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Theoretical explanation of the regioselectivity of polar cycloaddition reactions between furan derivatives and Danishefsky's diene

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ABSTRACT

The regioselectivity for a series of experimentally studied Diels–Alder reactions between furan derivatives and Danishefsky's diene has been rationalized within the framework of local DFT-based descriptors (i.e. electrophilicity and nucleophilicity indexes). The importance of the solvent in the calculations has been studied. It has been shown that the relative trend of an atomic center to behave as an electrophile is affected by the medium (gas phase or benzene solution) and the basis set used in the calculation of the reactivity descriptors. The local electrophilicity (ω_k) and nucleophilicity (N_k) indexes properly account for the observed regioselectivity only when B3LYP/LANL2DZ and HF/LANL2DZ levels of theory have been used.

1. Introduction

Numerous natural products and biologically important synthetic compounds are derived from benzofuran ring systems [1]. For instance, a number of benzofuran derivatives have been shown to be successful inhibitors of various enzymes and genes [2]. Also, other derivatives have been investigated as estrogen [3], androgen [4] and adenosine A1 receptor ligands [5]; H3 antagonists [6]; blood coagulation factor Xa inhibitors [7]; ligands of dopamine D3 receptor [8]; calcium entry blockers [9] and antifungal agents [10]. For those reasons, a wide number of methodologies for the preparation of benzofuran derivatives have been reported [11].

One simple route to achieve this class of compounds through Diels–Alder (D–A) reactions is using suitable furan derivatives (i.e. furan substituted with electron withdrawing groups) as dienophiles and performing further functional group transformations. We have recently shown that 2-nitrofuran, methyl 5-nitrofuran-3-carboxylate and methyl 5-nitrofuran-2-carboxylate can act as dienophiles in thermal D–A reactions with Danishefsky's diene leading to benzofuranol derivatives [11b,12]. In a simplified scheme these reactions proceeded by addition of the diene to the nitro-substituted double bond of the furan, exhibiting complete regioselectivity and siteselectivity. All cycloaddition products showed extrusion of the nitro group, hydrolysis of the silyl enol ether and elimination of methanol (Scheme 1).

As a part of our general interest in the D–A reactions between furan derivatives and Danishefsky's diene, we have also investigated these reactions from a theoretical point of view.

The D–A reactions that have been studied here involve unsymmetrically substituted reactants, therefore, different stereoisomers and regioisomers can be formed (Scheme 2). Using the nomenclature that has been proposed to name the regioisomers [13], we can assign the short notation [1 (OMe), 3 ($OSiMe_3$)] and [2 ($OSiMe_3$), 4 (OMe)] to distinguish the regiochemistry of the cycloadducts, and the terms *endo* and *exo* to differentiate the stereoisomers. The experimentally observed product (inside the chart) is the one originating from the [1 (OMe), 3 ($OSiMe_3$)] channel.

Frontier molecular orbital (FMO) theory suggests a simple way of interpreting the reactivity and regiochemistry of the D–A reaction [14]. This theory has been widely used giving satisfactory results [15]. Therefore, the stabilizations (ΔE_{TS}) for the transitions states of the possible cycloadditions and the orbital coefficients of the reactants were calculated at first to rationalize the exclusive formation of products **5.a**, **5.b** and **5.c**. The results obtained from gas phase and solvent calculations (B3LYP/6-31G(d) level of theory) accounted properly for the observed regioselectivity (see Tables 1 and 2 and Fig. 1 of the Supporting material). However, this analysis was shown to be unreliable in some cases, showing severe

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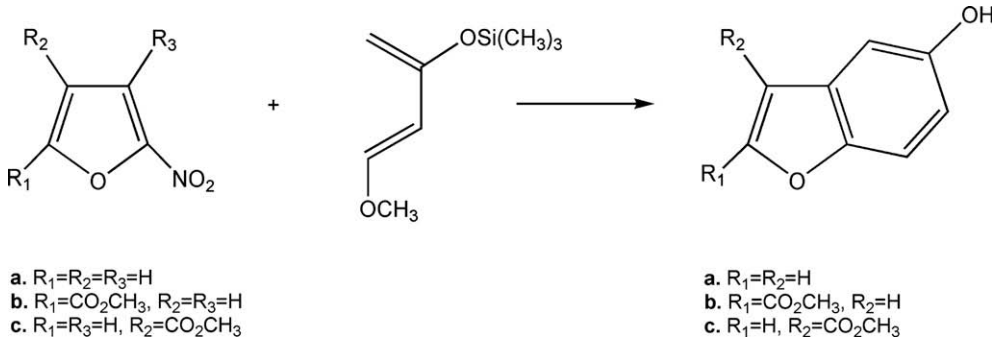


Scheme 1. Simplified reaction scheme for the D–A reaction between furan derivatives and Danishefsky's diene [11b,12].

