



# Nitropyrroles, Diels-Alder reactions assisted by microwave irradiation and solvent effect. An experimental and theoretical study



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## ABSTRACT

The behaviors of *N*-tosylnitropyrroles acting as electrophilic dienophiles in polar Diels-Alder reactions joint to different dienes of increased nucleophilicity are analyzed. The reactions were developed under microwave irradiation using toluene or protic ionic liquids (PILs) as solvents and in free solvent conditions. In all the cases explored we observed good yields in short reaction times. For these reactions, the free solvent condition and the use of protic ionic liquids as solvents offer similar results. However, the free solvent conditions favor environmental sustainability. The role of PILs in these polar Diels-Alder reactions has been theoretically studied within the Molecular Electron Density Theory.

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## 1. Introduction

The Diels-Alder (DA) reaction is one of the more important reactions in organic synthesis [1]. The substituents, properly selected, can be transformed into other functional groups after the cycloaddition to obtain a larger variety of compounds.

We have been working with polar Diels-Alder (P-DA) reactions [2] using aromatic carbo- and heterocyclic nitro-substituted dienophiles and different dienes. In general, these cited polar cycloadditions are a domino process initialized by a P-DA reaction to give the formally [4 + 2] cycloadduct followed for the subsequent irreversible elimination of nitrous acid which is the responsible factor for the feasibility of the overall process [3].

In these domino processes, electrophilically activated heterocycles react with nucleophilic dienes through P-DA reactions to obtain the respective aromatized cycloadducts. Considering the potential influence of the solvents and its specific effect, the reactions were developed under conventional thermal conditions and using toluene or protic ionic liquids (PILs) as reaction media. The experimental results showed that using neoteric solvents the

reactions were faster than those developed in traditional organic solvent [4]. (See [supplementary material](#)).

On the other hand, the microwave-assisted controlled heating has become a powerful tool in organic synthesis. The region of the microwave (MW) radiation is located between the infrared and radio waves. In the MW region, the electromagnetic energy affects the molecular rotation without changes in the molecular structure [5]. Using MW irradiation, the reaction mixture undergoes heating by a combination of thermal effect, dipolar polarization and ionic conduction. This methodology results in better reaction rates and yields [6]. This procedure has been employed successfully observing even modifications of the selectivity, although the MW effect is a topic of discussion yet [7].

Considering the influence of MW irradiation to improve organic reaction, the principal aim of this work is to study the P-DA reactions of electrophilic nitro substituted pyrroles with dienes of different nucleophilicity using MW irradiation, instead of conventional heating, in two experimental situations, in presence of PILs as solvent and complementary in free solvent conditions. Specially the last one could be important due to the low impact on the environment. Moreover, we discuss the behavior of the reaction between the nitropyrroles and electron-rich dienes in a theoretical way within the Molecular Electron Density Theory (MEDT) [8]. For this purpose, we choose the reactions between *N*-

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mesylnitropyrroles and isoprene as an example of these types of processes because it is the simplest representative system to work computationally.

## 2. Results and discussion

To explore the effect of the reaction media in P-DA, we chose 2-nitro-*N*-tosylpyrrole (**1**) and 3-nitro-*N*-tosylpyrrole (**2**) as electrophilic dienophiles and isoprene (**3**), 1-trimethylsilyloxy-1,3-butadiene (**4**) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky diene) (**5**) as nucleophilic dienes (Scheme 1).

Toluene and PILs were used as solvent, particularly 1-methylimidazolium tetrafluoroborate [HMIM][BF<sub>4</sub>], 1-methylimidazolium hexafluorophosphate [HMIM][PF<sub>6</sub>] and ethylammonium nitrate [NEA]. Simultaneously, the same reactions were developed under MW irradiation in free solvent condition (for the results of the reactions see supplementary material).

