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Understanding the participation of 3-nitropyridine in polar Diels–Alder reactions. A DFT study

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ABSTRACT

The reactivity of 3-nitropyridine acting as an electrophilic dienophile in polar Diels–Alder (P-DA) reactions toward three different dienes of increased nucleophilicity has been theoretically studied using DFT methods at the MPWB1K/6-31G(d) level. It has been observed that this aromatic heterocyclic system suffers cycloaddition reactions yielding isoquinoline derivatives. The present DFT study establishes that while the P-DA reactions with isoprene and 1-methoxy-1,3-butadiene take place through a *two-stage one-step* mechanism, the use of the strong nucleophilic Danishefsky's diene changes the mechanism to a two-step one with formation of a zwitterionic intermediate. These P-DA reactions are completely regioselective allowing the formation of a unique substituted isoquinoline. Analysis of the DFT reactivity indices at the ground state of the reagents correctly explains the reactivity and regioselectivity for these P-DA reactions.

1. Introduction

Every chemical process is primarily interesting if it provides a fast way to get basic rings containing a wide variety of functional groups and if it is "economic in atoms". The Diels–Alder (DA) reaction [1] is nowadays one of the most useful organic reactions in any synthetic strategy that needs, at least in one step, the formation of a six-membered ring [2]. DA reactions take place between a compound with two conjugated double bonds, the diene, and an ethylene derivative, the dienophile.

In the last years, it has been considered and proved that aromatic heterocyclic compounds can participate as the dienophile component in DA reactions when they are properly activated with electron-withdrawing groups (EWGs). According to the mechanism, it can be considered that these polar Diels–Alder (P-DA) reactions [3] involving electrophilic aromatic heterocyclic compounds and nucleophilic dienes usually take place through a *two-stage one-step* mechanism [4], *via* highly asynchronous transition state structures (TSs) with high polar character [5], although a two-step mechanism *via* the formation of a zwitterionic intermediate cannot be completely discarded. In this way, we have been working with P-DA reactions using aromatic carbo- and heterocyclic nitro-substituted dienophiles and different electron-rich dienes [6].

Understanding the chemical behavior of dienes and dienophiles participating in DA reactions is not experimentally an easy task. In this sense, theoretical studies using the Density Functional Theory (DFT) provide the best analysis of the reactivity of these compounds. The DFT study of the P-DA reaction between an electron-deficient nitropyridine dienophile and several electron-rich dienes indicates that in all the studied cases the reaction takes place through a one-step mechanism *via* highly asynchronous single bond formation processes. However, in one case a little valley in the intrinsic reaction coordinates was observed without the characterization of the corresponding zwitterionic intermediate, when the strong nucleophilic Danishefsky's diene was used [5]. With these precedent results, nitropyridines were considered as electrophilic dienophiles with the aim of analyzing the potential of the reaction.

The reactions of 3-nitropyridine **1** with isoprene **2**, 1-methoxy-1,3-butadiene **3** and Danishefsky's diene **4** yielding dihydroisoquinoline **8** or isoquinolines **11** and **12** are domino processes that comprise several consecutive steps (see Scheme 1). These domino reactions begin with a P-DA reaction between electron-deficient 3-nitropyridine **1** and electron-rich dienes **3** and **4** yielding the formal [4+2] cycloaducts (CAs) **5–7**. The subsequent nitroso acid elimination in these CAs affords dihydroisoquinolines **8–10**. Finally,

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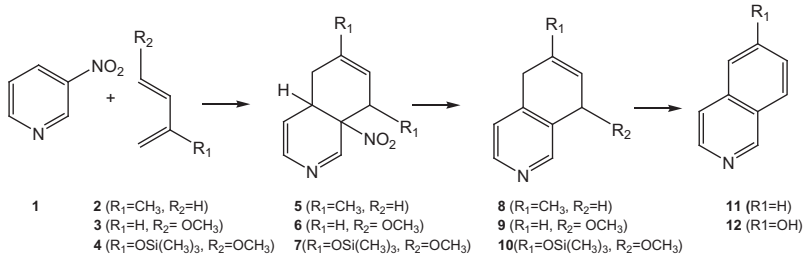


Scheme 1. Reactions begin 3-nitropyridine and electron-rich dienes.

dihydroisoquinolines **9** and **10** are converted into isoquinoline derivatives **11** and **12**, respectively.

