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Dienophilic reactivity of 2-phosphaindolizines: A conceptual DFT investigation

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Keywords:

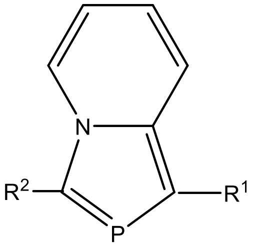
2-Phosphaindolizines; dienophilic reactivity; global hardness; electronic chemical potential; electrophilicity index; nucleophilicity index; Fukui function

Abstract

The >C=P- or –N=P- functionality in 1,3-azaphospholo[1,5-*a*]pyridine, named as 2-phosphaindolizine and its 1- and 3-aza derivatives act as dienophiles and undergo Diels-Alder reaction with 1,3-dienes. However, the dienophilic reactivity is affected by the nature of the substituent groups on the two sides of the σ^2,λ^3-P atom and also by the presence of more nitrogen atom (s) in the five-membered ring. The conceptual density functional theory (DFT) calculations have been used in recent years to predict the reactivity of organic molecules in their reactions. We calculated global hardness (η), global softness (S), electronic chemical potential (μ), electrophilicity (ω) and nucleophilicity (*N*) indices of four classes of 2-phosphaindolizines, on the basis of which their observed relative dienophilic reactivities could be rationalized. Besides, the Fukui functions of the carbon/nitrogen and phosphorus atoms of the >C=P- and –N=P- functionalities were also computed which revealed their hard electrophilic character and accorded well with the dienophilic reactivities observed experimentally. Furthermore, energies and symmetries of the lowest unoccupied molecular orbitals (LUMO) of 2-phosphaindolizines were found to be in conformity with their dienophilic reactivities.

Introduction

In the year 1988, we developed a simple synthetic method for 1,3-azaphospholo[1,5-*a*]pyridine derivative (**1**, R^1=Me, R^2=PhCO) from the reaction of 2-ethyl-1-phenacylpyridinium bromide with PCl_3 and Et_3N, which was named as 2-phosphaindolizine perceiving it to result from a formal CH/P exchange at the 2-position of indolizine (**2**) [1]. Subsequently a good library of these interesting compounds became accessible [1].



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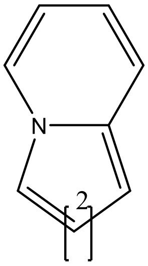

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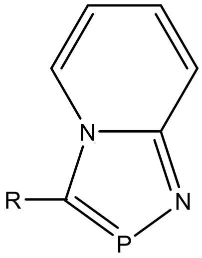
The methodology could be extended successfully to the synthesis of 1,3,4-diazaphospholo[1,2-*a*]pyridine, i.e.1-aza-2-phosphaindolizine (**3**) [2] and 1,2,3-diazaphospholo[1,5-*a*]pyridine, i.e. 3-aza-2-phosphaindolizine (**4**) [3] and 1,2,4,3-triazaphospholo[1,5-*a*]pyridine, i.e. 1,3-diaza-2-phosphaindolizines (**5**) [4]. We succeeded in developing another method involving 1,5-electrocyclization of the initially formed pyridinium alkoxycarbonyl-dichlorophosphinomethylide followed by 1,2-elimination affording 1,3-bis(alkoxycarbonyl)-2-phosphaindolizines [5].



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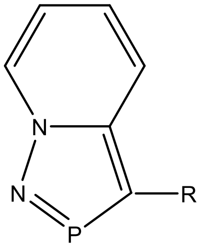

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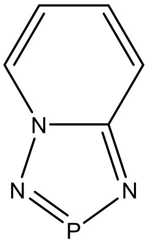

