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Review

Diels–Alder Polar Reactions of Azaheterocycles: A Theoretical and Experimental Study

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Abstract: A number of azaheterocycles (pyridines, pyrroles and indoles) have been properly functionalized so that they can act as dienophiles in cycloaddition Diels–Alder processes. This work analyzed the reactive behavior of these molecules through mechanistic analysis and the regioselectivity of the process using computational calculation tools. Based on this knowledge, a study was conducted on the influences of reaction variables, in particular solvent, catalyst and microwave irradiation, to achieve favorable changes—shorter reaction times, more acceptable temperatures and better yields. Theoretical calculations allowed the development of predictive approaches, which were later experimentally corroborated. This analysis allowed us to make reasonable assumptions related to reaction mechanisms, which allowed—through the analysis of corresponding transition states—us to consider such reactions at the boundary between pericyclic and polar processes.

Keywords: azaheterocycles; D-A reaction; polar processes

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1. Introduction

Since Diels and Alder, in 1928, observed the formation of a 1:1 adduct in reactions between a series of dienes and certain alkenes, including cyclopentadiene and p-benzoquinone, this process has become one of the synthetic methodologies most useful for the formation of carbon–carbon, carbon–heteroatom and heteroatom–heteroatom bonds contained in cyclic products.

The D-A reaction is of great interest in synthesis, not only as a consequence of its versatility but also because of its high regioselectivity, endo-stereoselectivity and cis-stereospecificity, with the retention of a configuration normally observed in the diene and in the dienophile and the exclusive, or at least preponderant, formation of one isomer among several possible ones.

Five-membered aromatic heterocycles, as well as their benzofused analogs, have also been traditionally studied as dienes; however, in recent years, interest in them as dienophiles has increased. In the 1980s, E. Wenkert [1] studied the behavior of α- and β-acylsubstituted furans in thermal Diels–Alder reactions with normal electron demand, showing the possibility that an aromatic system substituted by an electron-withdrawing group can act as a dienophile in such a reaction.

The reactive behavior of a series of azaheterocycles (pyridines, pyrroles and indoles) properly substituted was experimentally and computationally studied in recent years by our group [2–10]. These heterocycles can act as dienophiles in processes of DA cycloaddition. To explain reactive behaviors, their electrophilic character has been analyzed. However, the regioselectivity of these processes has been determined through a mechanistic analysis. The aim of the present work is to reconcile different aspects of experimental chemistry with the principles of theoretical chemistry. In particular, studying the influences of reaction variables, solvent and microwave irradiation contributes to the progress of knowledge about these reactions.

Theoretical studies allowed us to make reasonable assumptions related to reaction mechanisms, which allowed—via the analysis of corresponding transition states (TSs)—us to conceive these types of reactions at the boundary between pericyclic and polar processes. From the certainty provided by the experimental work, two models of nitroheteroaromatics electrophiles were discussed: pentaheterocycles and hexaheterocycles.

2. Materials and Methods

2.1. Experimental Section

DA cycloaddition reactions of azaheterocycles were carried out using different techniques to analyze the solvent effect (conventional solvent vs. ionic liquids), heating method (thermal or microwave) and reaction time.

Thermal reactions using molecular solvents: Thermal reactions were carried out in closed ampoules. Different temperature ranges and various reaction times were used. These reactions were considered as references. Toluene was used as the solvent.

Thermal reactions using ionic liquids: in order to improve the experimental conditions verified under thermal conditions, different types of ionic liquids (ethylammonium nitrate, 1-methylimidazolium tetrafluoroborate, 1-methylimidazolium hexafluorophosphate, 1-n-butyl-3-methylimidazolium tetrafluoroborate and 1-n-butyl-3-methylimidazolium hexafluorophosphate) were used as reaction media.