Herein, the molecular mechanisms of the P-DA reactions between electron-deficient 3-nitropyridine **1** and electron-rich dienes **2–4**, yielding CAs **5–7**, are theoretically investigated using DFT methods at the MPWB1K/6-31G(d) computational level. The aim of the present work is centered in the analysis of the reactivity of nitropyridine derivatives toward electron-rich dienes. More specifically, we analyze the reactivity, regio- and stereoselectivity of P-DA reactions involving 3-nitropyridine **1**.

2. Computational methods

Several works have shown that the B3LYP functional [7] is relatively accurate for kinetic data, although the reaction exothermicities are underestimated [8]. Recently, the Truhlar's group has proposed some functionals, such as the MPWB1K hybrid meta functional [9] which improve thermodynamic calculations. Consequently, DFT computations were carried out using the MPWB1K functionals, together with the standard 6-31G(d) basis set [10]. The optimizations were carried out using the Berny analytical gradient optimization method [11]. The stationary points were characterized by frequency computations in order to verify that TSs have one and only one imaginary frequency. The IRC paths [12] were traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism using the second order González–Schlegel integration method [13]. Solvent effects of chloroform were taken into account through single point energy calculations in the gas phase optimized geometries using the polarizable continuum model (PCM) as developed by Tomasi's group [14] in the framework of the self-consistent reaction field (SCRF) [15]. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method [16]. All computations were carried out with the Gaussian 09 suite of programs [17].

The global electrophilicity index [18], ω, is given by the following expression, $\omega = (\mu^2/2\eta)$, 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 orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively [19]. Recently, we introduced an empirical (relative) nucleophilicity index [20], *N*, based on the HOMO energies obtained within the Kohn–Sham scheme [21], and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. The nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. This choice allows us to handle conveniently a nucleophilicity scale of positive values. Electrophilic P_k^+ and nucleophilic P_k^- Parr functions [22], were obtained through the analysis of the Mulliken atomic spin density (ASD) of the radical anion and radial cation of the reagents.

3. Results and discussion

The present DFT study has been divided into two parts: (i) first, the P-DA reactions of electrophilic 3-nitropyridine **1** with the nucleophilic diene **2–4** are studied; (ii) in the second part, an analysis of these DA reactions based on the DFT reactivity indices of the reagents is performed.

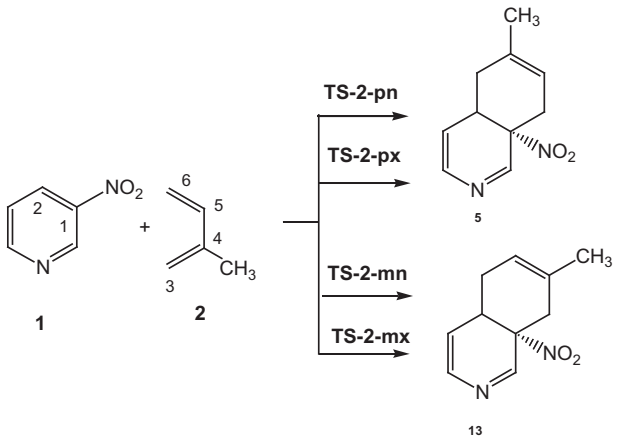
3.1. Mechanistic details of the P-DA reactions of 3-nitropyridine *1* with isoprene *2*, 1-methoxy-1,3-butadiene *3* and Danishefsky's diene *4*

The reactions of 3-nitropyridine **1** with dienes **2–4** are domino processes initialized by a P-DA reaction between **1** and dienes **2–4**. In order to understand the dienophilic behavior of 3-nitropyridine **1**, the corresponding P-DA reactions were studied. Due to the different reactivity shown by the three dienes, the three P-DA reactions are analyzed separately.

3.1.1. Study of the P-DA reaction of 3-nitropyridine *1* with isoprene *2*

Due to the asymmetry of both reagents four competitive approach modes are feasible for this P-DA reaction. They are related to the two stereoisomeric approach modes of the diene system of isoprene 2 relative to the nitro group of 3-nitropyridine **1**, named *endo* and *exo*, and the two regioisomeric approach modes of the C3 carbon toward the dienic system relative to the C1 and C2 carbon of 3-nitropyridine **1**; herein the two regioisomeric possibilities are named *para* and *meta* (see Scheme 2). Note that the two *endo* and *exo* stereoisomeric channels associated with each regioisomeric path yield the same formal [4+2] CA.