The P-DA reaction of 2-nitro-*N*-mesylpyrrole (2NMP) **7** with isoprene **3**, in the absence and in the presence of the PIL [HMIM][BF<sub>4</sub>], is herein theoretically studied and compared with the P-DA reaction of 3-nitro-*N*-mesylpyrrole (3NMP) **8** previously studied [9]. (See supplementary material) Unlike the P-DA reactions involving strong nucleophilic dienes such as **5** which is completely regioisomeric, those involving isoprene **3** are not regioselective [9]. In order to study the effects of the PIL and MW irradiation conditions in these P-DA reactions, the more favourable *endo/para* reaction channels associated with the P-DA reaction of isoprene **3** with nitro-*N*-mesylpyrroles (NMPs) **7** and **8** were chosen. The theoretical calculations were developed within the MEDT at the B3LYP/6-31G(d) computational level (Scheme 2). The combination of the DFT functional together with the basis set gives a great diversity of computational levels. Our expertise in the study of cycloaddition reactions indicates that the B3LYP and MPWB1K functionals together with the 6-31G(d) or the 6-311G(d) basis sets are the more adequate to study these type of organic reactions. In the last years, the M06-2X functional is being used in the study of

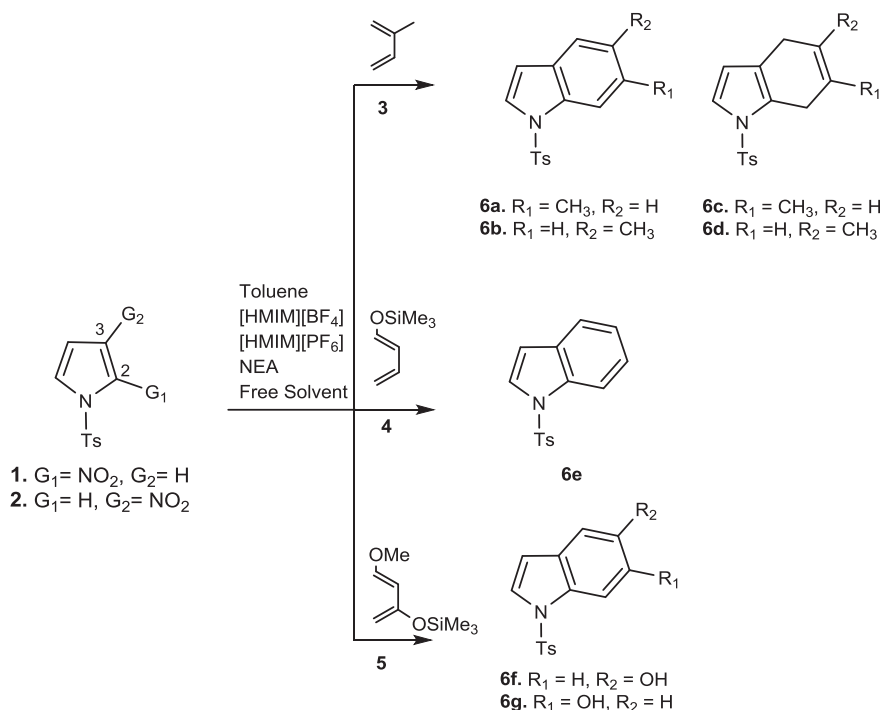
cycloaddition reactions, but it has been proved that it overestimates activation energies [10]. On the other hand, the use of diffuse functions did not have any sense in the study of organic reactions involving neutral species.

Analysis of the potential energy surfaces (PES) associated with the *endo/para* reaction paths shows that these P-DA reactions takes place through a one-step mechanism through a high asynchronous TS. Therefore, reagents one TS and the formal [4 + 2] CA were located and characterized for each one of these P-DA reactions.

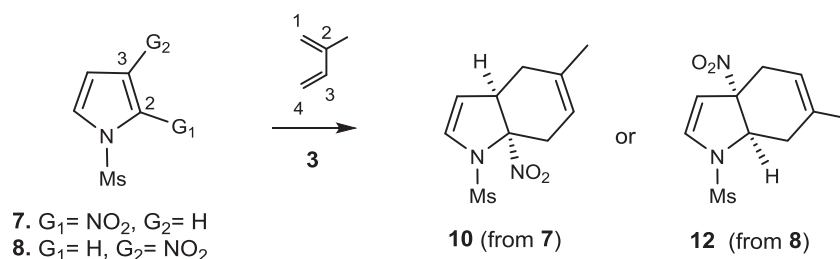
The effects of the PIL [HMIM][BF<sub>4</sub>] in these P-DA reactions were evaluated employing the supermolecular approach, particularly considering the implicit effects of the PIL by forming a hydrogen bond (HB) between the acidic hydrogen of HMIM cation and one oxygen atom of the nitro group. The counter BF<sub>4</sub> anion was also included to minimize the positive charge present in the HMIM cation. The values of the relative energies in gas phase and in the presence of PIL are summarized in Fig. 1.

