An investigation of the molecular mechanism, chemoselectivity and regioselectivity of cycloaddition reaction between acetonitrile N-Oxide and 2,5-dimethyl-2H-[1,2,3]diazaphosphole: a MEDT study

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Abstract. The [3+2] cycloaddition (32CA) reactions of acetonitrile N-oxide with 2,5-dimethyl-2H-[1,2,3]diazaphosphole has been studied using the Molecular Electron Density Theory (MEDT) through DFT calculations at the B3LYP/6-31G(d,p) computational level. Analysis of the relative free energies associated with the competitive *ortho* and *meta* reaction paths shows high chemo- and regioselectivity for this 32CA reaction in clear agreement with the experimental outcomes. The topological analysis of the electron localization function (ELF) of the selected points of the IRC associated with the formation of the P-C and C-O single bonds indicates a zwitterionic type structure. The 32CA reaction takes place through a two-stage one-step mechanism initialized with the formation of the P-C single bond.

Keywords. Diazaphosphole; acetonitrile N-oxide; MEDT; chemoselectivity; regioselectivity.

1. Introduction

The studies regarding the preparation of isoxazoline products were the object of extensive investigations in the recent years.^{1,2} This is due to their amazing chemical properties that make these very useful in many fields like veterinary medicine, chemical synthesis, etc. In veterinary medicine, these are used as highly effective drugs on ectoparasites.³ In chemical synthesis, these serve as intermediates in short, stereoselective syntheses of diverse natural and unnatural products.⁴ A variety of synthetic methods have been developed for the preparation of isoxazolines of which the most convenient and attractive route is probably the [3+2] cycloaddition (32CA) reaction of nitrile oxides to alkenes.⁵ In the context of such reactions, we have focused our work on the reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**, which leads chemo- and regioselectively to

a single product **3** (Scheme 1) realized by the group of Yeung Lam.⁶

The current progress made in the theoretical comprehending of 32CA reactions based on the Molecular Electron Density Theory⁷ (MEDT) has allowed creating a very good correlation among the electronic structure of three-atom-components (TACs) and their reactivity.⁸ Therefore, depending on the electronic structure of the simplest TACs, 32CA reactions have been categorized into *pdr-type*, *pmr-type*, *zw-type* and *cb-type* reactions,⁸ in such a method that while *pdr-type* 32CA reactions can be approved out easily, *zw-type* 32CA reactions demand adequate nucleophilic/electrophilic activations to take place⁹ (Chart 1).

A recent MEDT investigation of the reactivity and regioselectivity of the 32CA reaction between benzonitrile oxide **a** with methyl acrylate **b** (Scheme 2) explain that this zwitterionic TAC has a low nucleophilic and electrophilic character. This makes the reaction a non-polar process and, hence, the activation energies that are principally associated to the rupture

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Scheme 1. 32CA reaction of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** with acetonitrile N-oxide **2** in presence of THF as a solvent.

of the C-N triple bond of nitrile oxide, are somewhat high, $11.4 \text{ kcal}\cdot\text{mol}^{-1}$.¹⁰ This *zw-type* 32CA reaction demonstrated poor *ortho* regioselectivity given that the transition state (TS) associated with the formation of *meta* isoxazoline **d** was established to be only $1.6 \text{ kcal}\cdot\text{mol}^{-1}$ less favorable than that associated with the formation of *ortho* isoxazoline **c**.

Herein, an MEDT study of the 32CA reaction between acetonitrile N-oxide **2** and 2,5-dimethyl-2H-[1,2,3] diazaphosphole **1**, is performed in order to unveil the molecular mechanism that manage the chemo- and regioselectivity of this reaction.

2. Computational methods

DFT computations were executed using the B3LYP functional^{11,12} together with the 6-31G(d,p) basis set.¹³ Optimisations were carried out utilizing the Berny analytical gradient optimisation method.^{14,15} The stationary points were characterised by frequency calculations in order to prove that TSs have one and only one imaginary frequency. The intrinsic reaction coordinate¹⁶ (IRC) paths were drawn in order to verify the energy profiles relating each TS to the two associated minima of the proposed mechanism employing the second-order González-Schlegel integration method.^{17,18} Solvent effects of tetrahydrofuran (THF) were taken into account by full optimization of the gas phase structures using the polarisable continuum model (PCM)

Scheme 2. 32CA reaction of benzonitrile oxide **a** with methyl acrylate **b**.

developed by Tomasi's group¹⁹ in the framework of the self-consistent reaction field^{20–22} (SCRF). Values of enthalpies, entropies and Gibbs free energies in THF were calculated with standard statistical thermodynamics at 273.15 K and 1 atm. The global electron density transfer²³ (GEDT) was calculated by the sum of the natural atomic charges (q), obtained by a Natural Population Analysis,^{24,25} (NPA), of the atoms belonging to each framework (f) at the TSs; i.e., $\text{GEDT}(f) = \sum_{q \in f} q$. The sign shows the direction of the electron density flux in such a manner that positive values mean a flux from the considered framework to the other one.

