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THEORETICAL STUDIES OF FIVE-MEMBERED AROMATIC HETEROCYCLES IN CYCLOADDITION REACTIONS AS A COMPLEMENT OF THE EXPERIMENTAL RESEARCHES.

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Abstract. It has been demonstrated that five-membered aromatic heterocycles are capable of undergoing normal electron demand Diels-Alder reactions with a variety of dienes. The global electrophilicity index of these dienophiles have been studied in order to predict the relative reactivity towards cycloaddition reactions. Influence of the type of substitution have also been discussed and compared with experimental results.

Keywords: five-membered aromatic heterocycles, dienophiles, Diels-Alder, electrophilicity index

Introduction

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

In view of our interest in cycloaddition chemistry of substituted aromatic heterocycles with electron withdrawing groups, we have reported studies on the dienophilic character of aromatic systems such as indoles¹ and naphthalenes.² More recently, we have shown that nitrothiophenes³ and nitrofurans⁴ can act as dienophile in their exposure to dienes strongly and poorly activated.

In the last years, the density functional theory (DFT) has been successful in explaining the reactivity and regioselectivity of the cycloaddition reactions.⁵ Current studies applied to D-A reactions showed that the classification of the pair diene/dienophile within an unique scale of electrophilicity is a powerful tool to predict the feasibility of the process.⁶

The purpose of the present work is to study the dienophilic behavior of five-membered aromatic heterocyclic systems in D-A reactions from a theoretical point of view. Considering our interest in aromatic heterocycles substituted with electron-withdrawing groups, we attempt to determine the adequate substitutions that conduce to a high reactivity. We employed the global electrophilicity index (ω) to estimate the electrophilic character of the dienophiles and we compared these results with some experimental studies, in order to verify the validity of the theoretical calculations.^{3,4,7}

Computational Details

The global electrophilicity index (Eq. 1) was calculated using the electronic chemical potential (μ) and the chemical hardness (η). These two last parameters can be approximated in terms of the one-electron energies of the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) as in Eqs. 2 and 3. All the calculations were performed with the GAUSSIAN98 program.⁸

$$\omega = \frac{\mu^2}{2\eta} \quad (1)$$

$$\mu \approx \frac{\epsilon_{HOMO} + \epsilon_{LUMO}}{2} \quad (2)$$

$$\eta \approx \epsilon_{LUMO} - \epsilon_{HOMO} \quad (3)$$

Recent studies reveals that B3LYP method, even with 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.^{5a,9} So in these work the equilibrium geometries were obtained by full optimization at the B3LYP/6-31G(d) level.

Results and Discussion

In table I we present a classification of the dienophiles in decreasing order of the electrophilicity power (ω). As Domingo *et al.* proposes we can assume that high nucleophilicity and high electrophilicity corresponds to opposite extremes of this scale.^{6-a} In the table we also included some global properties such as the chemical potential and the chemical hardness. A good electrophile is characterized by a high value of μ and a low value of η .^{6-a}

In order to verify the validity of this scale we carried out the corresponding thermal D-A reactions of some dienophiles with dienes of different nucleophilicity such as isoprene and Danishefsky's diene.^{3,4,7}

Table I. Global properties for some common reagents participating in D-A reactions.

I. Dienes

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
Isoprene	-0.1209	0.1962	1.01
Danishefsky's diene	-0.0945	0.1851	0.66

II. Dienophiles

a. Furan and derivatives.

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
Methyl 5-nitrofuran-3-carboxylate	-0.1897	0.1814	2.70
2-Nitrofuran	-0.1810	0.1775	2.51
3-Nitrofuran	-0.1767	0.1808	2.35
Furan	-0.1024	0.2441	0.58

b. Thiophene and derivatives.

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
Methyl 5-nitrothiophene-3-carboxylate	-0.1922	0.1767	2.84
2-Nitrothiophene	-0.1845	0.1738	2.66
3-nitrothiophene	-0.1794	0.1821	2.40
Thiophene	-0.1545	0.1566	2.07

c. 1-Tosyl-pyrrole and derivatives.

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
1-Tosyl-methyl 5-nitropyrrole-3-carboxylate	-0.1734	0.1776	2.30
1-Tosyl-2-nitropyrrole	-0.1655	0.1739	2.14
1-Tosyl-3-nitropyrrole	-0.1668	0.1765	2.14

1-Tosylpyrrole	-0.1348	0.1752	1.41
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d. Selenophene and derivatives.

Molecule	Global properties		
	μ (a.u.)	η (a.u.)	ω (eV)
Methyl 5-nitroselenophene-3-carboxylate	-0.1899	0.1717	2.85
2-Nitroselenophene	-0.1829	0.1695	2.68
3-Nitroselenophene	-0.1776	0.1803	2.38
Selenophene	-0.1220	0.2195	0.92

We can appreciate that the structural and electronic effects induced by the chemical substitution produce different responses in the electrophilicity power, as it was expected.

The substitution of one hydrogen atom in all the dienophiles by one of the most powerful electron-withdrawing groups (nitro group) produces an increment in the electrophilicity character and therefore an increase in the reaction rate is expected. The 2-nitro-substituted heterocycles show high electrophilicity power respect to the 3-nitro-substituted ones. Experimentally we obtained higher yields when the nitro group is place in the position 2 of the thiophene's ring than when it is in the 3-position.^{3, 7a} So these last results support the tendency observed in the tables.

The dienophiles substituted by two different electron-withdrawing groups (methyl carboxylate and nitro groups) show the highest values in electrophilicity power, indicating that these disubstitutions are suitable in order to increment the reactivity of the dienophiles. Moreover, the yields corresponding to the D-A reactions of the disubstituted heterocycles with the dienes showed an increase respect of that corresponding to the monosubstituted heterocycles.^{3,4,7}

On the other hand, the differences in the global electrophilicity power between the dienophile/diene pair ($\Delta\omega$) are higher for the Danishefsky's diene than for isoprene. Therefore, we can expect a high reactivity and a high regioselectivity for the pairs dienophile/Danishefsky's diene. This fact is also consistent with the experimental researches.^{3,4,7}

Conclusions

The electrophilicity index is a useful tool to explain the effect produced by the substituents in five-membered aromatic heterocyclic dienophiles that undergo D-A reactions. In this way, increasing substitution by electron-withdrawing groups produce an increase in electrophilicity of the corresponding dienophile, which is in agreement with the increase of the reaction yields.

The differences in the global electrophilicity power for the pairs dienophile/isoprene are lower than the corresponding to the dienophile/Danishefsky's diene pairs, indicating that the last system leads to high reactivity and high regioselectivity.

From this theoretical calculations is possible to analyze the influence of the substituents place in each dienophile with the purpose of rationalize the reactivity or develop the more suitable reactions.

The theoretical results presented in these work are in good agreement with some experimental ones.

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