An exploration of the potential energy surface (PES) for the P-DA reaction of 3-nitropyridine **1** with isoprene **2** allowed finding only one TS connecting the separated reagents with the



Scheme 2. Regioisomeric *para* and *meta*.

corresponding formal [4+2] CAs, indicating that this reaction takes place through a one-step mechanism. Consequently the reagents, **1** and **2**, four TSs, **TS-2-pn**, **TS-2-px**, **TS-2-mn**, and **TS-2-mx**, and two CAs, **5** and **1**3, were located and characterized. The total and relative energies of the stationary points associated with this P-DA reaction are given in Table 1.

The activation energies in chloroform for the P-DA reaction of 3-nitropyridine **1** with isoprene **2** are 24.4 (**TS-2-pn**), 26.4 (**TS-2-px**), 26.7, (**TS-2-mn**), and 30.0 (**TS-2-mx**) kcal/mol. These reactions are exothermic by −18.8 kcal/mol. Some appealing conclusions can be obtained from these energy results: (i) this P-DA reaction presents a high activation energy, 24.4 kcal/mol, as a consequence of the aromatic character of 3-nitropyridine **1**, which is lost along the cycloaddition reaction [23,24]; (ii) this P-DA reaction is *para* regioselective, **TS-2-pn** being 2.3 kcal/mol lower in energy than **TS-2-mn**; and (iii) the reaction is *endo* stereoselective, **TS-2-pn** being 1.9 kcal/mol lower in energy than **TS-2-px**.

The geometries of the TSs involved in the P-DA reaction of 3-nitropyridine **1** with isoprene **2** are given in Fig. 1. At the *para* regioisomeric TSs the lengths of the C2–C6 and C1–C3 forming bonds are 1.809 and 2.583 Å at **TS-2-pn** and 1.832 and 2.522 Å at **TS-2-px**, respectively, while at the *meta* regioisomeric TSs the lengths of the C2–C3 and C1–C6 forming bonds are 1.909 and 2.385 Å at **TS-2-mn** and 1.838 and 2.350 Å at **TS-2-mx**, respectively. These lengths indicate that the TSs associated with the most favorable regioisomeric *para* channels are more advanced and more asynchronous than the *meta* ones. The high asynchronicity found at the *para* TSs, $\Delta l = 0.78$ (**TS-2-pn**), indicates that this P-DA reaction takes place through a two-stage one-step mechanism [4].

Recently, Domingo has reported that in cycloaddition reactions, the formation of the C–C single bond begins in the short C–C distance range of 1.9–2.0 Å by merging the non-bonding electron-density of two pseudoradical carbons [25]. This finding makes it possible to establish that at very advanced and asynchronous TSs, such as **TS-2-pn**, while the formation of the C2–C6 bond is very advanced, the formation of the C1–C3 one has not started yet. This behavior, which is also characterized at some points of the IRC of P-DA reactions taking place along a *two-stage one-step* mechanism, allows establishing that the bonding changes in these reactions are non-concerted [4].

The polar nature of this DA reaction was analyzed by computing the global electron density transfer (GEDT) [25] at the TSs. The natural atomic charges at the TSs, obtained through a natural population analysis (NPA), were shared between the 3-nitropyridine and the diene frameworks. The values of the GEDT that fluxes from the diene framework to the 3-nitropyridine one are 0.31e (**TS-2-pn**), 0.30e (**TS-2-px**), 0.25e (**TS-2-mn**) and 0.23e (**TS-2-mx**). These high values point to the polar character of this DA reaction [3]. The GEDT along the more favorable regioisomeric *para* channels is larger than that at the *meta* ones.

Table 1
MPWB1K/6-31G(d) total (E, in au) and relative (ΔE, in kcal/mol, relatives to **1**+**2**) electronic energies, in gas phase and in chloroform, for the stationary points involved in the P-DA reaction of 3-nitropyridine **1** with isoprene **2**.