Reactions applying the microwave irradiation technique: Reactions were developed in a microwave reactor—Monowave-300—using different temperature (or power) ranges and reaction times. The reactions were developed in the presence of classic organic solvents, using protic ionic liquids, and finally in the absence of a solvent. As such, it was possible to analyze the influence of microwave heating on these types of reactions and the degree of response to the different solvents.

2.1.1. Thermal Reactions

The reactions were performed in 5 mL glass ampoules containing a solution of 1 mmol of dienophile and an excess of diene (the diene/dienophile molar ratios being 12:1 for isoprene (the excess used in the case of isoprene is higher since it tends to polymerize) and 3:1 for the other dienes), using 1 mL of toluene as the reference solvent or, alternatively, the corresponding ionic liquid (IL). The solution was heated at 120 °C for 72 h for molecular solvents and 60 °C for 24 h when using IL. The reactions were monitored using thin-layer chromatography (TLC) carried out with 254 nm UV silica gel plates. Purification of the reaction crude and isolation of the different products were carried out using column chromatography, utilizing neutral alumina as the stationary phase and a hexane-ethyl acetate mixture as the eluent. Prior to purification, the reaction crudes were treated. In the case of the cycloadditions carried out in toluene, the solvent was removed using a rotary evaporator, and in the case of the crude reaction corresponding to the ionic liquids, an extraction was carried out with a molecular solvent.

2.1.2. Microwave Reactions

The reactions were developed in a single-mode-type microwave reactor in 10 mL glass vials, adding 1 mmol of the dienophile and different amounts of diene, using 1 mL of toluene as the solvent or, alternatively, the corresponding IL in the same amount. In this case, reactions were also developed in solvent-free conditions. The reactions were monitored using thin-layer chromatography (TLC) carried out with 254 nm UV silica gel plates. At the end of the reaction time, the reaction crude was separated and purified using column chromatography in the same way as in the thermal reactions. The reactions were performed at 180 °C for 30 min. The diene/dienophile ratio used was the same as that in the thermal reactions.

2.2. Computational Details

All the DFT [11] calculations were made using B3LYP functionals [12], with the standard 6-311+G(d,p) basis set [13,14].

The geometry optimizations were made using the Berny analytical gradient optimization method. Frequency computations were used to characterize the stationary points, verifying that the TSs only had one imaginary frequency. In order to determine the energy profiles, the IRC paths were searched [15] by connecting each TS to the two associated minima (reactants and products) of the proposed mechanism using the second-order González–Schlegel [16] integration method. The solvent effects of toluene were considered using the polarizable continuum model (PCM) from Tomasi's group in the framework of the self-consistent reaction field (SCRF) [17] utilizing a single point energy calculation of the geometries previously optimized in the gas phase. The stationary point electronic structures were analyzed using the natural bond orbital (NBO) method [18]. All the calculations were carried out with the Gaussian 09 suite of programs [19].

The global electrophilicity index [20], ω, is defined by the expression $\omega = (\mu^2/2\eta)$, μ being the electronic chemical potential and η the chemical hardness. Both values may be approximate in terms of the one-electron energies of the frontier molecular orbital HOMO (ε_H) and LUMO (ε_L) as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$ [21]. Later, an empirical (relative) nucleophilicity index [22], N, was introduced, which is based on the HOMO energies calculated within the Kohn–Sham scheme and defined as $N = E_{\mathrm{HOMO}}\,(\mathrm{Nu}) - E_{\mathrm{HOMO}}\,(\mathrm{TCE})$. The nucleophilicity index is referred to as tetracyanoethylene (TCE) due to the fact that it presents the lowest HOMO energy of a considerable series of molecules investigated in polar cycloadditions. As such, one can conveniently work with a scale of positive nucleophilic values. Electrophilic $P_k{}^+$ and nucleophilic $P_k{}^-$ Parr functions [23] were obtained with the analysis of the Mulliken atomic spin density (ASD) of the radical anion and radial cation of the reagents.