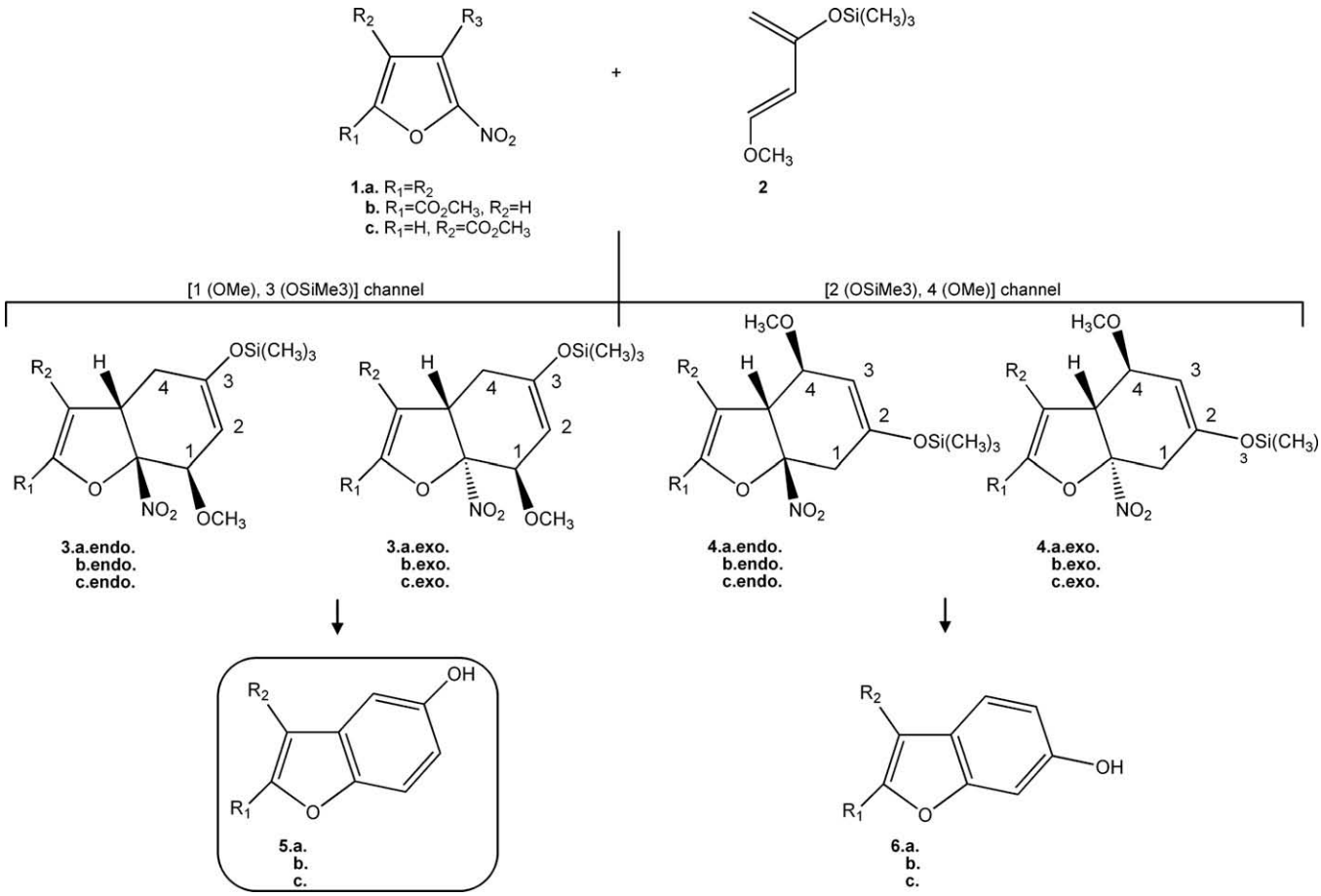
limitations in predicting the regioselectivity [16]. Consequently, besides the FMO model we have also used several other reactivity indexes (see below) to assess the regiochemistry of the title reaction. For instance, recent studies [17] have shown that while the FMO theory fails in the prediction of reactivity and/or regioselectivity of some DA reactions, DFT-based descriptors provide good results.