	Gas phase		Chloroform	
	E	ΔE	E	ΔE
1	−452.570196		−452.576047	
2	−195.180327		−195.181782	
TS-2-pn	−647.710054	25.4	−647.718960	24.4
TS-2-px	−647.707245	27.2	−647.715912	26.3
TS-2-mn	−647.708030	26.7	−647.715287	26.7
TS-2-mx	−647.702449	30.2	−647.709620	30.3
5	−647.782258	−19.9	−647.787751	−18.8
13	−647.782184	−19.9	−647.787721	−18.8

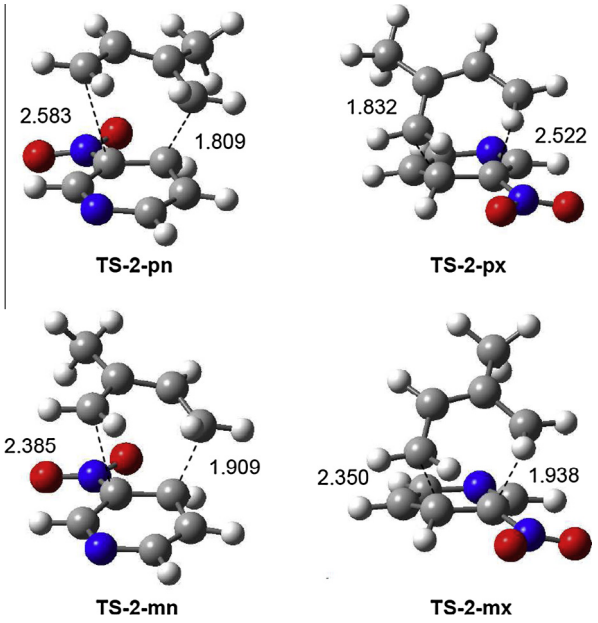
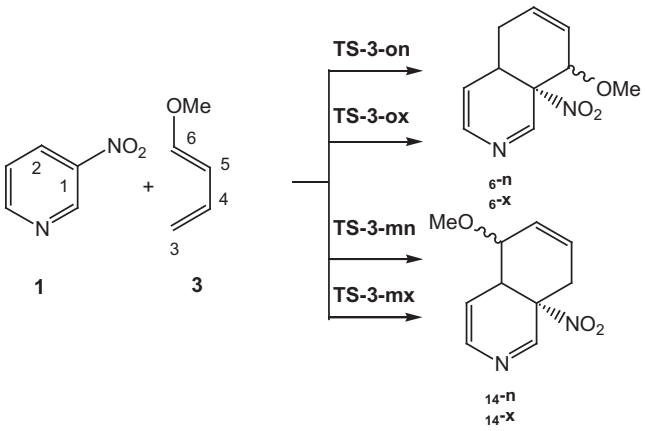


Fig. 1. Geometries of the TSs involved in the P-DA reaction of 3-nitropyridine **1** with isoprene **2**.



Scheme 3. Reaction of 3-nitropyridine with 1-methoxy-1,3-butadiene.

*3.1.2. Study of the P-DA reaction of 3-nitropyridine **1** with 1-methoxy-1,3-butadiene **3***

Due to the asymmetry of both reagents four competitive approach modes are feasible for these P-DA reactions. They are related to the two stereoisomeric approach modes of the diene system of **3** relative to the nitro group of 3-nitropyridine **1**, named *endo* and *exo*, and the two regioisomeric approach modes of the C3 carbon toward the dienic system relative to the C1 and C2 carbon of 1-methoxy-1,3-butadiene **3**; herein the two regioisomeric possibilities are named *ortho* and *meta* (see Scheme 3). An exploration of the PES for the P-DA reaction of 3-nitropyridine **1** with 1-methoxy-1,3-butadiene **3** allowed finding only one TS connecting the separated reagents with the corresponding formal [4+2] CAs, indicating that this reaction takes place also through a one-step mechanism. Consequently, the reagents, **1** and **3**, four TSs, **TS-3-on**, **TS-3-ox**, **TS-3-mn**, and **TS-3-mx**, and four CAs, **6-n**, **6-x**, **14-n** and **14-x**, were located and characterized. The total and relative energies of the stationary points associated with this P-DA reaction are given in Table 2.

Table 2
MPWB1K/6-31G(d) total (E, in au) and relative (ΔE, in kcal/mol, relatives to **1**+**3**) electronic energies, in gas phase and in chloroform, for the stationary points involved in the P-DA reaction of 3-nitropyridine **1** with 1-methoxy-1,3-butadiene **3**.