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After having access to a good number of differently substituted derivatives of these four classes of 2-phosphaindolizines, we were motivated to explore their reactivity as they apparently have many active functionalities. In view of the earlier reported results of the Diels-Alders (DA) reaction across the >C=P- functionality in phosphaalkenes [6], phosphaketernes [6], heterophospholes [7], phosphinines [8] and azaphosphinines [9] [A recent review incorporates all these classes 10], we investigated DA reaction across the >C=P- or –N=P- functionality present in these compounds and found that these compounds exhibit quite different dienophilic reactivity towards 2,3-dimethyl-1,3-butadiene (DMB). 2-Phosphaindolizines having electron-withdrawing groups (EWG) both at the 1 and 3-positions, namely 1,3-bis(ethoxycarbonyl)-1,3-azaphospholo[1,5-*a*]pyridine (**1**: R^1 = R^2 = COOEt) and its isoquinoline analogue, react with DMB and isoprene to give [2+4] cycloadducts, in the latter case, regioselectivity [11]. However, 2-phosphaindolizine having EWG at 3-position only, namely 3-ethoxycarbonyl-1-methyl-2-phosphaindolizine (**1**:R^1= Me, R^2 = COOEt) did not undergo DA reaction with DMB alone or in the presence of sulfur even on refluxing in toluene [12] and could be accomplished only in the presence of Lewis acid catalyst, namely ethylaluminium dichloride [13]. Furthermore, on carrying out the reaction of **1** (R^1=Me, R^2=COOMe, COOEt, $COOMe_3$) with DMB in the presence of O-menthoxyaluminium dichloride catalyst, generated in situ, complete diastereoselectivity was observed.

The DA reactions of 1-aza-2-phosphaindolizine (**3**) with DMB and isoprene occurred at r.t., though slowly and were speeded up by the use of sulfur or selenium which oxidized the phosphorus atom of the initially formed product thereby pushing the reaction in the forward direction [14].

The difference in the reactivities of two classes of 2-phosphaindolizines namely the 2-phosphaindolizine substituted by the EWG at 3-position only (**1**, R^1=Me, R^2=CO_2Me) and substituted by EWGs both at the 1- and 3- positions (**1**, R^1 =R^2=CO_2Me) could be rationalized on the bases of the DFT calculations at the B3LYP/6-31G (d,p) level wherein it was revealed that the nitrogen lone-pair is transferred effectively into the azaphospole ring. In **1** (R^1=Me, R^2=CO_2Me) the EWG at the 3-position accentuates this effect further with the result that the >C=P- functionality becomes electron-rich which does not undergo DA reaction with an electron-rich diene like DMB. However in the case of **1**_(R^1=R^2=CO_2Me), the EWG at the 1-position acts as electron-sink between the nitrogen lone-pair and the >C=P- functionality with the result that the latter retains its electron-deficient character and undergoes DA reaction with DMB (Figure1) [15].

Figure1. Transfer of nitrogen lone-pair in 2- phosphaindolizines .

The DFT based on the Hohenberg-Kohn theorems and later on the Kohn-Sham approximation made it possible to study progress of the organic reaction with manageable computational costs [16, 17]. Parr and co-worker [18] developed "Conceptual DFT", a sub field of DFT which makes it possible to calculate various reactivity descriptors, such as electrochemical potential, electrophilicity and nucleophilicity indices, global hardness, electronegativety, etc.

The concept of hard-soft acid-base (HSAB) was used to explain the reactivity of the organic molecules towards electrophilic and nucleophilic reagents [19]. Thus a quantitative descriptor, the Fukui function was defined as

$f^{+}(r) = \rho(N+1)(r) - \rho N(r)$ for nucleophilic attack (1)

$f^{-}(r) = \rho N(r) - \rho(N-1)(r)$ for electrophilic attack (2)

where $\rho_{N+1}(r)$, $\rho_{N}(r)$ and $\rho_{N-1}(r)$ are the electron densities at a point r in the system with N+1, N and N-1 electrons, respectively, all with the ground state geometry of the N electron system.

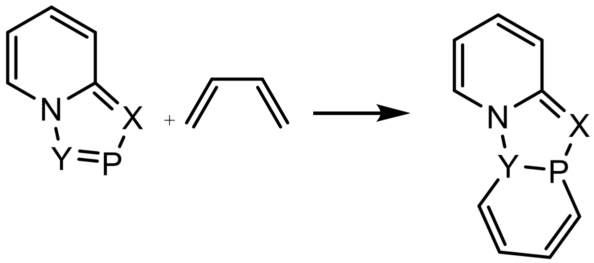
It was concluded that the regions of a molecule with a large Fukui function is chemically softer than the regions where the Fukui function is small. Thus by invoking HSAB principle it becomes possible to predict the behavior of a particular site in the molecule towards hard or soft reagent [19].

