefsky’s diene are completely regioselective and the product is the result of the bonding formation of the most nucleophilic atom of the diene with the most electrophilic atom of the dienophile. The TS_1 is the determinant step of these reactions due to it is higher value of activation energy.

The activation energies in all the reaction are lower when 3-nitrofuran is employed as dienophile. This could be due to the higher asynchronism of this reaction in relation to 2-nitrofuran, which favors the initial charge transference process between the most reactive atoms of the diene and dienophile.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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