In the gas-phase, the activation energy associated with the nucleophilic attack of the C1 carbon of isoprene **3** on the C3 carbon of 2NMP **7** presents a high value of 22.3 kcal/mol (TS **9a**), formation of the CA **10** beings exothermic by -21.2 kcal/mol. When the implicit effect of the PIL is considered, the activation energy value decreases to 18.1 kcal/mol (TS **11a**), and the exothermic character of formation of the corresponding CA changes to -19.7 kcal/mol. In the case of the P-DA reaction between 3NMP **8** and isoprene **3**, the nucleophilic attack of the C1 of the diene on the C2 carbon of dienophile presents an activation energy value of 21.4 kcal/mol (TS **9b**), formation of the CA **12** beings exothermic by 23.9 kcal/mol. When the implicit effect of the PIL is considered, the activation energy value decreases to 14.6 kcal/mol (TS **11b**), and the exothermic character of formation of the corresponding CA changes to -22.1 kcal/mol. In this sense, the activation energies of the P-DA reactions involving 2NMP **7** and 3NMP **8** decrease by 4.2 and 6.8 kcal/mol, respectively, when PILs are considered, making the process kinetically slightly more favourable.

The gas-phase geometry of the TS and TS-PIL involved in these



Scheme 1. Diels-Alder reaction of *N*-tosyl-nitropyrroles with different dienes in several reaction conditions.



Scheme 2. P-DA reactions of NMP 7 and 8 with isoprene 3.

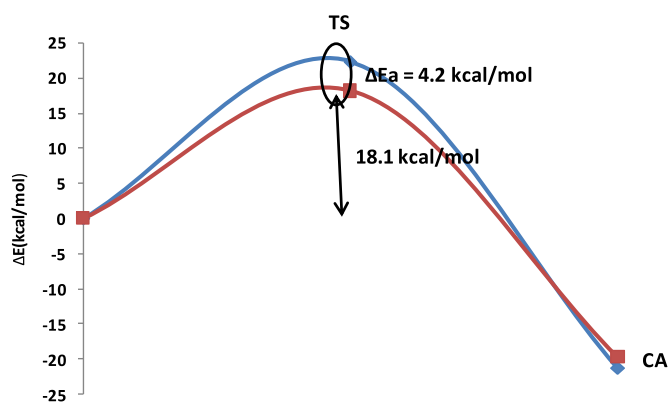


Fig. 1. Endo/para reaction path of the P-DA reaction of isoprene 3 with 2NMP 7, in gas phase (blue) and in the presence of the PIL [HMIM][BF<sub>4</sub>] (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

P-DA reaction is given in Fig. 2. The high asynchronicity in the C–C single bond formation, geometrically measured by  $\Delta r$  at the TSs of these P-DA reactions, suggests that they take place through a two-

stage one-step mechanism [11]. In these non-concerted mechanisms, the C–C single bond formation between the most nucleophilic center of the diene and the most electrophilic center of dienophile takes place in the first stage of the reaction, while the formation of the second C–C single bond takes place at the second stage of the reaction. The presence of the PIL (hydrogen bonded to the nitro group, and its polarity) increases the asynchronicity of the reactions considering the changes in the values of  $\Delta r$ .

The polar nature of these DA reactions was evaluated analyzing the global electron density transfer [12] (GEDT) at TSs. The natural charges were shared between the pyrrole derivatives and isoprene frameworks. At the TSs, the GEDT that flows from isoprene to the nitropyrrole framework is 0.16e (TS 9a) and 0.24e (TS 9b). When PIL is considered the GEDT values increase noticeably to 0.30e (TS 11a) and 0.32e (TS 11b). These values point out the zwitterionic character of the TSs, and consequently, the polar character of these DA reactions. The remarkable acceleration found, in terms of reaction times in the presence of the PIL ionic pair can be understood as an increase of the polar character of the reaction, which favors the GEDT process [2]. This leads to a lower activation energy values and higher asynchronicity in the C–C single bond formation. Note that in P-DA reaction, when more polar the reaction, faster the reactions is [2].