Recently, new Density Functional Theory (DFT) based concepts and indexes which are useful to model the chemical reactivity and siteselectivity in different cycloaddition reactions [18] have been developed. 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) 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 according to the following expressions (Eqs. 1 and 2) [19].

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

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

The global electrophilicity index (ω), introduced by Parr et al. [20], is a useful descriptor of reactivity that allows a quantitative



Scheme 2. Possible channels for the D–A reaction between furan derivatives and Danishefsky's diene.

Table 1
Global properties for the reactants. All quantities are shown in eV.

Molecule	Gas phase		Benzene		Level of theory
	μ	ω	μ	ω	
Furan	−2.786	0.584	−2.794	0.589	B3LYP/6-31G(d)
	−3.369	0.888	−3.390	0.902	B3LYP/LANL2DZ
	−2.676	0.278	−2.700	0.284	HF/LANL2DZ
2-Nitrofuran (**1.a**)	−4.925	2.511	−4.893	2.575	
	−5.696	3.620	−5.655	3.743	
	−5.138	1.204	−5.078	1.211	
Methyl 5-nitrofuran-2-carboxylate (**1.b**)	−5.249	2.964	−5.230	3.026	
	−6.012	4.156	−5.988	4.274	
	−5.527	1.413	−5.486	1.417	
Methyl 5-nitrofuran-3-carboxylate (**1.c**)	−5.162	2.700	−5.142	2.766	
	−5.940	3.844	−5.910	3.962	
	−5.389	1.300	−5.335	1.303	
Danishefsky's diene (**2**)	−2.688	0.678	−2.771	0.721	
	−2.930	0.854	−3.067	0.934	
	−2.387	0.241	−2.492	0.264	

Table 2
Local properties for 2-nitrofuran. ω_k values are shown in eV.

Molecule	Site k	Gas phase		Benzene		Level of theory
		f_k^+	ω_k	f_k^+	ω_k	
2-Nitrofuran (**1.a**)	C2	0.0403	0. 0124	0.0288	0.0741	B3LYP/6-31G(d)
		0.0407	0.1026	0.0290	0.0750	B3LYP/6-31G(d,p)
		0.0266	0.0826	0.0151	0.0483	B3LYP/LANL2DZ
		0.0756	0.0644	0.0571	0.0490	HF/6-31G(d)
		0.0759	0.0648	0.0573	0.0491	HF/6-31G(d,p)
		0.0587	0.0676	0.0382	0.0440	HF/LANL2DZ
	C3	0.1500	**0.3766**	0.1519	**0.3911**	
		0.1493	**0.3760**	0.1512	**0.3902**	
		0.1438	**0.4470**	0.1443	**0.4615**	
		0.1879	**0.1602**	0.1923	**0.1651**	
		0.1870	**0.1595**	0.1915	**0.1643**	
		0.1851	**0.2130**	0.1874	**0.2156**	
	C4	0.0026	0.0065	0.0032	0.0081	
		0.0026	0.0065	0.0031	0.0080	
		0.0001	0.0003	0.0008	0.0025	
		0.0041	0.0035	0.0034	0.0029	
		0.0041	0.0035	0.0033	0.0029	
		0.0003	0.0004	−0.0003	−0.0004	
	C5	0.1099	0.2760	0.1102	0.2839	
		0.1096	0.2760	0.1099	0.2835	
		0.1018	0.3164	0.1018	0.3256	
		0.1237	0.1054	0.1213	0.1041	
		0.1234	0.1053	0.1210	0.1038	
		0.1229	0.1414	0.1186	0.1364	

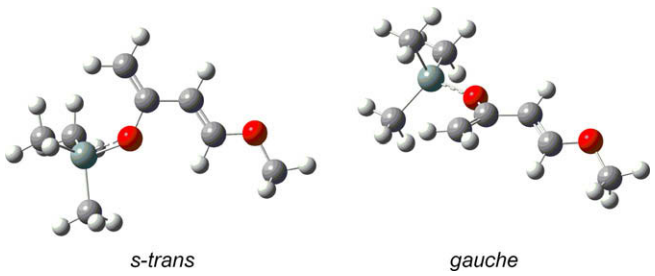


Fig. 1. Conformations of Danishefsky's diene in benzene.

classification of the global electrophilic character of a molecule within a unique relative scale [21]. This index is defined as

$$\omega = \frac{\mu^2}{2\eta} \tag{3}$$

Useful information about the polarity of the 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 [21].