	Gas phase		Chloroform	
	E	ΔE	E	ΔE
1	−452.570196		−452.576047	
3	−270.355287		−270.358472	
TS-3-on	−722.892563	20.7	−722.903123	19.7
TS-3-ox	−722.892004	21.0	−722.901619	20.6
TS-3-mn	−722.876868	30.5	−722.885220	30.9
TS-3-mx	−722.876655	30.6	−722.883893	31.8
6-n	−722.946284	−13.1	−722.952889	−11.5
6-x	−722.943786	−11.5	−722.950624	−10.1
14-n	−722.949178	−14.9	−722.955294	−13.0
14-x	−722.946920	−13.5	−722.954830	−12.7

The activation energies in chloroform for the P-DA reaction of 3-nitropyridine **1** with 1-methoxy-1,3-butadiene **3** are 19.7 (**TS-3-on**), 20.6 (**TS-3-ox**), 30.9 (**TS-3-mn**), and 31.8 (**TS-3-mx**) kcal/mol. These reactions are exothermic between −10 and −13 kcal/mol. Some appealing conclusions can be drawn from these energy results: (i) this P-DA reaction also presents a high activation energy, 19.7 kcal/mol; (ii) the activation energy associated with this P-DA reaction is 4.7 kcal/mol lower in energy than that associated with the reaction with isoprene **2** as a consequence of the more nucleophilic character of 1-methoxy-1,3-butadiene **3** than isoprene **2** (see later); (iii) this P-DA reaction is completely *ortho* regioselective, **TS-3-on** being 11.2 kcal/mol lower in energy than **TS-3-mn**; and (iv) this P-DA reaction is *endo* stereoselective, **TS-3-on** being 1.9 kcal/mol lower in energy than **TS-3-ox**.

The geometries of the TSs involved in the P-DA reaction of 3-nitropyridine **1** with 1-methoxy-1,3-butadiene **3** are given in Fig. 2. At the more favorable *ortho* regioisomeric TSs the lengths of the C2–C3 and C1–C6 forming bonds are 1.847 and 2.761 Å at **TS-3-on** and 1.827 and 2.849 Å at **TS-3-ox**, respectively, while at the *meta* regioisomeric TSs the lengths of the C2–C6 and C1–C3 forming bonds are 2.202 and 1.982 Å at **TS-3-mn** and 2.100 and 2.087 Å at **TS-3-mx**, respectively. These lengths indicate that while the TSs associated with the most favorable regioisomeric *ortho* channels are highly asynchronous, $\Delta l > 0.90$ (TS3-on), those associated with the more unfavorable *meta* channels are associated with low asynchronous processes. Such as in the P-DA reaction between

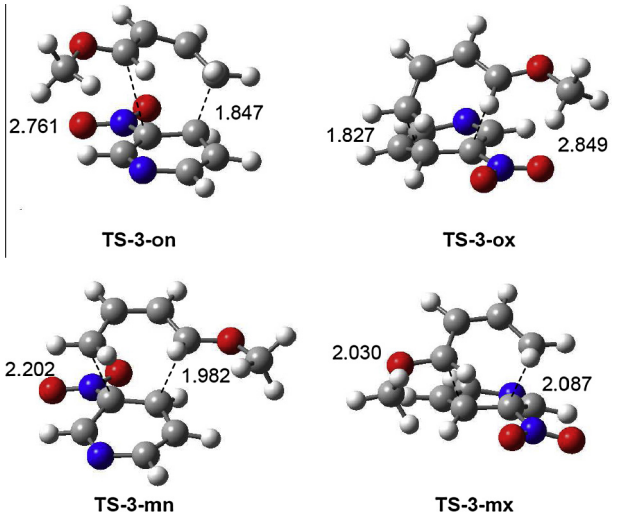


Fig. 2. Geometries of the TSs involved in the P-DA reaction of 3-nitropyridine **1** with 1-methoxy-1,3-butadiene **3**.

of 3-nitropyridine **1** and isoprene **2**, the high asynchronicity found at the most favorable *ortho* TSs indicates that this P-DA reaction takes place also through a *two-stage one-step* mechanism.

The values of the GEDT that fluxes from the diene framework to 3-nitropyridine one at the TSs are 0.43e (**TS-3-on**), 0.40e (**TS-3-ox**), 0.22e (**TS-3-mn**) and 0.35e (**TS-3-mx**). The high GEDT values found at the most favorable *ortho* TSs point to the high polar character of this DA reaction. Interestingly, the GEDT at the most favorable *ortho*/*endo* **TS-3-on** is twice than that associated with the *meta*/*endo* **TS-3-mn**.