Yang and Mortier [20] suggested the use of the gross charge (qr) at a particular atom r in a molecule obtained from the Mulliken Population Analysis (MPA) for the calculation of the condensed Fukui function (f(r)) at that atom. The condensed Fukui function using MPA often have negative values and in this context, use of Hirshfeld Population Analysis (HPA) based on the stock-holder idea was recommended [21,22].

We report herein different conceptual DFT descriptors of four classes of 2-phosphaindolizines and attempt to compare the dienophilic reactivities of the >C=P- or –N=P- functionality present in these compounds towards 1,3-butadiene.

Results and Discussion

We investigated the following model DA reactions (Scheme 1) at the DFT (B3LYP/6-31+G (d)) level.



6 **7** **8**

6	**Aa**	**Ab**	**Ac**	**Ad**	**Ba**	**Bb**	**Ca**	**Cb**	**D**
X	CH	C-CO$_2$Me	CH	C-CO$_2$Me	N	N	CH	C-CO$_2$Me	N
Y	CH	CH	C-CO$_2$Me	C-CO$_2$Me	CH	C-CO$_2$Me	N	N	N

Scheme 1. Model DA reactions of 2-phosphaindolizines with 1,3-butadiene computed at the B3LYP/6-31+G(d) level

The values of the energies of the frontier molecular orbitals (FMOs) global hardness (η), global softness (S), electronic chemical potential (μ), electrophilicity (ω) and nucleophilicity (*N*) indices of 2-phosphaindolizines (**6**) and 1,3-butadiene (**7**) are given in Table1.

Table1. Energies of frontier molecular orbitals, global hardness, global softness, electronic chemical potential, electrophilicity and nucleophilicity indices of 2-phosphaindolizines and 1,3-butadiene.

S.No 6	**E$_{HOMO}$ (eV)**	**E$_{LUMO}$ (eV)**	**Global hardness (η eV)**	**Global softness (S eV)**	**Electronic chemical potential (μ eV)**	**Electrophilicity index (ω eV) x 10^2**	**Nucleophilicity index^c (N eV)* x 10^2**
Aa	-0.211	-0.025^a	0.079	6.361	-0.132	0.110	-
Ab	-0.222	-0.033^a	0.076	6.548	-0.146	0.139	-
Ac	-0.221	-0.068	0.077	6.510	-0.144	0.135	-
Ad	-0.230	-0.080	0.075	6.644	-0.155	0.160	-
Ba	-0.232	-0.001^b	0.084	5.952	-0.148	0.128	-
Bb	-0.242	-0.080	0.081	6.184	-0.161	0.160	-
Ca	-0.231	-0.042^a	0.085	5.899	-0.146	0.125	-
Cb	-0.240	-0.078	0.081	6.161	-0.159	0.156	-
D	-0.256	-0.052^a	0.091	5.494	-0.164	0.148	-
7	-0.242	-0.042	0.100	5.000	-0.142	-	0.104

[a] LUMO +1 as LUMO is not of proper symmetry; [b] LUMO +3 as LUMO is not of proper symmetry

[c] with respect to TCNE = E(HOMO) = -0.346

2-Phosphaindolizines and 1,3-butadiene are soft electrophiles and nucleophile respectively and in accordance with the HSAB principle, they are expected to react. In the series 6A of 2-phosphaindolizines, the softness decreases in the order 6Ad > 6Ab > 6Ac > 6Aa. No representatives of 6Aa and 6Ab have been prepared so far. Thus, 6Ad is expected to undergo DA reaction faster than 6Ac which is in conformity with the reported results; the former reacts with DMB without the aid of a catalyst [11] whereas the latter undergoes DA reaction only in the presence of a catalyst [13]. However, it may be noted that although 6Bb and 6D are less soft than 6Ac, they undergo DA reaction without the aid of a catalyst [14]. As discussed later, it can be rationalized on the basis of the local hardness represented by Fukui function.