The global electrophilicity index²⁶ ω was given by the following expression, in terms of the electronic chemical potential μ and the chemical hardness η . Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L as $\mu = \frac{\varepsilon_H + \varepsilon_L}{2}$ and $\eta = \varepsilon_L - \varepsilon_H$, respectively. The empirical nucleophilicity index N ²⁷ based on the HOMO energies obtained within the Kohn-Sham and defined as $N = E_{\text{HOMO}}(\text{Nu}) - E_{\text{HOMO}}(\text{TCE})$ the nucleophilicity was referred to as tetracyanoethylene (TCE). Electrophilic and nucleophilic Parr functions were obtained through the analysis of the Mulliken atomic spin density (ASD) of the

Azomethine ylide	Azomethine imine	Nitrone	Nitrile ylide
Structure			
<i>pseudodiradical</i>	<i>pseudoradical</i>	<i>zwitterionic</i>	<i>carbenoid</i>
Reactivity			
<i>pdr-type</i>	<i>pmr-type</i>	<i>zw-type</i>	<i>cb-type</i>

Chart 1. Electronic structure of TACs and the proposed reactivity types in 32CA reactions

radical anion and radical cation of the reagents.²⁸ All computations were carried out with the Gaussian 09 suite of programs.²⁹

Topological analyses of the Electron Localisation Function³⁰ (ELF) were performed with the TopMod³¹ package using the corresponding mono determinantal wave functions. The characterization of the bond formation processes along the most favourable reaction path was carried out by performing the topological analysis of the ELF for some selected structures along with the IRC profile.

3. Results and Discussion

The present MEDT study has been divided into four sections: (i) first, the CDFT reactivity indices of the reagents are analysed; (ii) in the second part, ELF analysis of the electronic structure of acetonitrile N-oxide **2** is performed; (iii) the competitive reaction paths associated with the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2** are studied; and finally, (iv) in the fourth part, the formation of the new single bonds along the most favourable reaction path associated with the formation of 3,5,7-trimethyl-5,7a-dihydro-[1,2,3]diazaphospholo[3,4-d][1,2,4]oxaphosphole **3** is characterized through the topological study of the ELF.

3.1 Analysis of the CDFT indices of the reagents

The 32CA reaction between 2,5-dimethyl-2H-[1,2,3]-diazaphosphole **1** and acetonitrile N-oxide **2** was investigated analyzing the CDFT reactivity indices of the reagents. The electronic chemical potential μ , the chemical hardness η , the electrophilicity ω , and the nucleophilicity N , are given in Table 1.

Referring to the values obtained for the electronic chemical potential, we observe that the value of electronic chemical potential of acetonitrile N-oxide **2**, -2.89 eV, is higher than that of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1**, -3.65 eV, indicating that along a polar reaction, the electron density will flux

from the acetonitrile N-oxide **2** framework towards the 2,5-dimethyl-2H-[1,2,3]diazaphosphole one.

The electrophilicity ω and nucleophilicity N index of the 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** are 1.24 and 2.76 eV, respectively, and is classified as a strong electrophile and a moderate nucleophile within the electrophilicity and nucleophilicity scales. The electrophilicity ω and nucleophilicity N indices of acetonitrile N-oxide **2** are 0.54 and 2.39 eV, respectively, being classified marginal electrophile as a poor nucleophile. Consequently, it is expected that acetonitrile N-oxide **2** participates as a poor nucleophile towards the electrophilic 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** in this *zw-type* 32CA reaction. However, analysis of the GEDT at the most favorable **TS1** indicates that the GEDT fluxes from **1** towards **2**, the former acting as a nucleophile and the nitrile oxide as an electrophile (see later).

