

Type of the Paper (Abstract, Meeting Report, Preface, Proceedings, etc.)

A theoretical analysis of the reactivity of acyl derivatives of azaheterocycles as dienophiles in cycloaddition reactions[†]

Carla M. Ormachea ¹, María N. Kneeteman ¹ and Pedro M. E. Mancini ^{1,*}

¹ IQAL (UNL-CONICET), Laboratorio Fester – QUIMICA ORGANICA (FIQ), Santiago del Estero 2829- Universidad Nacional del Litoral, 3000 Santa Fe, Argentina; fiq@fiq.unl.edu.ar

* Correspondence: pmancini@fiq.unl.edu.ar; Tel.: +54-342-457-1164

Abstract: A theoretical study of the behavior of *N*-tosylacylpyrroles and *N*-tosylacylindoles being electrophilic dienophiles in polar Diels-Alder reactions is developed. Their reactivity is evaluated joint to different nucleophilic dienes. Calculations were developed considering the experimental results of these reactions in thermal conditions. The computational theoretical methods employed are based in the Density Functional Theory. It was observed that the acyl pentaheterocycles suffer the cycloaddition yielding indol derivatives and the benzofused ones convert into carbazole derivatives through a concerted and asynchronous cycloaddition mechanism. The stereochemistry is defined by the acyl group in the dienophile and the substituent groups of the dienes.

Keywords: azaheterocycles, Diels-Alder, DFT.

1. Introduction

One of the more important reactions in synthetic chemistry is the Diels-Alder (DA) cycloaddition. As it allows to form carbon-carbon, carbon-heteroatom, and heteroatom-heteroatom bonds, the reaction is very useful for the preparation of various carbocyclic and heterocyclic compounds. Due to this fact, the reaction has been used as a key step in the synthesis of many natural products with biological properties [1]. Its application not only leads to a strong increase in molecular complexity, but also can result in structures that lend themselves to additional amplification of complexity by the use of other powerful synthetic transformations [2].

Recently, it has been shown that *N*-tosyl-3-nitroindole is a very good dienophile in normal electron demand Diels-Alder reactions in thermal conditions facing different dienes. This leads to mixtures of *N*-tosyl-4-substituted dihydrocarbazoles and *N*-tosylcarbazoles. The thermal extrusion of nitrous acid accompanying the reaction of this dienophile and the subsequent aromatization with the loss of substituent groups of the dienes from the resultant dihydrocarbazoles makes this two-step reaction sequence to produce highly stable heteroaromatic compounds, a facile, new method for dihydrocarbazole and carbazole synthesis [3]. Wenkert's previous observations have already demonstrated the feasibility of normal Diels-Alder chemistry with five-membered, aromatic heterocycles bearing electron-withdrawing groups, as dienophiles [4], and the better reactivity of 3-substituted heterocycles compared to 2-substituted ones. In particular, azaheterocycles such as *N*-tosylpyrroles, and *N*-tosylindoles nitro substituted, are involved as dienophiles in normal Diels-Alder reactions with Danishefsky's diene, 1-trimethylsilyloxy-1,3-butadiene and isoprene, at elevated temperatures, leading to mixtures of regioisomers in moderate to high yields.[5] Even though that as the nitro group, the acyl group is also electron donor, its structure does not allow the same extrusion to aromatize the product. In this way, the aim of the present work is to analyze the acyl group behavior in this type of reactions. Some *N*-tosylacetylpyrroles and *N*-tosylacetylindoles showed to act in normal Diels-Alder reactions with functionalized conjugated dienes (Figure 1), considering these experimental results obtained under thermal and/or high-pressure conditions

[4,6], we evaluate the reactivity in a theoretical way of 3-acyl-*N*-tosylazaheterocycles, and we extend the analysis to their analogues substituted in position 2.