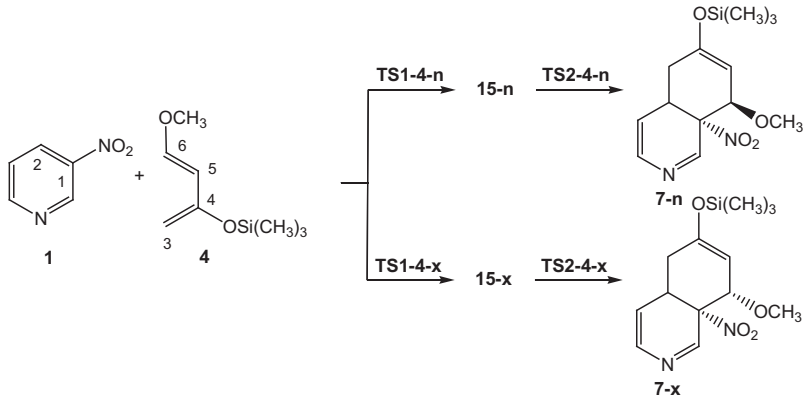
3.1.3. Study of the P-DA reaction of 3-nitropyridine *1* with Danishefsky's diene *4*

Due to the asymmetry of 3-nitropyridine **1** and Danishefsky's diene **4**, four competitive channels are feasible for this P-DA reaction. They are related to the two stereoisomeric approach modes of the diene system relative to the nitro group of 3-nitropyridine, named *endo* and *exo*, and the two regioisomeric approach modes of the C3 carbon of Danishefsky's diene **4** relative to the C1 and C2 carbon of 3-nitropyridine **1**. Due to the total regioselectivity found in these P-DA reactions, only the regioisomeric channels associated with the nucleophilic attack of the C3 carbon of diene **4** on the C2 carbon of 3-nitropyridine **1** were considered. An exploration of the PES for this P-DA reaction allowed finding two TSs and one zwitterionic intermediate connecting the two TSs, indicating that this reaction takes place through a two-step mechanism. Consequently, the reagents, two TSs, one zwitterionic intermediate, and the corresponding formal [4+2] CA were located and characterized for each stereoisomeric channel (see Scheme 4). The total and relative energies of the stationary points associated with this P-DA reaction are given in Table 3.

The activation energy associated with the nucleophilic attack of Danishefsky's diene **4** on 3-nitropyridine **1** is 14.4 (**TS1-4-n**) and 13.3 (**TS1-4-n**) kcal/mol; formation of the zwitterionic intermediates **15-n** and **15-x** is endothermic by 8.4 and 6.2 kcal/mol, respectively. Finally, formation of the formal [4+2] CA **7-n** and **7-x** via **TS2-4-n** and **TS2-4-x** presents an activation energy of 0.9 and 3.0 kcal/mol, respectively. This P-DA reaction is exothermic by −7.5 kcal/mol.

The geometries of the TSs involved in the P-DA reaction of 3-nitropyridine **1** with Danishefsky's diene **4** are given in Fig. 3. The lengths of the C2–C3 and C1–C6 forming bonds along the stepwise P-DA reaction are 1.932 and 2.975 Å at **TS1-4-n**, 1.940 and 3.105 Å at **TS1-4-x**, 1.605 and 2.738 Å at **15-n** and 1.603 and 2.999 Å at **15-x**, and 1.598 and 2.457 Å at **TS2-4-n**, and 1.581 and 2.357 Å at **TS2-4-x**. The lengths at **TS1-4-n** and **TS1-4-x** are similar to those found at the *ortho* TSs associated with the P-DA reaction with 1-methoxy-1,3-butadiene **3**. The geometrical and electronical similitude between the TSs associated with the *two-stage one-step* mechanism and the TSs associated with the first step of the stepwise mechanism allows establishing that DA reactions taking place through one-step mechanisms are non-concerted processes. The unique difference between both mechanisms is the presence of a weak stabilized zwitterionic intermediate in the P-DA reaction involving the most nucleophilic Danishefsky's diene **4** (see latter). At the zwitterionic intermediates, while the C2–C3 single bond is practically formed, the C1–C6 bond length remains very long. The C2–C3 and C1–C6 lengths at the zwitterionic intermediates are similar to those found at the points of the IRCs of the *two-stage one-step* mechanisms that share the two stages of the cycloaddition.