3. Results and Discussion

3.1. Experimental Results

To explore the behaviors of azaheterocycles as electrophilic dienophiles in D-A reactions, isoprene, 1-trimethylsilyloxy-1,3-butadiene and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) were selected as nucleophilic dienes. This selection was chosen to be able to compare the influences of ILs and molecular solvents on the reactivity and the regioselectivity of the P-D-A reactions. Figure 1 shows all the products of the Diels–Alder reactions carried out using the different techniques mentioned above. Table 1 details the yields obtained in each case.

Protic ionic liquids, with their specific properties, high polarizability and ability to form hydrogen bonds, first produce a drastic reduction in time and an increase in reaction yields. This acceleration cannot be explained based on a single theory; however, hydrophobic interactions and Lewis acid catalysis may be useful concepts for understanding the effect of these salts on the D-A reaction [24].

The yields obtained in each case are detailed in Table 1. The products a and b of each reaction were considered as a 50/50 mixture of their isomers (substitution of the methyl group in C5 and C6 for products I and II derived from pyrrole; C2 and C3 for products III and IV derived from indole; and C6 and C7 for product VI derived from pyridine). The yields were considered based on the consumption of dienophiles and were calculated by weighing them. In order to be able to easily compare the different reaction conditions, the percentage corresponding to IL was calculated as an average of the yields obtained with [HMIM] [BF_4], [HMIM] [PF_6] and NEA.