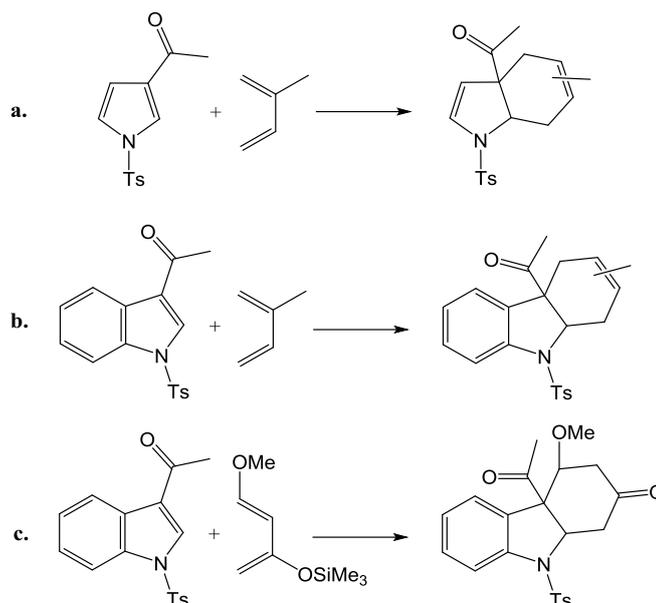


Figure 1. Diels-Alder cycloadducts previously obtained with azaheterocycles acyl substituted

2. Materials and Methods

All calculations were carried out within the DFT framework using the Gaussian09 suite of programs.[7] For this purpose, the hybrid functional B3LYP was used together with the 6-31G(d) basis set.[8] Optimizations were carried out using the Berny analytical gradient optimization method.[9] To validate the geometry of optimized structures, frequency vibrations were calculated. Reactants and CA structures were verified by the absence of negative frequencies, and the TSs by the presence of only one imaginary frequency correspondent to the formation of the new sigma bonds. The electronic structures of critical points were analyzed by the natural bond orbital (NBO) method.[10]

The global electrophilicity index [11] ω , is given by the expression (1), in terms of the electronic chemical potential μ and the chemical hardness η . Both quantities may be approached in terms of the one-electron energies of the frontier molecular orbitals HOMO and LUMO, ϵ_H and ϵ_L , as is showed in equations (2) and (3), respectively.[12] The global nucleophilicity index[13], N , based on the HOMO energies obtained within the Kohn-Sham scheme [14], is defined as (4), where tetracyanoethylene (TCE) is the reference.

$$\omega = \mu^2/2\eta \quad (1)$$

$$\mu = (\epsilon_H + \epsilon_L)/2 \quad (2)$$

$$\eta = (\epsilon_L - \epsilon_H) \quad (3)$$

$$N = \epsilon_{HOMO(Nu)} - \epsilon_{HOMO(TCE)} \quad (4)$$

3. Results

The geometry of the proposed dienes and dienophiles were optimized and frequency vibrations analyzed with the basis set 6-31G(d) and the B3LYP functional. Orbital energies were also calculated to get the reaction indexes of dienes and dienophile.

In addition to the tosylated azaheterocycles, their mesylated equivalents were also evaluated. This is due to the fact that, computational calculations are simpler with a smaller group, especially in the mechanism analysis. Also, both protecting groups have the same chemical behave.

The electronic chemical potentials μ of dienes, between -3.30 and -2.69 eV, are higher than those of acyl substitute heterocycles, from -4.03 to -3.85 eV. Therefore, it is expected that along a polar D-A reaction, the charge transfer (CT) will take place from the electron-rich dienes to dienophiles.

Table 1. Reaction indexes of the dienophiles. The values are expressed in eV.

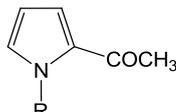
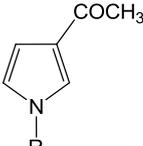
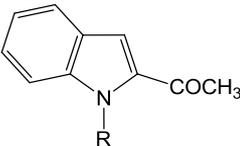
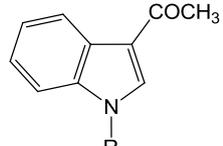
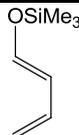
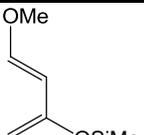
					
a. R= Ts	η	5.00	4.89	4.51	4.47
	μ	-3.88	-4.03	-3.85	-3.87
	ω	1.51	1.66	1.65	1.68
	N	2.74	2.65	3.01	3.01
b. R= Ms	η	5.01	5.47	4.56	4.83
	μ	-4.08	-3.95	-3.97	-3.87
	ω	1.66	1.43	1.73	1.55
	N	2.64	2.43	2.87	2.84

Table 2. Reaction indexes of the dienes. The values are expressed in eV.