The values of the GEDT that fluxes from the diene framework to 3-nitropyridine at these stationary points are 0.45e (**TS1-4-I**), 0.42e (**TS1-4-x**), 0.74e (**IN-4-n**), 0.67e (**IN-4-x**) and 0.58e (**TS2-4-n**) and 0.60e (**TS2-4-x**). These values indicate that along this stepwise reaction there is an increase of the GEDT along the nucleophilic



Scheme 4. Reaction of 3-nitropyridine and Danishefsky's diene.

Table 3
MPWB1K/6-31G(d) total (E, in au) and relative (ΔE, in kcal/mol, relatives to **1**+**4**) electronic energies, in gas phase and in chloroform, for stationary points involved in the P-DA reaction of 3-nitropyridine **1** with Danishefsky's diene **4**.

	Gas phase		Chloroform	
	E	ΔE	E	ΔE
1	−452.570196		−452.576047	
4	−754.203979		−754.208492	
TS1-4-n	−1206.751153	14.4	−1206.761543	14.4
15-n	−1206.757772	10.3	−1206.771209	8.4
TS2-4-n	−1206.757394	10.5	−1206.769735	9.3
7-n	−1206.788771	−9.2	−1206.796411	−7.5
TS1-4-x	−1206.753429	13.0	−1206.763410	13.3
15-x	−1206.761140	8.2	−1206.774710	6.2
TS2-4-x	−1206.758462	9.9	−1206.769953	9.2
7-x	−1206.787813	−8.6	−1206.796309	−7.4

attack of Danishefsky's diene **4** on 3-nitropyridine **1** to reach the maximum value with the formation of the first C2–C3 single bond at the corresponding zwitterionic intermediates. From these intermediates to the final [4+2] CAs there is a decrease of the GEDT as a consequence of a retro-donation process along the formation of the second C–C single bond.

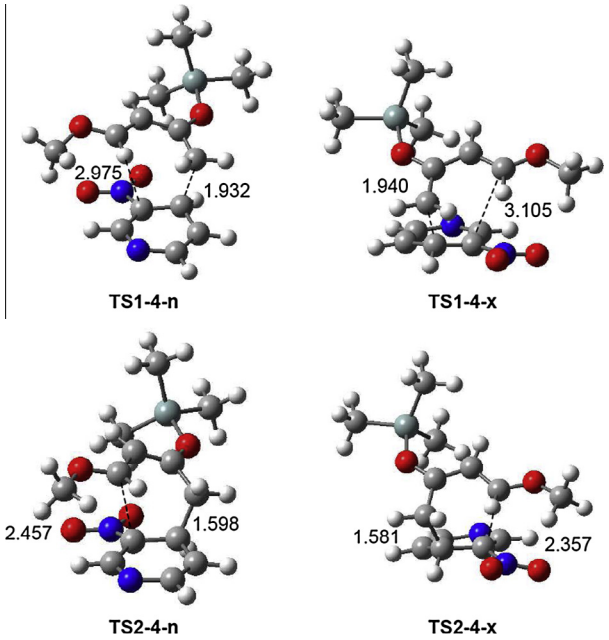


Fig. 3. Geometries of TSs involved in the P-DA reaction of 3-nitropyridine **1** with Danishefsky's diene **4**.

Table 4
MPWB1K/6-31G(d) electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and global nucleophilicity N indices, in eV, for the series of reagents involved in the studied P-DA reactions of 3-nitropyridine **1** with dienes **2–4**.

	μ	η	ω	N
1	−5.42	7.32	2.00	1.15
2	−3.29	7.85	0.69	3.01
3	−2.86	7.36	0.55	3.69
4	−2.70	7.39	0.49	3.83

3.2. Analysis of the DFT reactivity indices of the reagents involved in these P-DA reactions

Finally, these P-DA reactions were analyzed using the reactivity indices defined within the conceptual DFT [26]. The values of global descriptors, namely, electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and global nucleophilicity N indices for the series of reagents involved in these P-DA reactions are given in Table 4.

The electronic chemical potential μ of the three dienes, between −3.29 (**2**) and −2.70 (**4**) eV, is higher than the electronic chemical potential of 3-nitropyridine **1**, −5.42 eV. Consequently, along these P-DA reactions the GEDT will flux from these dienes to 3-nitropyridine **1**, in clear agreement with the GEDT computed at the TSs.