The electronic chemical potential (μ) is another useful descriptor that reveals efficacy of charge transfer from the species of higher chemical potential to a species with lower chemical potential [23]. The reactivities of two substrates A and B with the same reagent C can be compared on the basis of the relative values of ΔμAc and ΔμBC, greater the value of the Δμ, faster will be the reaction. In this context, it may be noted that except 6Aa, i.e. unsubstituted 2-phosphaindolizine, the electronic chemical potentials of other 2-phosphaindolizines are smaller than the electronic chemical potential of 1,3-butadiene indicating the possibility of an effective charge transfer from the latter to the former. Furthermore the gap between the chemical potentials of 2-phosphaindolizines and 1,3-butadiene decreases in the order 6Ad > 6Ab >6Ac; 6Bb > 6Ba; 6Cb > 6Ca. This order is similar to the one derived on the basis of global hardness discussed earlier and is also in conformity with the experimental results.

The electrophilicity (ω) [24] and nucleophilicity (N) [25] indices are other useful descriptors that explain relative reactivities of molecules in chemical reactions [26]. The electrophilicity indices of 2-phosphaindolizines also decrease in the same order as observed on the basis of global hardness and electronic chemical potential. Furthermore, the electrophilicity index of 6D (0.148) is close to that of 6Cb (0.156) and like 6Cb, it is expected to undergo DA reaction with 1,3-diene without the aid of a catalyst, a fact in conformity with the experimental results.

Concept of local hardness/softness

Fukui function analysis

As discussed earlier, the descriptor Fukui function was developed to determine the hard/soft character of the reactive site in a molecule [19-21]. The Fukui functions at the carbon/nitrogen and phosphorus atoms of the >C=P- or -N=P- functionality of 2-phosphaindolizines calculated from the Mulliken and Hirshfeld charges are given in Table 2.

Table 2: Fukui functions at the Y (C or N) and phosphorus atoms of the >Y=P- functionality of 2- Phosphaindolizines (dienophile).

Compounds 6	**Fukui function $f^+(r)$ for nucleophilic attack** **Mulliken**	 **Hirshfeld**	**Fukui function $f^-(r)$ for electrophilic attack** **Mulliken**	 **Hirshfeld**
Aa	C -0.086 P -0.276	C-0.162 P-0.186	-	
Ab	C-0.019 P -0.269	C -0.042 P -0.184	-	
Ac	C -0.206 P -0.130	C-0.039 P-0.124	-	
Ad	C - 0.154 P -0. 112	C -0.025 P -0.105	-	
Ba	C -0.057 P -0.296	C -0.048 P -0.222	-	
Bb	C -0.008 P -0.382	C -0.044 P -0.305	-	
Ca	N -0.058 P -0.321	N -0.054 P -0.222	-	
Cb	N -0.042 P -0.298	N -0.049 P -0.217	-	
D	N(9) -0.047 P(8) -0.361	N(9) -0.052 P(8) -0.278	-	
7	-	-	C(1) -0.166 C(4) -0.191	C(1) -0.186 C(4) -0.197

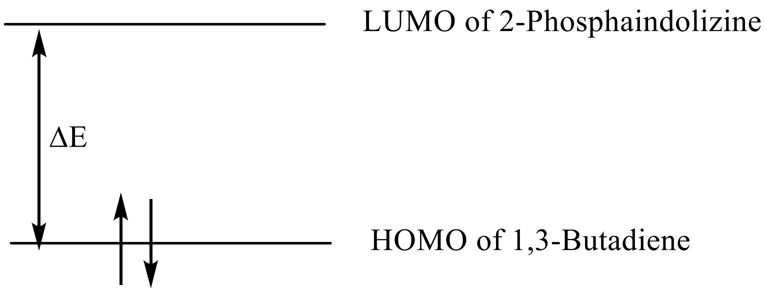
A close look at the Fukui functions calculated from the Mulliken and Hirshfeld charges reveals that they follow almost a similar pattern; in view of this, our further discussion is based on the Fukui functions calculated from the former. As the P atom is common in the >C=P– and –N =P – functionalities, we concentrate on the relative values of the Fukui functions of the P atom in different 2-phosphamdolizines.The value of the fukui functions of the P atom in different series of 2-phosphaindolizines decrease in the order:

Ad > Ac > AB > Aa;   Ba > Bb;   Cb > Ca.