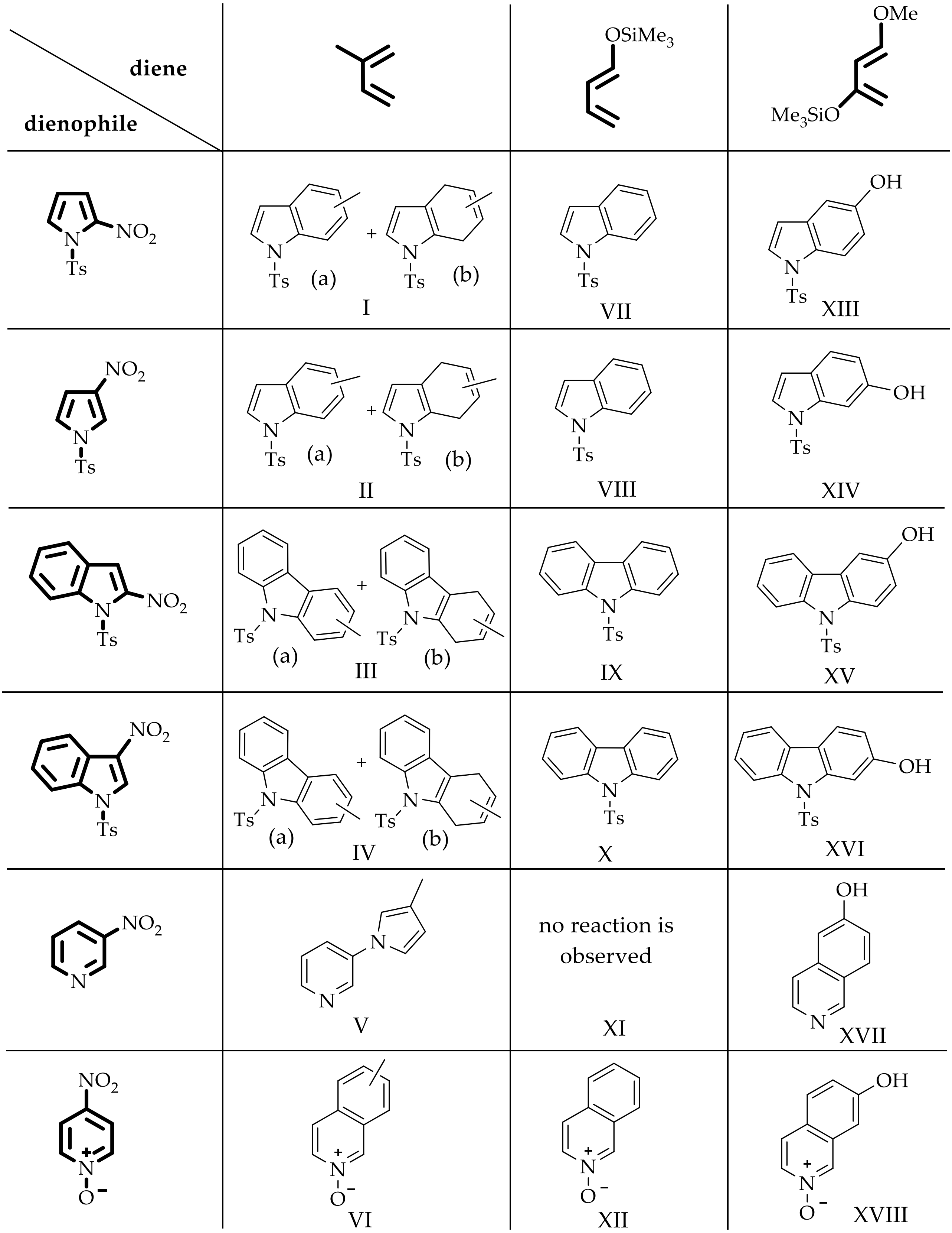

Figure 1. Reaction products of DA cycloadditions between azaheterocycles dienophiles and the different dienes.

Table 1. Yields obtained from the reaction products of the DA cycloadditions.

Reaction	**Condition**				
	Thermal/MS	**Thermal/IL**	**MW/MS**	**MW/IL**	**MW/SF**
I	50% a + 10% b	45% a + 10% b	30% a	55% a	60% a
II	50% a + 10% b	50% a + 10% b	24% a	56% a	59% a
III	36% a + 8% b	50% a + 2% b	50% a	60% a	62% a
IV	32% a + 8% b	50% a + 2% b	53% a	60% a	63% a
V	43%	56%	57%	60%	58%
VI	15%	25%	30%	35%	35%
VII	45%	55%	51%	67%	68%
VIII	45%	54%	42%	66%	63%
IX	45%	56%	61%	75%	73%
X	40%	65%	61%	75%	72%
XI	-	-	-	-	-
XII	20%	25%	23%	25%	30%
XIII	48%	58%	63%	77%	76%
XIV	48%	58%	55%	72%	72%
XV	44%	74%	68%	78%	77%
XVI	44%	72%	72%	80%	78%
XVII	26%	30%	32%	31%	32%
XVIII	41%	50%	52%	50%	54%

MSMS: molecular solvent, IL: ionic liquid, SF: solvent free.

3.2. Computational Results

3.2.1. Electron Demand

For the reactivity study, the calculation of the global electrophilicity values ω was performed in terms of the electronic chemical potential μ and the chemical hardness η (Table 2). As such, whether the proposed dienophiles behave as electrophiles and the maximum number of electrons that they can accept can be evaluated. The values calculated taking into account the reaction media modify the values but not the tendency of them (see Supplementary Materials). In Table 2, only the gas-phase values are considered.

Table 2. Global properties calculated using B3LYP method and 6-311+G(d,p) level of theory.

Dienophile	$\varepsilon_{\mathrm{HOMO}}$	$\varepsilon_{\mathrm{LUMO}}$	μ	η	ω	N
N-tosylpyrrol	−6.63	−1.96	−4.30	4.68	**1.97**	**2.49**
N-tosyl-2-nitropyrrol	−7.27	−2.81	−5.04	4.47	**2.84**	**2.22**
N-tosyl-3-nitropyrrol	−7.32	−2.66	−4.99	4.66	**2.68**	**2.17**
N-tosylindol	−6.08	−1.79	−3.93	4.28	**1.81**	**3.05**
N-tosyl-2-nitroindol	−6.74	−2.69	−4.71	4.05	**2.74**	**2.39**
N-tosyl-3-nitroindol	−6.67	−2.52	−4.81	4.12	**2.81**	**2.26**
3-nitropyridine	−7.68	−2.76	−5.22	4.91	**2.77**	**1.44**
4-nitropiridine-*N*-oxide	−7.25	−3.53	−5.39	3.71	**3.91**	**2.24**

All the values are expressed in eV and correspond to the gas phase. Bolding is because both columns are calculated using the values of the previous ones.