The electrophilicity index of 3-nitropyridine **1** is ω = 2.00 eV, being classified as a strong electrophile within the electrophilicity scale [27]. On the other hand, its nucleophilicity is N = 1.15 eV being classified as a moderate nucleophile [28].

The electrophilicity index of the diene series ranges from 0.69 (**2**) to 0.49 (**4**) eV. While **2** is classified as a moderate electrophile, dienes **3** and **4** are classified as marginal electrophiles. The nucleophilicity index of the diene series ranges from 3.01 (**2**) to 3.83 (**4**) eV. The three dienes are classified as strong nucleophiles.

Thus, the high electrophilic character of 3-nitropyridine **1** together with the high nucleophilic character of the dienes indicates that these cycloaddition reactions will have a high polar character. In spite of this high polar character, the lost of aromaticity of the pyridine ring is responsible for the high activation energies found in these P-DA reactions [23,24].

Along a polar reaction involving the participation of asymmetric reagents, the most favorable reactive channel is that involving the initial two-center interaction between the most electrophilic and the nucleophilic centers of the two reagents. Recently, we have

Table 5
Electrophilic P_k^+ Parr functions in 3-nitropyridine **1** and nucleophilic P_k^- Parr functions in substituted dienes **2–4**.

P_k^+	C1	C2		
1	0.18	0.07		
P_k^-	C3	C4	C5	C6
2	0.53	0.09	0.06	0.37
3	0.40	−0.05	0.29	0.17
4	0.60	−0.06	0.18	0.11

proposed the electrophilic and nucleophilic P_k^- Parr functions derived from the excess of spin electron density reached via the GEDT process from the nucleophile to the electrophile as powerful tools in the study of the local reactivity in polar processes [22]. Accordingly, the electrophilic P_k^+ Parr functions of 3-nitropyridine **1** and nucleophilic P_k^- Parr functions of ER dienes **2–4** are analyzed (see Table 5).

Analysis of the electrophilic P_k^+ Parr functions in 3-nitropyridine **1** indicates that the C1 carbon of **1** is the most electrophilic center of pyridine, =0.18. Note that the C3 carbon of **1** is twice as electrophilic as the C2 carbon of **1**. On the other hand, the nucleophilic P_k^- Parr functions at the two final C3 and C6 carbons of the three substituted dienes are: 0.53 (C3) and 0.37 (C6) (**2**), 0.40 (C3) and 0.17 (C6) (**3**), and 0.60 (C2) and 0.11 (C6) (**4**). Consequently, the C3 carbon is the most nucleophilic center of these dienes. Therefore, the most favorable regioisomeric channels associated with these P-DA reactions will be those associated with the initial C2–C3 bond formation.

4. Conclusions

The mechanisms of the P-DA reactions of 3-nitropyridine **1** with three dienes of increased nucleophilicity, isoprene **2**, 1-methoxy-1,3-butadiene **3** and the Danishefsky's diene **4**, have been studied using DFT methods at the MPWB1K/6-31G(d) computational level. While the P-DA reactions with dienes **2** and **3** take place through a *two-stage one-step* mechanism, the reaction with Danishefsky's diene **4** takes place through a two-step mechanism with formation of a zwitterionic intermediate. In spite of the high electrophilic character of 3-nitropyridine **1** and the high nucleophilic character of these dienes, the P-DA reactions present high activation energies, 24.4 (**2**), 19.7 (**3**) and 13.3 (**4**) kcal/mol as a consequence of the aromatic character of 3-nitropyridine 1, which is lost along the cycloaddition reaction. These P-DA reactions present a low *endo*/*exo* stereoselectivity; in fact, while the reactions with dienes **2** and **3** are *endo* selective, the reaction with Danishefsky's diene **4** is *exo* selective. The P-DA reactions with dienes **3** and **4** are completely regioselective; this selectivity is controlled by the most favorable nucleophilic/electrophilic interaction between the C2 carbon of 3-nitropyridine **1** and the C3 carbon of these dienes.

Analysis of the global reactivity indices at the ground state of the reagents correctly explains the reactivity of these reagents in P-DA reactions. On the other hand, analysis of the electrophilic P_k^+ and nucleophilic P_k^- Parr functions correctly explains the regioselectivity and asynchronicity of these polar reactions.

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