			
η	5.77	5.33	5.31
μ	-3.30	-2.79	-2.69
ω	0.94	0.73	0.68
N	2.94	3.67	3.77

The larger difference between the electrophilicity of dienophiles and dienes ($\Delta\omega = \omega_{\text{dienophile}} - \omega_{\text{diene}}$) is an indicator of the better viability of the cycloaddition.

Figures 2 and 3 showed that the $\Delta\omega$ of these reactions are between 0.49 and 1.05 eV. As is expected, the cycloadditions that involves the Danishefsky's diene (the most nucleophilic of the series), are the ones that presents the higher $\Delta\omega$, being the most favourable reactive pairs, this diene with indol derivatives (more electrophilics that pyrrol ones).

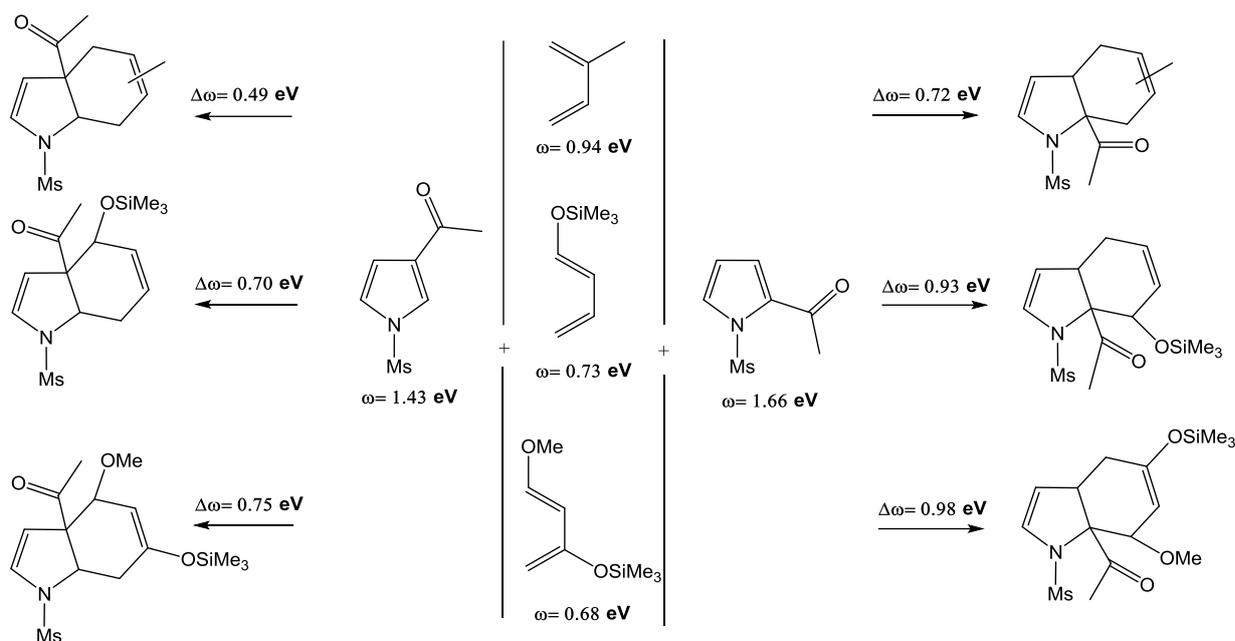


Figure 2. Diels-Alder reactions between the dienes and pyrrole derivatives and its respective $\Delta\omega$ value