Because of the non-symmetric reagents, the most favorable regioisomeric reactive channel is the one that relates to the initial two-centre interaction between the most electrophilic center of the electrophile and the most nucleophilic center of the nucleophile. The nucleophilic P_k^- and electrophilic P_k^+ Parr functions,²⁸ derived from the changes of spin electron-density reached *via* the GEDT process from the nucleophile to the electrophile, were recently proposed as a powerful tool to study the local reactivity in polar and ionic processes. Accordingly, the nucleophilic P_k^- and electrophilic P_k^+ Parr functions of the 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**, respectively, were analyzed in order to define the most electrophilic and nucleophilic centers of the species elaborate in this cycloaddition reaction and, thus, to explicate the regioselectivity experimentally detected (Figure 1).

After the nucleophilic P_k^- Parr functions analysis at the reactive sites of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** it can be concluded that the P atom is the most nucleophilic center of this species with a P_k^- value of 0.41 (P). Otherwise, the electrophilic P_k^+ Parr functions analysis at the reactive sites of acetonitrile N-oxide **2** reveals that the carbon C3' carbon, $P_k^+ = 0.30$, is significantly more nucleophilically activated than oxygen atom, $P_k^+ = 0.09$. Therefore, it is predictable that the most favorable nucleophile–electrophile interaction along the nucleophilic attack of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** to acetonitrile N-oxide **2** in a polar process will take place between the most electrophilic center of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** P phosphor atom and the most nucleophilic center of acetonitrile N-oxide, the

Table 1. B3LYP/6-31G(d,p) the chemical hardness η , electronic chemical potential μ , the electrophilicity ω , and the nucleophilicity N , in eV, of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**.

System	η	μ	ω	N
1	5.38	-3.65	1.24	2.76
2	7.66	-2.89	0.54	2.39

Figure 1. Three-dimensional (3D) representations of the Mulliken atomic spin densities (ASD) of radical cation $1^{+\bullet}$, and radical anion $2^{\bullet-}$, together with the nucleophilic P_k^- and electrophilic P_k^+ Parr functions, respectively, of the 2,4-dimethyl-2H-phosphorus **1** and acetonitrile N-oxide **2**.

C3' carbon atom. This prediction is in complete agreement with the experimental outcomes.

3.2 ELF analysis of the electronic structure of acetonitrile N-oxide

Nitrile oxides are lineal TACs with a propargylic zwitterionic structure participating in *zw-type* 32CA reactions.⁹ Regardless of the electron-releasing or electron-withdrawing nature of the nitrile oxide substitution, these TACs usually exhibit a relatively low reactivity and yield low regioselectivity. Illustration of the ELF attractor positions and the proposed ELF-based Lewis structure of the acetonitrile N-oxide **2** are illustrated in Figure 2.

The topological analysis of the ELF of acetonitrile N-oxide **2** shows the presence of two disynaptic basins, $V(C1, N2)$ and $V(N2, O1)$, integrating 2.03 and 1.58 e, respectively, associated with the C1-N2 and N2-O3 bonding regions, as well as three $V(C1, N2)$ disynaptic basins, integrating a total of 6.23 e, associated to the C1-N2 triple bonding regions, and three $V(O1)$ monosynaptic basins, integrating a total of 5.69 e, related to the O1 non-bonding region (Figure 1).

NPA of acetonitrile N-oxide **2** reveals that while the O3 oxygen gathers a relatively high negative charge, -0.41 e, the N2 nitrogen is positively charged by 0.15 e; for its part, the C3 carbon is also positively charged by 0.17 e. These values indicate that acetonitrile N-oxide **2** presents a charge separation that makes them some dipolar character.

The proposed ELF-based Lewis structure of acetonitrile N-oxide **2** indicates that it has a propargylic lineal structure associated with a *zw-type* TAC participation in *zw-type* 32CA reaction.

Figure 2. B3LYP/6-31G(d,p) ELF basin attractor positions, together with the valence basin populations, and the proposed ELF-based Lewis structure, together with the natural atomic charges of acetonitrile N-oxide **2**. Negative charges are colored in red, while positive charges are colored in blue. ELF valence basin populations and natural atomic charges are given in an average number of electrons, e.

3.3 Study of the competitive reaction paths associated with the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**

2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** has two reactive sites: one P-C double bond and one C-N double bond. Due to the non-symmetry of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**, up to four competitive reaction paths are feasible. They are related to the different chemo- and regioisomeric approach modes of acetonitrile N-oxide **2** to 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1**. Formation of 3,5,7-Trimethyl-5,7a-dihydro-[1,2,3]diazaphospholo[3,4-d][1,2,4]oxaphosphole **3** as the single reaction product indicates that this 32CA reaction has to present total region and chemoselectivity.

