

2-Nitrobenzofuran and 3-Nitrobenzofurans as dienophiles in Polar Diels-Alder Reactions. Theoretical studies using DFT Methods

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Abstract

2- and 3-nitrobenzofurans are studied in polar thermal Diels-Alder reactions with normal electron demand using several and structural different dienes. A very strong electron-acceptor group, such as nitro group, push the dienophilic character of these heterocyclic compounds and owing to this substituent is easily extruded under thermal conditions make this reaction sequence a simple method of organic compound's families with heteroatom rings preparation. This work is specifically concerned with theoretical studies using DFT methods. 2-nitrobenzofuran and 3-nitrobenzofuran react as dienophile against isoprene, 1-trimethylsilyloxy-1,3-butadiene, the Danishesky diene and the Rawal's diene, taking part in a normal demand DA cycloaddition reactions. These reactions could be considered a domino process that is initialized by a polar D-A reaction, and the latter concerted elimination of nitrous acid from the [4 + 2] cycloadduct yields the corresponding dibenzofurans.

Introduction

The Diels-Alder (D-A) reaction is one of the most significant and useful tool available in synthetic chemistry. It allows the simple construction of a six-membered ring from a diene and a dienophile bearing an almost unlimited numbers of variants.¹

It has been known for some time that aromatic heterocyclic, such as furan, pyrrole and thiophene undergo D-A reactions despite their aromaticity and hence expected inertness. In view of their electron rich constitution and electron-donor properties, there have been mostly involved as the diene component in the cycloaddition process. However, there are a limited number of examples of five-membered aromatic heterocycles acting as dienophiles in D-A reactions with normal electron demand.² For example, 3-acilated furans and 2- and 3-nitrofurans have to be excellent dienophiles with isoprene and others dienes.³ Due to our interest in the cycloaddition chemistry of substituted aromatic heterocycles with electron withdrawing groups, we have reported that 2-nitrofurans, 2-nitrothiophene, 2-nitro-*N*-tosylpyrrole and 2-nitroselenophene react with strong and poor dienes under different conditions.⁴ Further studies focused on the dienophilic character of indoles since their adducts seemed to be appealing for the total synthesis of carbazole and *Aspidosperma* alkaloids.⁵

Dibenzofurans are important heteroatomic compounds which display a wide variety of biological activities. The dibenzofuran containing pytoalexins show manifold biological activities, eliciting a strong interest from chemist and biologists.⁶ Considerable efforts have been devoted to the development of efficient methods for the building of these heteroatomic ring systems. More of the general procedures involved several steps and the overall yield usually are not very good.⁷

Benzofurans have been shown in a few cases, to react as dienophiles in D-A reaction. The benzo[b]furan itself can act an electron-rich dienophile in a inverse electron demand process. In other way, several years ago was informed the reaction between 3-formylbenzofuran and isoprene as an example of a D-A cycloaddition.^{2a} Recently have been reported a study of acyl substituted benzofurans as efficient dienophiles in a normal electro demand [4 + 2] cycloaddition using high pressure reaction conditions.⁸

Recently we have reported a simple, economical and efficient one-step scheme to synthesize the dibenzofuran ring system in good to excellent yield through the D-A reaction of 2-benzofuran and different dienes.⁹ A very strong electron-acceptor group, such as nitro group, push the dienophilic character of this heterocyclic compounds and owing to this substituent is easily extruded under thermal conditions make this reaction sequence a simple method of organic compound families with heteroatom rings preparation.

The aim of this work is rationalized through theoretical calculations the behavior as dienophiles of 2- and 3-nitrobenzofurans in its reactions with different dienes. The polarity of the normal electron demand D-A process propose has been studied by means of global electrophilicity index difference between reactants. Moreover, it was analyzed the regioselectivity of the normal electron demand D-A reaction using the local electrophilicity index for dienophiles (electrophiles in the reaction) and the local nucleophilicity index for dienes (nucleophiles in the reaction).

Results and Discussion

In the last years the density functional theory (DFT) has been successful in explaining the reactivity and regioselectivity of cycloaddition reactions. In this sense the regioselectivity for a series of experimentally studied D-A reactions between furan derivatives and the Danishefsky diene have been rationalized within the framework of local DFT-based descriptors. In this direction there are several parameters which can be used as global or local reactivity descriptors. For instance, the chemical hardness (η) describes the resistance of the chemical potential to a change in the number of electrons. The electronic chemical potential (μ) it is usually associated with the charge-transfer ability of the system in its ground state geometry. Both quantities can be approximated in terms of the energies of the HOMO and LUMO frontier molecular orbitals (Eqs. 1 and 2)¹⁰

$$\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO}) \quad (1)$$

$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2} \quad (2)$$

The global electrophilicity index (ω), introduced by Parr *et al.*¹¹ is a useful descriptor of the reactivity that allows a quantitative classification of the global electrophilicity character of a molecule within a unique scale.¹² Current studies based on the DFT and applied to D-A reactions, have shown this classification of the diene/dienophile pair is a powerful tool to predict the feasibility of the process and the type of mechanism involved. This index is defined as