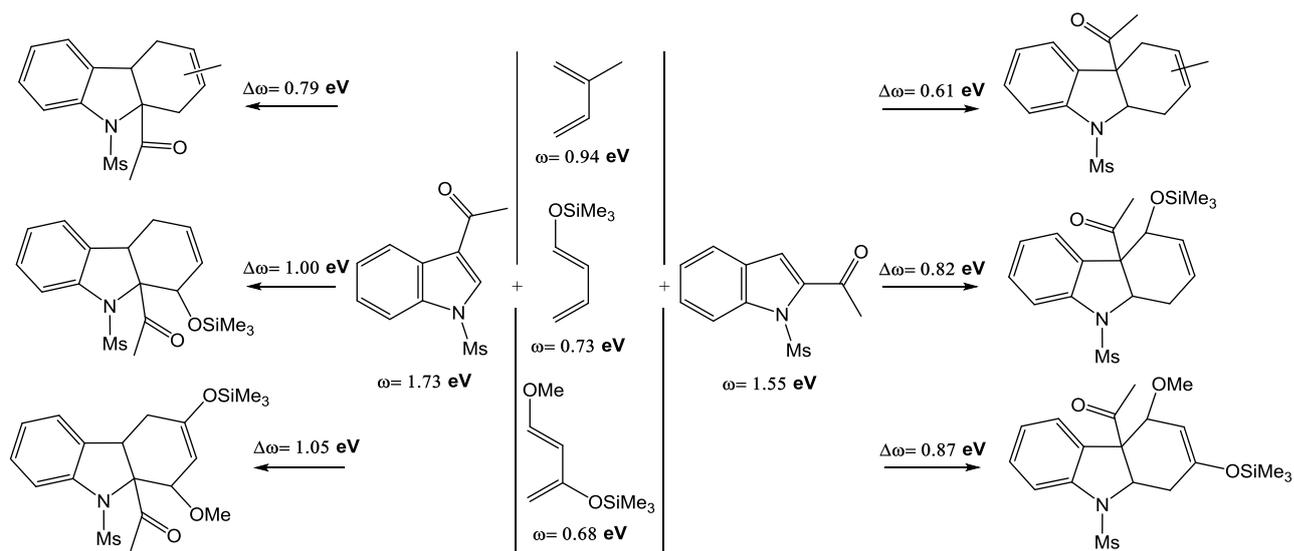


Figure 3. Diels-Alder reactions between the dienes and indol derivatives and its respective $\Delta\omega$ value

The mechanism of the reactions was evaluated using the cycloaddition between 3-acyl-N-mesylpyrrol vs. the less nucleophilic diene of the serie – isoprene- and vs. the most

nucleophilic one – Danishefsky's diene-. In the Figures 4 and 5 the possible cycloadducts corresponding to each diene are showed. The ΔE is defined in equation 5.

$$\Delta E = E_{\text{cycloadduct}} - (E_{\text{diene}} + E_{\text{dienophile}}) \quad (5)$$

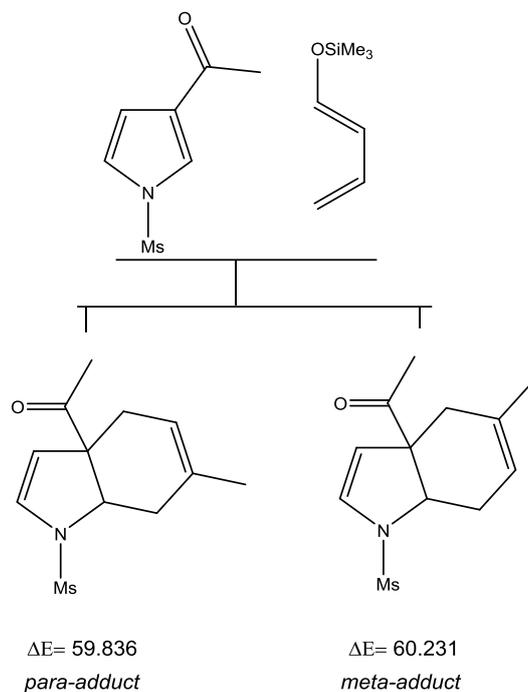


Figure 4. Possible cycloadducts corresponding to the reaction of 3-acyl-N-mesylypyrrol with isoprene and its ΔE in kcal/mol.