In the same way, to determine the reactivity of the dienes, their global reactivity indices were calculated based on the energies of the frontier molecular orbitals (Table 3).

When compared with the chemical potential of the dienophiles, the dienes present a larger value, for which the charge transfer is from the diene to the dienophile. These reactions, controlled by the HOMO orbitals of the diene and the LUMO of the dienophile, are located within those deemed to be "with normal electron demand".

Table 3. Global properties calculated using B3LYP method and 6-311+G(d,p) level of theory.

Diene	ε_{HOMO}	ε_{LUMO}	μ	η	ω	N
Isoprene	−6.57	−0.98	−3.77	5.59	**1.27**	**2.92**
1-trimetylsililoxy-1,3-butadiene	−5.90	−0.72	−3.31	5.18	**1.06**	**3.58**
Danishefsky's diene	−5.91	−0.52	−3.22	5.39	**0.96**	**3.57**

All the values are expressed in eV and correspond to the gas phase. Bolding is because both columns are calculated using the values of the previous ones

3.2.2. Stereochemistry

To analyze the stereochemistry of the reaction, the local indices were calculated. Considering that the most favorable charge transfer is from the most nucleophilic to the most electrophilic center, the bond formed between this to atoms is the one that determines the isomer obtained.

Local indices were determined using the Fukui function. It must be taken into account that the values of the local indices are numerically comparable for the different atoms within the same molecule since they are relative to each system. For the dienophiles (Table 4), the beta carbon to the nitro group turns out to be the most electrophilic in all cases, and it will be the one that reacts with the most nucleophilic center of the diene. Regarding local properties, the nitro group, in addition to providing the molecule with the necessary electrophilic character, becomes responsible for the regiochemistry of the reaction.

Table 4. Local electrophilicity indices for dienophiles.

Dienophile	ω_k (eV)	
	C2	**C3**
N-tosyl-2-nitropyrrol	0.03	0.19
N-tosyl-3-nitropyrrol	0.12	0.04
N-tosyl-2-nitroindol	0.05	0.36
N-tosyl-3-nitroindol	0.48	0.07
	C3	**C4**
3-nitropyridine	0.13	0.35
4-nitropiridine-*N*-oxide	0.35	0.17

With the diene being the nucleophilic counterpart of the process, the local nucleophilicity indices in C1 and C4 and the atoms involved in the new cycloadduct were calculated for it (Table 5). For isoprene, the most nucleophilic center corresponds to C1. However, the values of the nucleophilicity of carbons 1 and 4 do not present a significant difference, which explains why isomers are obtained in comparable proportions in the experimental work. For 1-trimethylsilyloxy-1,3-butadiene, although the difference in local indices is more marked than in the case of isoprene, in the reactions detailed below, it was observed that there is only one product; this is due to the fact that the substituent in position 1 has a tendency to be eliminated in the aromatization process, for which it is not possible to determine whether both isomers or only one of them are formed in the first stage, or in what proportion. The Danishefsky diene would be located as a marginal electrophile, being the most nucleophilic of the series. The greatest difference in nucleophilicity observed is for the Danishefsky diene (0.91 eV), a value sufficient for only one of the isomers to be the product of cycloaddition. In each reactive pair, the favored isomer is the one corresponding to the C4 bond of the Danishefsky diene and C adjacent to the nitro group of each dienophile, which agrees with the experimental results.

Table 5. Local nucleophilicity indices for dienophiles.