On the other hand, local reactivity indexes are associated with siteselectivity 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 [22]. Subsequently, other local reactivity parameters were introduced (e.g. softness [23], hardness [24], electrophilicity [25] and nucleophilicity [26]).

Eq. (4) provides a simple and direct formalism to obtain the Fukui function from an approach based on a relationship with the FMOs [27]. The condensed Fukui function for electrophilic (nucleophilic) attack involves the HOMO (LUMO) FMO coefficients (c) and the atomic overlap matrix elements (S).

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

This scheme has been corroborated for several reactions that are well documented [28].

Eq. (5) has been introduced to analyze at which atomic site of a molecule the maximum electrophilicity power will be developed [25c].

$$\omega_k = \omega f_k^+ \tag{5}$$

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 [26a].

$$N_k = N f_k^- \tag{6}$$

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

where $\varepsilon_{\mathrm{HOMO,TCE}}$ 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) [29], 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 (i.e. captodative ethylenes, quadricyclane, boryllithium compounds) toward electrophiles in cycloaddition reactions as well as substitution reactions [29a,30].

In this work the regioselectivity for the D–A reactions shown in Scheme 1 has been studied by means of local reactivity projectors (ω_k and N_k described above). Our main aim is to contribute to a better understanding of the origins of the regiochemical outcomes.

2. Computational details

Recent studies reveal that the B3LYP method [31], even with the 6-31G(d) basis set, is adequate to model D–A reactions concerning medium-sized molecules. This method was successfully probed on different diene–dienophile combinations giving satisfactory results [32]. Hence, the gas and condensed-phase equilibrium geometries of all species described here were obtained by full optimization at the B3LYP/6-31G(d) level using the GAUSSIAN03 program [33]. All stationary points found were characterized as true minima by frequency calculations.

Solvent effects have been considered by full optimization of the gas phase structures using a self-consistent continuum method [34] in its conductor-like approximation (CPCM) [35]. The solvent used was benzene, as in the experiments [11b,12].

The chemical hardness, the chemical potential and the global electrophilicity index have been calculated using Eqs. 1.

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, using different levels of theory and basis sets (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).

3. Results and discussion

Firstly, the global reactivity indexes (μ, ω) of the reactants were calculated in order to determine the electron demand (normal or inverse) and the polarity (polar or non-polar character) of these cycloadditions. A general interpretation on the effect of the substituents on the electrophilicity of furan was also done. Secondly, local reactivity descriptors (ω_k, N_k) were calculated in order to rationalize the exclusive formation of products **5.a**, **5.b** and **5.c**.

3.1. Optimized geometries of the dienophiles and the diene

A complete description of all the optimized geometries is available in the Supporting information.

The most stable conformation of the Danishefsky's diene is the antiperiplanar or so-called *s-trans* conformer (Fig. 1). This conformation is 2.60 kcal mol^{-1} more stable than the synclinal arrangement where the two double bonds are twisted by 33° (*gauche* form).

In all the ground state structures of the dienophiles the nitro plane is coplanar with the heterocyclic plane, as well as the ester plane (Fig. 2). Both possible orientations of the ester carbonyl group with respect to the endocyclic C=C double bond, *s-cis* and *s-trans*, have comparable relative energies, B3LYP/6-31G(d) + ZPE: ΔE (**1.b**) = −0.74 (gas phase) and −0.41 kcal mol^{-1} (benzene solution); ΔE (**1.c**) = −0.07 (gas phase) and +0.02 kcal mol^{-1} (benzene solution). Consequently, FMO coefficients as well as Fukui functions were evaluated for both conformers of **1.b** and **1.c**.