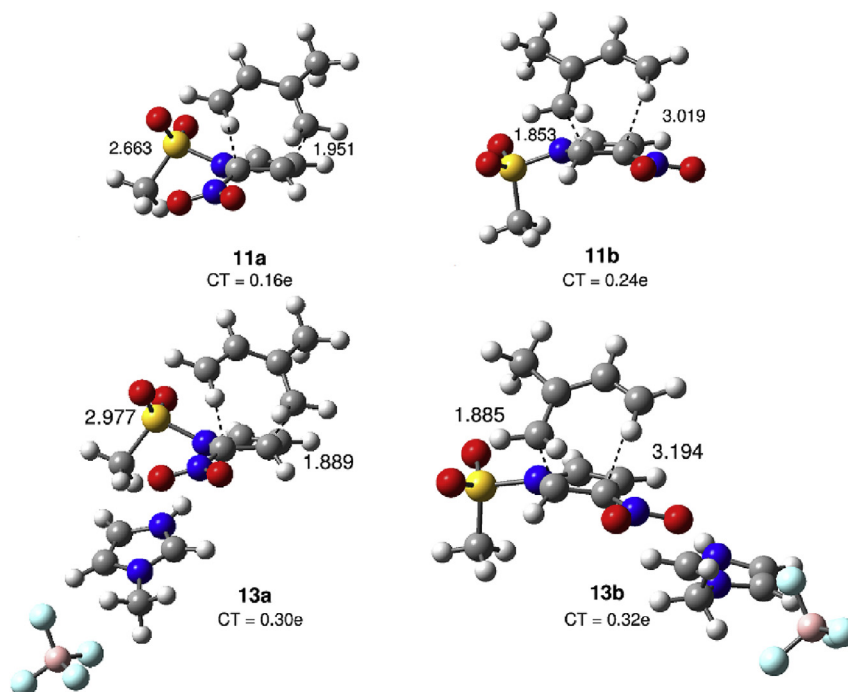


Fig. 2. B3LYP/6-31G(d) Geometries of the TSs associated with the P-DA reactions of isoprene 3 with NMPs 9 and 10, in absence and in presence of PIL the [HMIM][BF<sub>4</sub>]. The lengths are given in Angstroms.

Analysis of the displacement vectors of the IR frequency vibrations of the reactive systems shows the presence of stretching vibrations with atomic movements similar to the electronic changes involved in the formation of the corresponding TSs. The stretching vibrations of **9a** and **11a** are  $1425\text{ cm}^{-1}$  and  $1421\text{ cm}^{-1}$ , respectively. In the case of **9b** and **11b**, these stretching vibrations are  $1423\text{ cm}^{-1}$  and  $1420\text{ cm}^{-1}$ , respectively. This means that any additional energy comprised between  $1700$  and  $1400\text{ cm}^{-1}$ , can favor the process by favoring the electronic changes needed to reach the TS geometry. Consequently, experimentally it is observed a decrease in the reaction time when MW irradiation is employed. Note that the stretching vibration values between TS and TS-PIL are similar within systems, which means that the MW effects should be similar in free solvent condition and when PILs are employed. This is in agreement with the experimental results in terms of yields and reaction times.

In order to analyze the evolution of the C–C single bond formation at the TSs, a topological analysis of the electron localization function (ELF) [13] of the TSs **9a,b** and **11a,b** was performed. A comparative ELF topological analysis of the valence basins of TSs **9a** and **9b** reveals that while the presence of the two  $V(C3)$  and  $V(C1')$  monosynaptic basins in TS **9a** suggests that the formation of the C3–C1' single bond does not have begun, the presence of a  $V(C2, C1')$  disynaptic basin in TS **9b** indicates that the formation of the C2–C1' single bond have already begun with an initial population of 1.19e (see Fig. 3) [12]. This behavior indicates that TS **9b** is slightly more advanced than TS **9a**. On the other hand, the absence of any  $V(C4')$  monosynaptic basin in the four TSs indicates that the formation of the second C2–C4' (TSs **9a** and **11a**) and C3–C4' (TSs **9b** and **11b**) single bond, respectively, is much delayed. These behaviors are characteristic of a non-concerted *two-state one-step* mechanism [11].