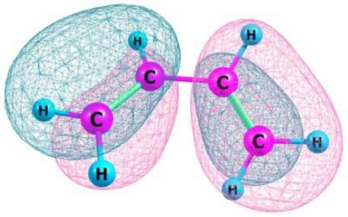
Except the series, Ba > Bb, this order is similar to those obtained on the basis of the other descriptors discussed earlier. It may be noted that values of the Fukui functions of the P atom in D (-0.361) and Bb (-0.382) are comparable with that in Ca indicating their comparable reactivities towards the DA reaction with 1,3-butadiene, i.e. they are expected to undergo the DA reaction without the aid of a catalyst.

Frontier molecular orbital (FMO) treatment of the DA reaction

The FMOs of a molecule are very important parameters to reveal its reactivity towards a reagent [27]. In the DA reaction of 2-phosphaindolizines with 1, 3-butadiene, the HOMO of the latter will interact with the LUMO of the former and the energy gap (ΔE) between the two will give an indication about the reactivity of 2-phosphaindolizine.

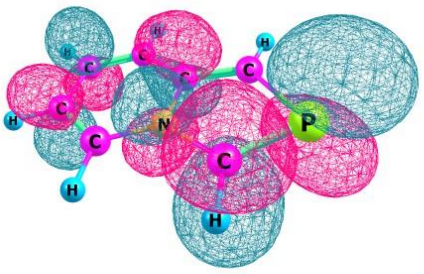


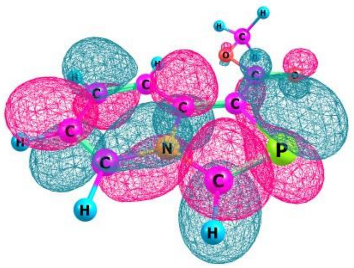
The HOMO of 1, 3-butadiene (Ψ_2) and LUMOs of different 2-phosphaindolizines are given in Figure 2. It may be mentioned that for Aa, Ab, Ba, Ca and D, the respective LUMOs were not found to be of the appropriate symmetry. Instead, LUMO +1 for Aa, Ab, Ca and D and LUMO +3 for Ba have the required symmetry.