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

Useful information about polarity of de D-A processes may be obtained from the difference in the global electrophilicity power of the reactants. This difference has been proposed as a measure of the polar character of the reaction. On the other hand, local reactivity indexes are associated with site selectivity in a chemical reaction. These descriptors should reflect the sites in a molecule where the reactivity pattern stated by the global quantities should take place. For instance, an important local reactivity parameter was introduced by Parr *et al.* And it was defined as the Fukui function.¹³

Eq. (4) provides a simple and direct formalism to obtain the Fukui function from an approach based on a relationship with the FMOs.¹⁴ The condensed Fukui function for electrophilic (nucleophilic) attack involves the HOMO (LUMO) FMO coefficients (c) and the atomic overlap matrix elements (S).

$$f_k^{\alpha} = \sum_{\mu \in k} |c_{\mu\alpha}|^2 + \sum_{\nu \neq \mu} c_{\mu\alpha} c_{\nu\alpha} S_{\mu\nu} \quad (4)$$

This scheme has been corroborated for several reactions that are well documented.¹⁵

Eq. (5) has been introduced to analyze at which atomic site of a molecule the maximum electrophilicity power will be developed.¹⁶

$$\omega_k = \omega f_k^+ \quad (5)$$

Furthermore, the first approaches toward a quantitative description of nucleophilicity, in the form of a regional reactivity index, have also been reported. Eq (6) has been developed by Domingo *et al* with the purpose of identifying the most nucleophilic site of a molecule and assessing the activation/deactivation caused by different substituents on the electrophilic aromatic substitution reactions of aromatic compounds.¹⁷

$$N_k = N f_k^- \quad (6)$$

$$N = (\varepsilon_{HOMO, Nu} - \varepsilon_{HOMO, TCE}) \quad (7)$$

where $\epsilon_{\text{HOMO,TCE}}$ is the HOMO energy of tetracyanoethylene (TCE) (taken as a reference molecule because it exhibits the lowest HOMO energy in a large series of molecules previously considered in the framework of polar D-A cycloadditions).¹⁷ N is the global nucleophilicity index and N_k is its local counterpart.

This nucleophilicity index has been useful to explain the nucleophilic reactivity of some molecules towards electrophiles in cycloaddition as well as substitution reactions.^{18a,19}

In this work the polarity of the normal electron demand D-A process propose has been studied by means of global electrophilicity index difference between reactants and the regioselectivity of the normal electron demand D-A reaction shown in Schemes 1 and 3 using the local electrophilicity index for dienophiles (electrophiles in the reaction) and the local nucleophilicity index for dienes (nucleophiles in the reaction).

Computational Details

Studies show that the B3LYP method,²⁰ using 6-311+G(d,p) basis set, is adequate to model D-A reactions concerning medium-sized molecules. Hence, the gas-phase equilibrium geometries of all species described here were obtained by full optimization at the B3LYP/6-311+G(d,p) level using the GAUSSIAN03W program.²⁰ All the stationary points found were characterized as true minima by frequency calculations.

The chemical hardness, the electronic chemical potential and the global electrophilicity index have been calculated using Eqs 1 and 2. Regional Fukui functions for the dienophiles (f_k^+) and for the diene (f_k^-) were obtained from single-point calculations on the optimized structures at the ground state (Eq. 4). A program that reads the FMO coefficients and the overlap matrix from the Gaussian output files and performs the required calculation was developed and tested. Once the Fukui functions were computed, the local electrophilicity and nucleophilicity values were calculated (Eqs 5 and 6).

Reactions

To explore the normal electron demand D-A dienophilicity of nitrobenzofurans **1a-b** we choose isoprene (**2**), 1-Trimethylsilyloxy-1,3-butadiene (**3**), 1-Methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky diene) (**4**) and the Rawal's diene (**5**) as dienes (Figure 1). The selection of the dienes taken into account the type of substitution present and the relative nucleophilicity. Also, the reactivity of 2-nitrobenzofuran was explored with the Rawal diene (Scheme 2)