On the other hand, a comparative ELF topological analysis of the

valence basins of TSs **9a** and **11a**, and TSs **9b** and **11b** reveals that the presence of the PIL in TSs **11a** and **11b** does not produce any appreciable changes (see Figs. 3 and 4 in supplementary material). In TS **11a**, the slight higher population of the  $V(C3)$  and  $V(C1')$  monosynaptic basins than those in TS **9a** indicates that former is slightly more advanced in clear agreement with the slight shorter C3–C1' distance found at TS **11a** respect to that at TS **9a**.

In order to corroborate the presence of a HB between one of the two oxygen atoms of the nitro group belonging to NMPs **7** and **8** and the acidic imidazolium N–H hydrogen of HMIM cation at the TSs associated with the corresponding P-DA reactions, a topological analysis of the favourable non-covalent interactions (NCI) [14] taking place at **11a** and **11b** was performed. Favourable NCI gradient isosurfaces are shown in Fig. 4. NCIs topological analysis of **11a** and **11b** shows the presence of a small, thin and circular surface of a dark blue colour between the acidic N–H hydrogen of the HMIM cation and one of the two nitro oxygen atoms, which is characteristic of strong HBs [14]. Consequently, according to the previous geometry analysis, PIL [HMIM][BF<sub>4</sub>] enhances the reactivity of ethylenes NMPs **7** and **8** towards isoprene **3** by increasing the electrophilic character of the former through the formation of an H...O HB (see later). Note that the imidazolium N–H hydrogen is considerably acid. Additionally, some green surfaces associated with weak, attractive interactions can be observed between the tetrafluoroborate and the methylimidazolium molecules of PIL [HMIM][BF<sub>4</sub>], emphasising that NCIs reinforce the electrostatic interactions between the IL cationic/anionic pair.

Finally, in order to understand the polar nature of these DA reactions, the global and local reactivity indices defined within CDFT [15] were analyzed at the ground state of the reagents. The global indices, namely, the electronic chemical potential ( $\mu$ ), chemical hardness ( $\eta$ ), global electrophilicity ( $\omega$ ) and global nucleophilicity ( $N$ ) for isoprene **3** and NMPs **7** and **8**, in absence and in presence of

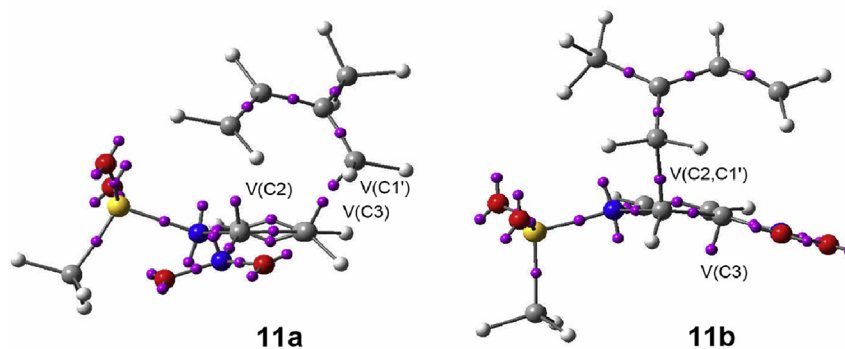


Fig. 3. ELF attractor positions for TSs **9a** and **9b**.