3.2. Character of the cycloaddition reactions

We consider the D–A reactions between dienophiles **1.a**, **1.b**, **1.c** and Danishefsky's diene **2**. For each reaction four channels, which lead to the isomers **3.a**, **3.b**, **3.c** (*exo* and *endo*) and **4.a**, **4.b**, **4.c** (*endo* and *exo*) are feasible (Scheme 2). The dienophiles contain the electron-accepting substituent [-NO_2 and -CO_2CH_3] and the diene holds the electron-donating substituents [-OCH_3 and -$OSi(CH_3)_3$]. Therefore, it is expected that these reactions proceed with normal electron demand (NED), with the most important orbital interactions between the HOMO of the diene and the LUMO of the dienophile [36,37].

The electron demand of these reactions can be predicted by means of a DFT analysis based on the global properties of the reacting species [21].

Table 1 summarizes relevant global properties of the reactants. Different levels of theory were included because of the subsequent results depicted in Table 3 (see below). The electronic chemical potential of the diene is higher than that of the dienophiles, thereby suggesting that the net charge-transfer will take place from the diene towards the furan derivatives. This indicates that the diene will more likely behave as electron donor species (i.e. as nucleophile).

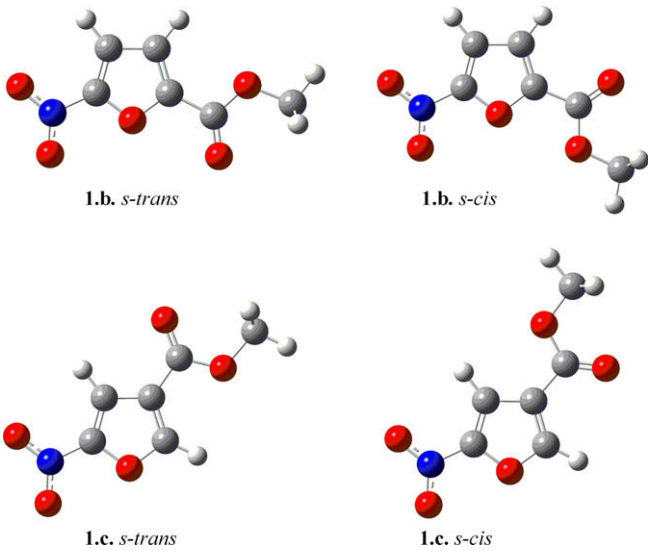


Fig. 2. Possible orientations of the ester carbonyl group with respect to the endocyclic C=C double bond in benzene.

Table 3
Local properties for methyl 5-nitrofuran-2-carboxylate. ω_k values are shown in eV. The local properties for the *s-cis* conformer are shown in brackets.

Molecule	Site k	Gas phase		Benzene		Level of theory
		f_k^+	ω_k	f_k^+	ω_k	
Methyl 5-nitrofuran-2-carboxylate (**1.b**)	C2	0.1123	**0.3330**	0.1094 (0.1095)	**0.3309**(0.3329)	B3LYP/6-31G(d)
		0.1123	**0.3332**	0.1094 (0.1094)	**0.3310**(0.3330)	B3LYP/6-31G(d,p)
		0.1052	**0.3740**	0.1014 (0.1013)	0.3687(0.3704)	B3LYP/LANL2DZ
		0.1353	**0.1439**	0.1297 (0.1291)	**0.1384**(0.1386)	HF/6-31G(d)
		0.1353	**0.1437**	0.1296 (0.1290)	**0.1381**(0.1383)	HF/6-31G(d,p)
		0.1328	**0.1824**	0.1248 (0.1243)	0.1710(0.1715)	HF/LANL2DZ
	C3	0.0159	0.0471	0.0125 (0.0125)	0.0377 (0.0381)	
		0.0158	0.0468	0.0124 (0.0124)	0.0374 (0.0378)	
		0.0116	0.0413	0.0084 (0.0087)	0.0305 (0.0317)	
		0.0341	0.0363	0.0291 (0.0294)	0.0311 (0.0316)	
		0.0339	0.0360	0.0289 (0.0292)	0.0308 (0.0313)	
		0.0285	0.0391	0.0236 (0.0246)	0.0324 (0.0340)	
	C4	0.1017	0.3015	0.1067 (0.1075)	0.3229 (0.3268)	
		0.1014	0.3007	0.1064 (0.1071)	0.3220 (0.3260)	
		0.1031	0.3666	0.1071 (0.1072)	**0.3898**(0.3919)	
		0.1211	0.1288	0.1286 (0.1299)	0.1372 (0.1395)	
		0.1208	0.1283	0.1283 (0.1295)	0.1367 (0.1389)	
		0.1260	0.1731	0.1322 (0.1320)	**0.1812** (0.1819)	
	C5	0.0674	0.1999	0.0543 (0.0535)	0.1643 (0.1628)	
		0.0676	0.2005	0.0544 (0.0536)	0.1647 (0.1632)	
		0.1018	0.1879	0.0383 (0.0377)	0.1393 (0.1380)	
		0.1078	0.1144	0.0912 (0.0901)	0.0974 (0.0967)	
		0.1076	0.1143	0.0912 (0.0900)	0.0972 (0.0966)	
		0.0924	0.1269	0.0723 (0.0714)	0.0990 (0.0984)	