So as to explicate the regio- and chemoselectivity experimentally observed, two approach modes associated to the chemoselective attack on the P-C2 and N1-C3 double bonds of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** along with the two regioisomeric approach modes of acetonitrile N-oxide **2**, were considered. Thus, four TSs, **TS1** to **TS4**, and the corresponding cycloadducts were located and characterized (Scheme 3), demonstrating that the aforementioned reaction paths proceed through a one-step mechanism.

Scheme 3. The four considered regio- and chemo isomeric reaction paths associated with the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**. B3LYP/6-31G(d,p) relative energies, in the gas phase and in THF (the latter in parentheses), are given in kcal·mol⁻¹ relative to the separated reagents.

Relative energies, in the gas phase and in THF, are given in Scheme 3, while total electronic energies are given in Table S1 (Supplementary Information).

The activation energies related with the four selected reaction paths range from 11.43 (TS3) to 33.19 (TS5) kcal·mol⁻¹; formation of the corresponding cycloadducts being two exothermic by between 7.92 (**3**) and 25.62 (**4**) kcal·mol⁻¹, and two endothermic by 02.96 (**5**) and 26.35 (**6**). Several engaging conclusions can be drawn from these energy results: (i) the most favourable reaction path is that related to the formation of **3** via TS1, 11.43 kcal·mol⁻¹. This reaction path corresponds to the approach of acetonitrile N-oxide **2** towards the P-C1' double bond of 2,4-dimethyl-2H-phosphorus **1**; (ii) this 32CA reaction presents a total chemoselectivity as TS3 is 11.16 kcal·mol⁻¹ higher in energy than TS1; (iii) this 32CA reaction presents a total regioselectivity as TS2 is 3.45 kcal·mol⁻¹ higher in energy than TS1; (vi) formation of cycloadduct **4** is more exothermic than the formation of cycloadduct **3**; -25.26 and -7.92 kcal·mol⁻¹, respectively. Therefore, it is expected that product **3** results from a kinetic control of the reaction.

Inclusion of the solvent effects of THF produces negligible changes in activation and reaction energies of the products **3**, **4** and **5** between only 0.97 and 1.53 kcal·mol⁻¹, but in the fourth activation energy of product **6** a very large load of 5.95 kcal mol⁻¹. Whilst in THF the activation energies slightly increase and the exothermic character of the reaction paths a little diminish, as a result of better solvation of the reagents than that of the TSs and cycloadducts. Consequently, in THF, TS1 and TS2 present alike activations energies. The outcomes found in the gas phase are not modified in THF.

The enthalpy profiles of the reaction paths associated with the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2** are illustrated in Figure 2, while the complete thermodynamic data are given in Table S2 (Supplementary Information). Again, the addition of thermal corrections to the electronic energies in THF does not considerably change the relative enthalpies; while the activation enthalpies slightly increase by ca. 1.0 kcal·mol⁻¹, the reaction enthalpies slightly decrease by ca. 3.0 kcal·mol⁻¹. Though, the inclusion of entropies to enthalpies strongly increases the activation of Gibbs free energies by between 11–12 kcal·mol⁻¹, due to the unfavourable entropies associated with these biomolecular processes. The activation Gibbs free energies associated with the formation of **3** and **4** reach 25.2 and 28.27 kcal·mol⁻¹, respectively. The activation Gibbs free energies also account for the total chemo- and regioselectivity.

The geometries of the TSs associated with the four reaction paths are exposed in Figure 3. The comparative scrutiny of the geometrical parameters of the TSs found in the gas phase and those found in THF demonstrate that the implicit consideration of the solvent in the geometry optimisations does not create significant changes. Some attractive conclusions can be drawn from the geometrical parameters of the TSs illustrate in Figure 3: (i) the lengths of the two forming bonds at the TSs associated with the reaction paths involving the participation of the P-C double bond of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** show that they are associated with asynchronous processes in which the formation of the P-C1 single bond involving the P-C double bond phosphor atom is more advanced than the double bond N-C; (ii) along the two

Figure 3. Enthalpy profiles, in $\text{kcal}\cdot\text{mol}^{-1}$, for the studied reaction paths of the 32CA 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**, in THF at 25 °C ($\text{kcal}\cdot\text{mol}^{-1}$).

chemoisomeric reaction paths involving the participation of the P-C double bond of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1**, the more favourable **TS1** is more advanced and more asynchronous than **TS3**; and finally, (iii) inclusion of the solvent effects makes the TSs slightly more earlier and more asynchronous.