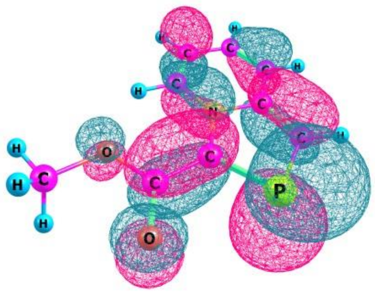


HOMO

1,3-Butadiene

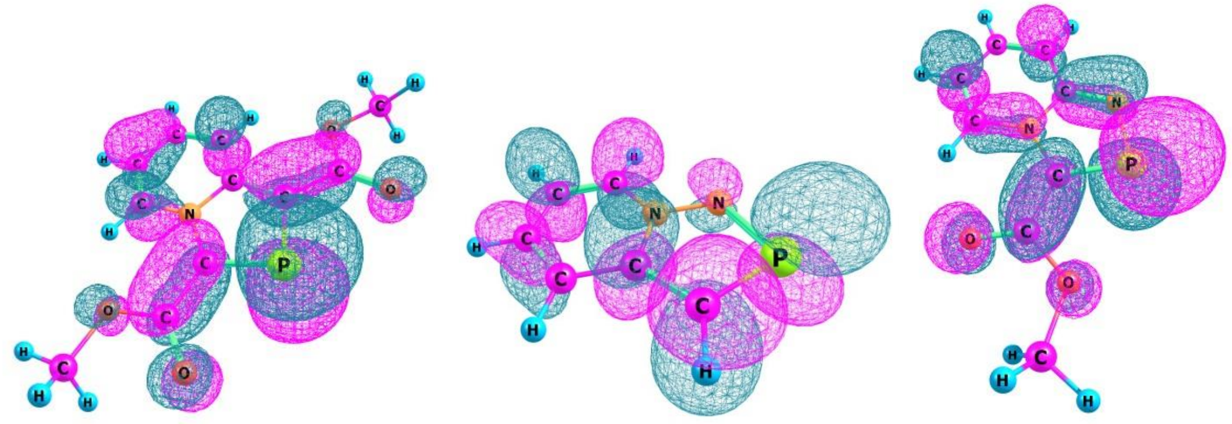






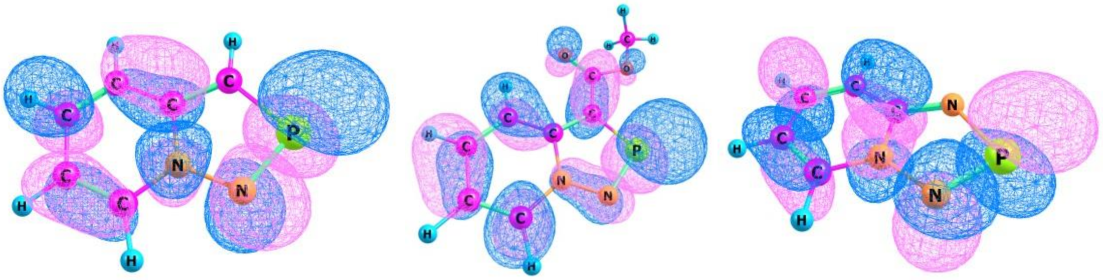
LUMO + 1 **LUMO + 1** **LUMO**

Aa **Ab** **Ac**



LUMO **LUMO + 3** **LUMO**

Ad **Ba** **Bb**



LUMO + 1 **LUMO** **LUMO + 1**

Ca **Cb** **D**

<u>Figure</u> 1. Kohn-Shan HOMO of 1,3-butadiene and LUMOs of 2-phosphaindolizines computed at the B3LYP/6-31+G(d) level.

A close look at the energies of the LUMOs (or LUMO +1 for Aa, Ab, Ca, D and LUMO +3 for Ba) reveals that they increase in the following order

Ad < Ac < Ab < Aa

In view of this, the reactivity of 2-phosphaindolizines towards DA reaction with 1,3-butadiene is expected to chane in the order: Ad > Ac > Ab > Aa.

Similarly the order of reactivity in the other two classes would be

Bb > Bc ; Cb >Ca.

These orders of reactivities are almost similar to those obtained on the basis of other reactivity descriptors discussed earlier.

Conclusion

The reactivity descriptors, namely global hardness/softness, electronic chemical potential, electrophilicity and nucleophilicity indices as well as the Fukui functions computed from the conceptual DFT calculation at the B3LYP/6-31+G (d) level could be used successfully to rationalize the experimentally observed dienophilic reactivites of four classes of 2-phosphaindolizenes . The energies of the LUMOs (or in some cases LUMO + 1 or LUMO + 3) of 2-phosphaindolizines with respect to the energy of HOMO of 1,3-butadiene were also found in accordance with their relative dienophilic reactivites. Thus, conceptual DFT descriptors can be advantageously used to predict the reactivities of the organophosphorus compounds.

Computational methods

All calculations were done using *Gaussian 16* suite of programs [28].

All geometries were optimized using a hybrid of Becke 3 and LYP correlation functional [30] with Gaussian basis sets 6-31+G (d).

Frequency calculations were done at the same level to determine zero-point correction and to characterize energy minimum with no imaginary frequency.

Chemical reactivity descriptors were calculated as follows:

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

$$S = \frac{1}{2\eta}$$

$$\mu = \frac{E_{HOMO} + E_{LUMO}}{2}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$$N = E_{HOMO}\,(\text{nucleophile}) - E_{HOMO}\,(\text{TCNE})$$

$$f^{+}(r) = qr_{(N+1)} - qr_{(N)} \quad [\text{nucleophilic attack}]$$

$$f^{-}(r) = qr_{(N)} - qr_{(N-1)} \quad \text{[electrophilic attack]}$$

Supporting Information

Cartesian coordinates of the geometries optimized (Table S1) at the B3LYP/6-31+G (d) level.

Acknowledgements

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