The electrophilicity of the diene is 0.721 eV, a value that falls in the range of marginal electrophiles within the scale proposed by Domingo et al. [21]. On the other hand, the furan derivatives display the highest values in electrophilicity power, so they can be classified as strong electrophiles. This suggests that they will in general act as electron acceptors during their interaction with the diene.

In order to completely characterize the nature of these cycloadditions, the polarity of the process was assessed comparing the electrophilicity index of the diene/dienophile interacting pairs. The marked differences in electrophilicity power between the furan derivatives and Danishefsky's diene (1.85–2.30 eV) indicate the polar character of these D–A reactions. The D–A reactions with the disubstituted dienophiles (**1.b**, **1.c**) are predicted to be more polar than the one between **1.a** and **2**. This prediction can be reinforced considering the values of the electronic chemical potential. In conclusion, the D–A reactions of furan derivatives **1.a**, **1.b**, **1.c** with Danishefsky's diene are characterized by a NED nature and a polar character. Such polar cycloadditions between electron-rich and electron-poor molecules are thought to be initialized by a two-center interaction between the most nucleophilic and electrophilic center of the respective reactant. Thus, reactivity and regioselectivity can be described by global and local nucleophilicity and electrophilicity indexes based on conceptual DFT [21,25c,26a,29a,38].

3.3. Substituent effects

The activation of the furan ring toward NED D–A reactions can be achieved by incorporation of electron-withdrawing substituents [13a].

As expected (Table 1), substitution of one hydrogen atom in the furan ring by one of the most powerful electron-withdrawing groups (nitro group) produces a significant increase in the electrophilic character. The dienophiles substituted by two different electron-withdrawing groups (methyl carboxylate and nitro groups) show the highest values in electrophilicity power. Therefore, these substitutions are suitable in order to enhance the electrophilicity of furan.

3.4. Local properties

The furan derivatives used as dienophiles have two possible reaction sites due to the existence of two double bonds (C_2–C_3 and C_4–C_5). Therefore, all the ring carbon atoms of the dienophiles were taken into consideration when computing the Fukui functions (Fig. 3).

The condensed Fukui functions were calculated using different levels of theory and the basis set dependence was also studied. The effect of the solvent was considered by computing this local quantity in gas and solvent media. The results are compiled in Tables 2–5. The highest local electrophilicity (nucleophilicity) value is in bold.

2-Nitrofuran displays the highest electrophilic activation at C_3 and methyl 5-nitrofuran-3-carboxylate displays it at C_4 regardless of the media (gas phase, benzene solution) or the level of theory. It can also be seen that there is a marginal enhancement of the reactivity at the site for nucleophilicity attack in benzene solution (i.e. ω_3 for **1.a** and ω_4 for **1.c**).

A similar behaviour is observed in the case of Danishefsky's diene, which shows its maximum nucleophilicity value at the C_4 site.

Analysis of the ω_k values for **1.b** reveals that there is a different reactivity tendency depending on the basis set used. In the case of the slightly more stable *s-cis* conformer, the site for nucleophilicity attack is predicted by B3LYP and HF to take place at C_4 only when the LANL2DZ basis set is used.

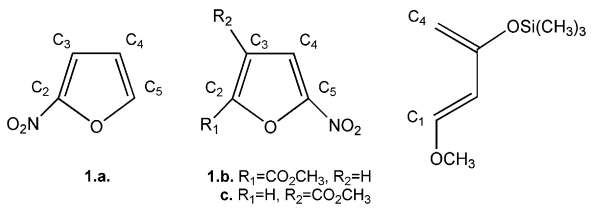


Fig. 3. Sites which were taken into consideration for the Fukui function calculations.