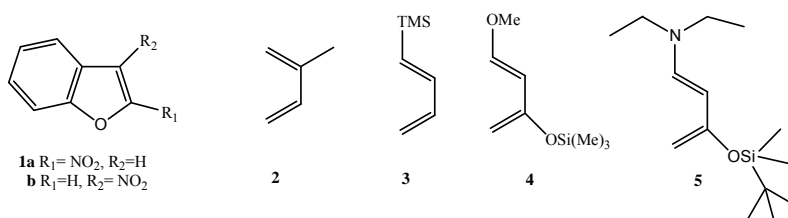
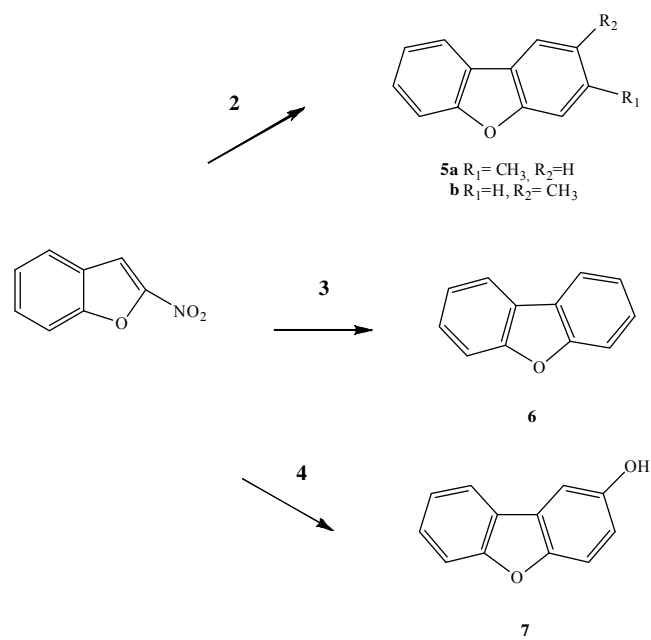
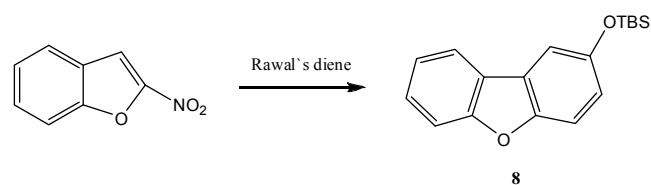


Figure 1

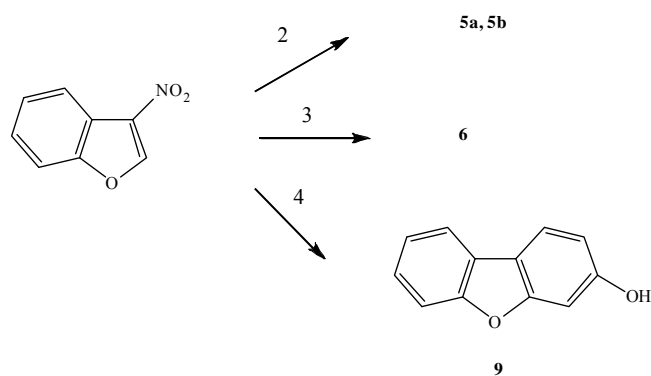
According to the global electrophilicity index ω shown in Table 4 the dienes will act as nucleophiles and the dienophiles as electrophiles. To study the regioselectivity we used the local electrophilicity and nucleophilicity indexes for dienophiles and dienes respectively (Tables 5 and 6). The sites of study were C2 and C3 in **1a** and **1b** and C1 and C4 in dienes **2**, **3**, **4**, **5**. The more favoured adducts are the ones where the most electrophilic and nucleophilic sites interact first. In the reactions in which it is possible discussed the regioselectivity the experimental data agree with the computational results. However, the influence of the methyl group when isoprene is the diene is less than the groups present in Danishefsky's diene.



Scheme 1



Scheme 2



Scheme 3

Table 4. Global electrophilicity indexes of the used dienophiles and dienes.

Compound	$\omega(\text{eV})$
1a	3.3275
1b	3.0002
2	1.2746
3	1.0558
4	0.9611
5	0.4969

Table 5. Local electrophilicity indexes for dienophiles **1a** and **1b**

Dienophile	Site	ω_k (eV)
1a	2	0.1571
	3	0.5359
1b	2	0.7263
	3	0.0482

Table 6. Local nucleophilicity index for dienes **2**, **3**, **4**

Diene	Site	N_k (eV)
2	1	1.1183
	4	0.7519
3	1	0.7496
	4	0.9281
4	1	0.5441
	4	1.3401

Conclusions

These reactions could be considered a domino process that is initialized by a polar D-A reaction, and the latter concerted elimination of nitrous acid from the [4 + 2] cycloadduct yields the corresponding dibenzofurans. A very strong electron-acceptor group, such as a nitro group, induces a similar reactivity at 2- and 3-positions in the benzofuran ring.

DFT calculations of the electrophilicity and nucleophilicity indexes give us the result expected on reactivity and also the local descriptors explain the general trend in regiochemistry. This result supports the use of this synthesis pathway as a viable one of important heteroatomic compounds which display a wide variety of biological activities.

Acknowledgments

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