Finally, the polar character of these 32CA reactions was evaluated computing the values of the GEDT at the corresponding TSs. The values of the GEDT, which flux from diazaphosphole framework to the nitrile oxide one are 0.18 e at **TS1**, 0.01 e at **TS2**, 0.05 e at **TS3**, 0.17 e at **TS4** and 0.11 e at **TS4**. Thus, most favourable **TS1** is the most polar one. The corresponding EDT value indicates that this *zw-type* 32CA has polar character (Figure 4).

3.4 ELF topological analysis of the P-C and C-O bond formation along with the 32CA reaction of between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide

In order to characterise the P-C and C-O bond formation along with the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**, a topological analysis of the ELF along the IRC associated with the most favourable *ortho* reaction path was performed. The IRC structures directly

Figure 4. B3LYP/6-31G(d,p) optimised geometries of the TSs involved in the four considered chemo- and regioisomeric reaction paths associated with the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**. Distances are given in angstroms; Å. Distances in THF are given in parentheses.

involved in the formation of the new P-C and C-O single bonds were selected by performing the topological analysis of the ELF for all the structures of the IRC having $2.6 \text{ \AA} > d(\text{P-C}) > 1.9 \text{ \AA}$ and $2.9 > d(\text{O-C}) > 1.6$. The complete ELF analysis is given in the Supplementary Information, while the attractor positions of the ELF basins are given in Figure S1 (Supplementary Information).

Some appealing conclusions can be drawn from this ELF topological study: (i) the relatively high activation energy of the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**, $11.43 \text{ kcal}\cdot\text{mol}^{-1}$ for **TS1**, can mainly be related to the rupture of the $\text{C}\equiv\text{N}$ triple bond of the nitrile oxide framework, which conduct the formation of non-bonding electron density at the N nitrogen and the C1 carbon; (ii) formation of the first P-C single bond takes place at a P-C distance of ca. $1.95 \text{ \AA}$ with an initial population of 1.22 e by sharing part of the non-bonding electron density of the P center and that of the C *pseudo radical* center (see **P5** in Figure 5); (iii) formation of the second O-C single bond takes place at a C-O distance of ca. $1.5 \text{ \AA}$, with an initial population of 0.73 e, by donating some O3 oxygen non-bonding electron density to the C5 carbon (see **P6** Figure 5); and finally (iv) taking into account the IRC values of the structures at which formation of the two single bonds occurs, i.e., **P5** and **P6**, the bond formation can be considered highly asynchronous. Note that the formation of the second O-C single bond begins when the formation of the first P-C single bond is completed by 100%. This behaviour indicates that this 32CA reaction takes place through a non-concerted *two-stage one-step* mechanism.³²

Figure 5. ELF attractor positions for the structures involved in the formation of the P–C and C–O single bonds along the most favourable **TS1** reaction path associated with the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]-diazaphosphole **1** and acetonitrile N-oxide **2**.

4. Conclusions

The 32CA reaction of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** with acetonitrile N-oxide **2** yielding 3,5,7-Trimethyl-5,7a-dihydro-[1,2,3]diazaphospholo[3,4-d][1,2,4]oxaphosphole **3**, has been studied within MEDT through DFT calculations at the B3LYP/6-31(d,p) computational level. Due to the non-symmetry of **1** and acetonitrile N-oxide **2**, up to four competitive reaction paths are feasible. The chemo- and regioisomeric reaction paths involving the two double bonds P–C and C–N of 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** have been studied.

Analysis of the activation energies indicates that this 32CA reaction is completely chemo- and regioselective, under kinetic control. Analysis of the ELF of the selected points of the IRC associates with the formation of the new P–C and C–O single bonds along with the *ortho* reaction path accounts of the *zw-type* reactivity of acetonitrile N-oxide **2**. ELF analysis indicates that the reaction begins with the formation of the P–C single bond involving the phosphor double bond and the C1 carbon of acetonitrile N-oxide **2**, after passing the TS. Formation of the second C–O single bond takes place at the end of the reaction, thus characterizing the mechanism of this 32CA reaction by a non-concerted *one-step two-stage*.

Supplementary Information (SI)

ELF topological analysis of the P–C and C–O bond formation along with the 32CA reaction between 2,5-dimethyl-2H-[1,2,3]diazaphosphole **1** and acetonitrile N-oxide **2**. Tables include B3LYP/6-31g(d,p) total and relative electronic energies, in the gas phase and in THF, and B3LYP/6-31G(d,p) thermodynamic data, computed at 25 °C and 1 atm in THF, for the stationary points involved in the 32CA reaction of 2,4-dimethyl-2H-phosphorus **1** with acetonitrile N-oxide **2**. Supplementary information is available at www.ias.ac.in/chemsci.

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