Table 4
Local properties for methyl 5-nitrofuran-3-carboxylate. ω_k values are shown in eV. The local properties for the *s-cis* conformer are shown in brackets.

Molecule	Site k	Gas phase		Benzene		Level of theory
		f_k^+	ω_k	f_k^+	ω_k	
Methyl 5-nitrofuran-3-carboxylate (**1.c**)	C2	0.1085	0.2928	0.1025 (0.1009)	0.2835 (0.2802)	B3LYP/6-31G(d)
		0.1084	0.2930	0.1024 (0.1071)	0.2834 (0.2801)	B3LYP/6-31G(d,p)
		0.0997	0.3285	0.0940 (0.0929)	0.3181 (0.3153)	B3LYP/LANL2DZ
		0.1341	0.1264	0.1212 (0.1174)	0.1145 (0.1112)	HF/6-31G(d)
		0.1340	0.1263	0.1210 (0.1173)	0.1143 (0.1110)	HF/6-31G(d,p)
		0.1331	0.1657	0.1183 (0.1166)	0.1468 (0.1449)	HF/LANL2DZ
	C3	0.0026	0.0069	0.0029 (0.0031)	0.0079 (0.0086)	
		0.0025	0.0069	0.0028 (0.0030)	0.0078 (0.0085)	
		0.0000	−0.0002	0.0004 (0.0005)	0.0013 (0.0017)	
		0.0051	0.0048	0.0037 (0.0035)	0.0035 (0.0033)	
		0.0051	0.0048	0.0037 (0.0035)	0.0035 (0.0033)	
		0.0010	0.0013	−0.0002 (−0.0003)	−0.0002 (-0.0003)	
	C4	0.1507	**0.4067**	0.1541 (0.1553)	**0.4262**(0.4313)	
		0.1499	**0.4052**	0.1534 (0.1545)	**0.4246**(0.4298)	
		0.1449	**0.4775**	0.1468 (0.1475)	**0.4967**(0.5008)	
		0.1847	**0.1740**	0.1922 (0.1945)	**0.1816** (0.1842)	
		0.1837	**0.1731**	0.1912 (0.1936)	**0.1806** (0.1833)	
		0.1814	**0.2257**	0.1869 (0.1879)	**0.2318** (0.2335)	
	C5	0.0438	0.1182	0.0332 (0.0330)	0.0919 (0.0917)	
		0.0441	0.1193	0.0334 (0.0333)	0.0926 (0.0925)	
		0.0296	0.0977	0.0188 (0.0185)	0.0635 (0.0628)	
		0.0775	0.0730	0.0610 (0.0607)	0.0577 (0.0575)	
		0.0778	0.0733	0.0612 (0.0608)	0.0578 (0.0576)	
		0.0602	0.0749	0.0413 (0.0407)	0.0512 (0.0506)	

In contrast, for *s-trans* **1.b** irrespective of whether HF or B3LYP is used, the regional Fukui function obtained with the 6-31G(d) and 6-31G(d,p) basis sets indicate preferential reaction at C_2 rather than the observed attack at C_4. A similar result is also obtained when d-type polarization functions for the first-row elements carbon, nitrogen, and oxygen ($\alpha = 0.8$) are added to the LANL2DZ basis set.

In summary only when the LANL2DZ basis set is used and the solvent is considered in the calculations, the local indexes account properly for the observed regioselectivity in all cases. In those situations the preferred addition is to the nitro-substituted double bond of the furan derivatives (Scheme 3). Therefore, the nitro group, as a stronger electron-withdrawing moiety than the ester substituent, acts as a regiodirector orienting the cycloaddition towards the double bond to which it is directly attached. The regioisomer [1 (OMe), 3 (OSiMe3)] (*endo* and *exo*) is expected to predominate, leading to the exclusive formation of products **5.a**, **5.b**, **5.c**, in agreement with the experimental results.

4. Conclusions

The DFT analysis of the global properties of the interacting pairs illustrates the normal electron demand character of the D–A reactions between nitro-substituted furans and the Danishefsky's diene, and suggests the participation of the furan derivatives in polar D–A reactions.