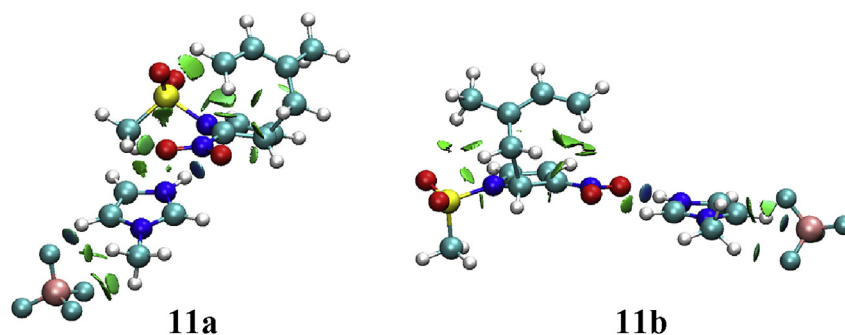


Fig. 4. Favourable NCI gradient isosurfaces, represented at an isovalue of 0.5 a.u., of the TSs involved in the PIL-catalysed P-DA reactions of isoprene **3** with NMPs **7** and **8**.

**Table 1**

B3LYP/6-31G(d) electronic chemical potential,  $\mu$ , chemical hardness,  $\eta$ , global electrophilicity,  $\omega$ , and global nucleophilicity,  $N$ , in eV, isoprene **3** and NMPs **7** and **8**, in absence and in presence of PIL.

	$\mu$	$\eta$	$\omega$	$N$
<b>9</b> PIL	-5.46	3.14	4.74	2.09
<b>10</b> PIL	-5.41	3.24	4.52	2.09
<b>9</b>	-4.86	4.57	2.58	1.97
<b>10</b>	-4.72	4.92	2.26	1.94
<b>3</b>	-3.30	5.77	0.94	2.94

PIL were evaluated (see Table 1).

The electronic chemical potential  $\mu$  of isoprene **3**, -3.30 eV, is higher than that of NMPs **7** and **8**, -4.86 and -4.72 eV, and than that of NMPs **7** and **8** in presence of PIL, -5.46 and -5.41 eV, respectively. Consequently, along polar DA reactions the GEDT will take place from isoprene **3** toward these NMPs, in clear agreement with the flux of the GEDT computed at the corresponding TSs.

Isoprene **3** has an electrophilicity  $\omega$  index of 0.94 eV and a nucleophilicity  $N$  index of 2.94 eV, being classified as a moderate electrophile [16], it being in the borderline of strong nucleophiles [17]. Consequently, isoprene **3** can participate only as a strong nucleophile in polar reactions.

NMPs have an electrophilicity  $\omega$  index of 2.58 (**7**) and 2.26 (**8**) eV, and a nucleophilicity  $N$  index of 1.97 (**7**) and 1.94 (**8**) eV, being classified as strong electrophiles and moderate nucleophiles. When these NMPs are hydrogen bonded to PIL, their electrophilicity  $\omega$  index increases noticeably to 4.74 (**7**) and 4.25 (**7**) eV, while nucleophilicity  $N$  index remains practically unchanged. Consequently, it is expected that in PIL, these P-DA reactions will be accelerated to have a more polar character.

By approaching a non-symmetric electrophilic/nucleophilic pair along a polar process, the most favourable reactive channel is that associated with the initial two-center interaction between the most electrophilic center of the electrophile and the most nucleophilic center of the nucleophile. Recently, Domingo proposed the nucleophilic  $P_k^-$  and electrophilic  $P_k^+$  Parr functions [18], derived from the changes of spin electron-density reached via the GEDT process as a powerful tool in the study of the local reactivity in polar processes. Accordingly, the nucleophilic  $P_k^-$  Parr functions of isoprene **3** and the electrophilic  $P_k^+$  Parr functions of NMPs **7** and **8** were analyzed in order to characterize the most nucleophilic and electrophilic centers of the species involved in these P-DA reactions (see Fig. 5).

Analysis of the nucleophilic  $P_k^-$  Parr functions at the reactive sites of isoprene **3** indicates that the C1' carbon atom, with a  $P_k^-$  value of 0.53, is more nucleophilically activate than the C4' carbon

atom, with a  $P_k^-$  value of 0.37. On the other hand, these closer values account for the low regioselectivity found in P-DA reactions involving isoprene **3**.