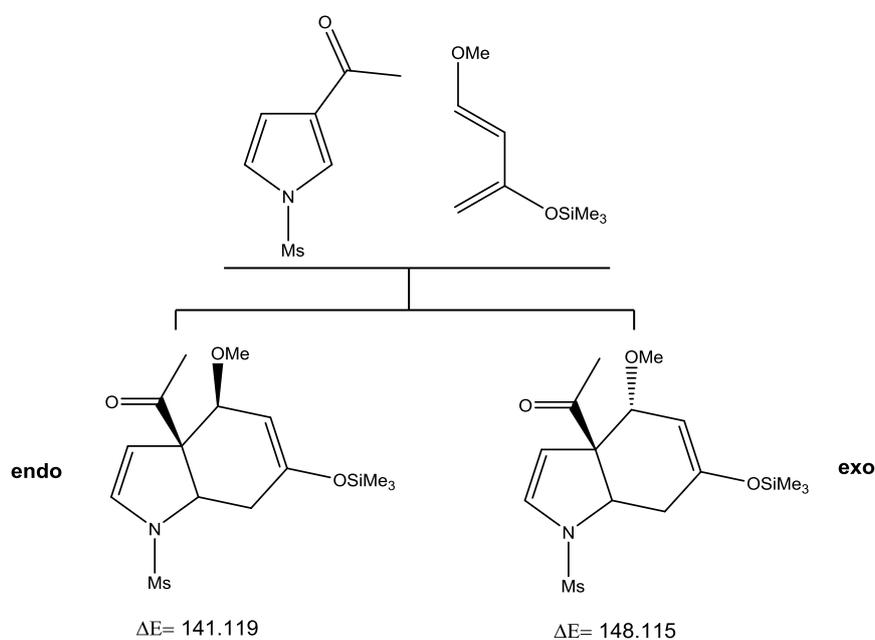


Figure 4. Possible cycloadducts corresponding to the reaction of 3-acyl-N-mesylypyrrol with Danishefsky's diene and its ΔE in kcal/mol.

4. Discussion

Although E. Wenkert considered that α -substituted heterocycles were not reactive at all, in the last years, it could be demonstrated that they react as dienophiles in the same way than the β -substituted ones, especially with the nitro group as substituent [15].

Azaheterocycles' electrophilicity ω index is between 1.51 and 1.68 eV, and the nucleophilicity N index is found between 2.65 and 3.01 eV, being classified as strong electrophiles and moderate nucleophiles.

Isoprene's electrophilicity ω index is 0.94 eV while its nucleophilicity N index is 2.94 eV. It is classified as a moderate electrophile [16]. On the other hand, 1-trimethylsilyloxy-1,3-butadiene (3.67 eV) and Danishefsky's diene (3.77 eV) are on the borderline of strong nucleophiles [17].

If we compare the reactivity indexes between acyl and nitro substituting groups, the last one, increase the electrophilicity of the dienophiles more than the acyl group (1.51-1.68 eV for the acyl and 2.14-2.83 eV for nitro group).[18]

In the mechanism analysis is only considered the Diels-Alder cycloaddition in order to evaluate the viability of the pericyclic reaction in itself. Is important to know that in the case of Danishefsky's diene, the product suffers a loss of the trimethylsilyloxy group and a consequent keto-enol equilibrium. Unlike acyl substituted heterocycles, the nitro substituted ones have the advantage that they can lose this substituent -as nitrous acid- and the donor groups in C1 of the dienes giving an aromatic, and more stable product, transforming the whole reaction in exothermic [18]. At any rate, the reactions that involve the acyl derivatives are still important in organic synthesis to obtain an acyl substituted six-membered ring in only one step.

5. Conclusions

As nitro substituted azaheterocycles, the acyl substituted ones showed to act as dienophiles in Diels-Alder reactions, although its reactive behavior is different.

It was possible to demonstrate that the reactivity with the electron withdrawing group in position 2 and 3 is similar.

From the mechanism analysis we can conclude that all the cycloadditions are endothermic, being the activation energy lower as the $\Delta\omega$ grows. In the case of isoprene C1 and C4 have a similar nucleophilicity so both isomers -meta and para- are expected to be the products of the cycloadditions while in the case of Danishefsky's diene only one isomer (in its endo and exo form) is expected - the one that results of the union of C1 of the diene and the substituted carbon of the dienophile- as product due to the high nucleophilicity difference between the extreme carbons.

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