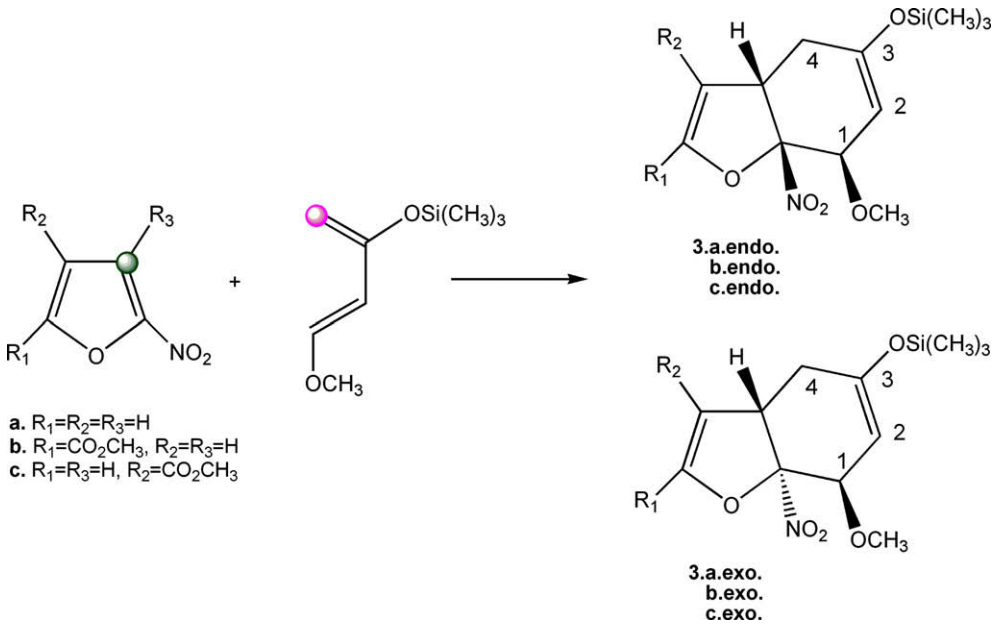
It is shown that the local indexes employed here provide useful clues about the regiodirector effects of the nitro group on the D–A reactions between furan derivatives and Danishefsky's diene.

The relative tendency of an atomic center to behave as an electrophile is affected by the media and the basis set. The presence of benzene media does not impart a prominent influence on the relative reactive sites of 2-nitrofuran, methyl 5-nitrofuran-3-carboxylate and Danishefsky's diene. In contrast, the relative reactive sites of methyl 5-nitrofuran-2-carboxylate are affected by the solvent and basis set.

At the B3LYP/LANL2DZ and HF/LANL2DZ levels of theory an acceptable explanation for the regioselectivity (and siteselectivity)

Table 5
Local properties for Danishefsky's diene. N_k values are shown in eV.

Molecule	Site k	Gas phase		Benzene		Level of theory
		f_k^-	N_k	f_k^-	N_k	
Danishefsky's diene (**2**)	C1	0.1481	0.5578	0.1466	0.5080	B3LYP/6-31G(d)
		0.1471	0.5527	0.1458	0.5039	B3LYP/6-31G(d,p)
		0.1493	0.5724	0.1465	0.5078	B3LYP/LANL2DZ
		0.1806	0.0269	0.1782	0.6657	HF/6-31G(d)
		0.1797	0.0267	0.1774	0.6635	HF/6-31G(d,p)
		0.1920	0.0274	0.1876	0.6593	HF/LANL2DZ
	C4	0.3886	**1.4641**	0.3851	**1.3343**	
		0.3860	**1.4498**	0.3824	**1.3214**	
		0.3777	**1.4480**	0.3770	**1.3069**	
		0.3760	**0.0559**	0.3745	**1.3992**	
		0.3741	**0.0557**	0.3726	**1.3937**	
		0.3663	**0.0523**	0.3668	**1.2893**	



Scheme 3. Simplified illustration showing the prefer interaction between the reactants (i.e. electrophile and nucleophile) at the B3LYP/LANL2DZ and HF/LANL2DZ levels of theory in benzene. The highest ω_k value is shown in green colour and the highest N_k value is highlighted in pink. The prefer D–A cycloadducts are also included (i.e. 1 (OMe), 3 ($OSiMe_3$) regioisomer).

was found when analyzing the electrophilicity and nucleophilicity values on the individual atoms of the reactants at the possible reacting centers.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.theochem.2009.07.008.

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