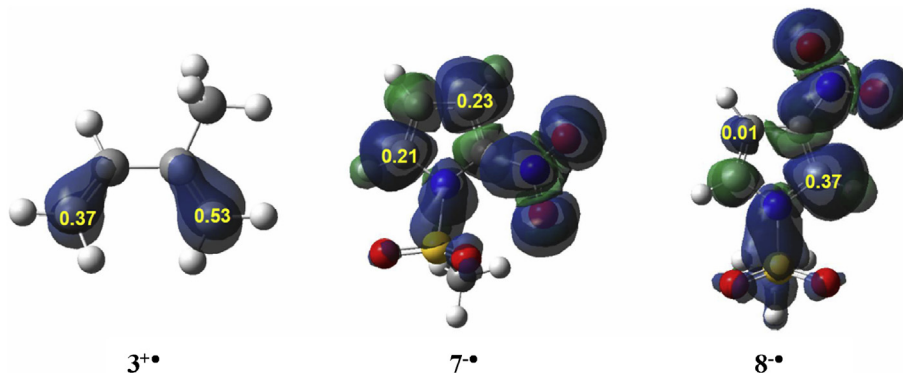
Analysis of the electrophilic  $P_k^+$  Parr functions at the pyrrole ring of 2NMP **7** indicates that the C3 carbon atom, with a  $P_k^+$  value of 0.23, and the C5 carbon atom, with a  $P_k^+$  value of 0.21, are the more electrophilic centers of this nitro derivative. On the other hand, analysis of the electrophilic  $P_k^+$  Parr functions at the pyrrole ring of 3NMP **8** indicates that the C2 carbon atom, with a  $P_k^+$  value of 0.37, is the most electrophilic center of this derivative. In any case, the C3 carbon of 2NMP **7** and the C2 carbon of 3NMP **8** are electrophilically deactivated. Consequently, Parr analysis at the C2 and C3 carbons of these nitropyrroles accounts for the complete regioselectivity experimentally observed when the diene **5** is employed.

### 3. Conclusions

The tosyl-nitropyrroles explored in this work react as electrophilic ethylenes with dienes of different nucleophilicity under microwave heat in P-DA reactions. The presence of the nitro substituent induces the electrophilic activation of the pyrrole ring in which this strong electron-drawing group is present. This group is responsible of the reaction orientation and the selectivity observed. Although the reactions with different pairs diene/dienophile offer similar behavior when are developed under conventional heating or with microwave irradiation, in the last experimental conditions we observe times of reaction significantly short to get comparable yields when the solvents are PILs or in free solvent conditions. In the last two situations, the yields obtained are similar. This result explains why the free solvent conditions is frequently used as a tool in microwave systems due to more simple manipulations, low cost, guarantee of good products separation, and friendship with the environment.

A NCI analysis of the TSs in the presence of PIL clearly evidences the presence of a HB between one oxygen atom of the nitro group and the acidic hydrogen atom of the methylimidazolium cation, which accounts for the acceleration found in these P-DA reactions in PILs respect to the use of classical molecular solvent in thermal condition.

Finally, an analysis of the global and local CDFT reactivity indices at the ground state of the reagents allows explaining the reactivity and selectivity in these P-DA reactions. The nucleophilic character of dienes, together with the high electrophilic character of NMPs **7** and **8** account for the polar character of these DA reactions. Inclusion of one PIL molecule hydrogen bonded to these NMPs markedly increases the corresponding electrophilicity  $\omega$  indice. This behavior accounts for the catalytic role of PILs to permit the



**Fig. 5.** 3D representations of the ASD of the radical cation  $3^+$  and the radical anions  $7^-$  and  $8^-$ , together with the nucleophilic  $P_k^-$  Parr functions of isoprene **3** and the electrophilic  $P_k^+$  Parr functions of NMPs **7** and **8**.

reaction to take place through a more polar process. On the other hand, analysis of the electrophilic and nucleophilic Parr functions accounts for the regioselectivity found experimentally in some cases.

It is noteworthy that in spite of the high polar character of these DA reactions involving strongly electrophilically activated NMPs, the aromatic character of this heterocyclic compound, which is lost along the cycloaddition reactions, accounts for the high activation energy found in these P-DA reactions [19].

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.molstruc.2017.06.109>.

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