Diene	**N_k (eV)**	
	C1	**C4**
Isoprene	1.11	0.80
1-trimetylsililoxy-1,3-butadiene	0.80	0.97
Danishefsky's diene	1.47	0.56

3.2.3. Mechanism Analysis

The analysis of the synchronous or asynchronous character of the reaction can be carried out by relating the values of the bond formation distances of the atoms involved in the transition state; that is, $\Delta r = r1 - r2$, where r1 and r2 are the distances from C2 and C3 of the dienophile to C1 and C4 of the diene, always taking r1 as the greatest distance. However, the energy of the reaction was evaluated through the difference in energy (ΔE) of the TSs (activation energy) and of the cycloadduct/s (CAs) (enthalpy of reaction) with respect to the sum of the energy of the reagents (see Supplementary Materials).

The activation energy (in the gas phase) associated with the nucleophilic attack of the diene is higher than the one involving the effect of IL. The polar nature of D-A reactions was assessed by analyzing charge transfer (CT) in the TS. In the TSs, the CT flowing from the diene to the dienophile is higher when ILs are considered. These values indicate the zwitterionic character of the TSs and explain why the reactions that involve IL achieve similar yields in shorter times. The polar character of the reaction increases because of the hydrogen bond formed, which improves the CT process and increases the asynchronous character of the reactions.

To study the effects of microwave irradiation on polar Diels–Alder processes, the displacement vectors of the IR frequency vibrations were analyzed. This values shows that there are stretching vibrations with similar atomic motions to the electronic changes implicated in the formation of the TSs.

The stretching vibrations of the dienophiles and the systems dienophile+diene are between 1300 and 1400 cm^{-1}. This indicates that any extra energy between 1700 and 1400 cm^{-1} can favor the process by improving the electronic changes that are necessary to obtain TS geometry. Experimentally, this is observed as a reduction in the reaction time. It should be noted that the values of the stretching vibrations between the TS and the TS-IL are close for the studied systems, which means that the microwave irradiation effect should be equivalent in all cases. This agrees with the experimental results, considering that microwave irradiation significantly reduces reaction times and improves yields, although no significant difference is observed between the type of solvent chosen.

4. Conclusions

Throughout this research, a series of D-A reactions were analyzed, both from an experimental point of view and a theoretical point of view.

The theoretical analysis, based on the DFT theory, in combination with a series of complementary experiences, contributes to a better degree of understanding of these particular types of cycloaddition reactions.

Knowing that the theoretical studies are consistent with the experimental results, we were able to develop predictive approaches, reducing the experimental expense of chemical tests. However, these studies made it possible to understand the mechanism of the reactions evaluated, which allowed, via the corresponding proposed transition states, us to conceive this type of reaction at the boundary between pericyclic and polar processes.

It was experimentally feasible to discuss two models of nitroheteroaromatic electrophiles in the function types of the rings—pentaheterocycles (and benzofused-pentaheterocycles) vs. hexaheterocycles—and the consequences of the type of structure on reactivity and regioselectivity.

It was possible to demonstrate that the indices of the chosen reactivity are good indicators of the feasibility of the reaction, and that its derived local indices are very useful in determining the region and stereochemistry of each cycloaddition. Regarding the solvent effect, although the continuous dielectric method is the most used, in the case of PILs, alternative methods of supermolecules should be considered since the reactions are affected by hydrogen bonding interactions and the effect of polarization.

An analysis of the reaction mechanisms made it possible to identify cycloadducts and the corresponding transition states, which allowed us to determine the energies of activation of each process. In all cases, transition states were obtained. Within the mechanistic studies, we observed that the charge transfer was greater when ILs were involved than in solvent-free conditions. The acceleration of reaction times can be understood as an increase in the polar character of the reaction due to the hydrogen bond.

The effect of microwave irradiation seems to be enough in itself to speed up reactive processes, regardless of the solvent used.

It is likely that the main contribution is the theoretical detection of a type of polar Diels–Alder reaction that presents a reaction intermediate, which is significant for this type of process.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org3020008/s1. File S1: Computational calculations including solvent effect and Mechanistic calculations.

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