

## P-C bond oxidation

## Oxidation of a P-C bond under mild conditions

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**Abstract:** The reactivity of phosphenium dication  $[(Ph_3P)_2C-P-NiPr_2]^{2+}$ , **1**<sup>2+</sup>, towards pyridine N-oxide (O-py) has been investigated. The resulting oxophosphonium dication  $[(Ph_3P)_2C(NiPr_2)P(O)(O-py)]^{2+}$ , **2**<sup>2+</sup>, was surprisingly stabilized by a less nucleophilic O-py ligand instead of pyridine (py). This compound was then identified as an analogue of the elusive Creigee intermediate as it underwent oxygen insertion into the P-C bond via a mechanism usually observed for Baeyer-Villiger oxidations. This oxygen insertion appears to be the first example of a Baeyer-Villiger oxidation involving O-py.

It is generally accepted that organic oxidation reactions are considerably less developed than the corresponding reductions.<sup>[1,2]</sup> Even though insertion of an oxygen atom into C-H or C-C bonds are mainly recognized as oxidations,<sup>[2]</sup> oxygen insertions into C-Si (Fleming-Tameo-Kumada oxidations<sup>[3]</sup>) and C-B (Brown oxidations<sup>[4]</sup>) bonds are also known. With respect to C-P bond oxidation reactions only a handful of examples have been reported and all of them involved phosphorus heterocycles containing ringstrained P-C bonds (Scheme 1).<sup>[5]</sup> These reactions also required the use of highly reactive *m*-chlorperoxybenzoic acid (*m*CPBA) or hydrogenperoxide (under elevated temperatures) as oxygen sources. Herein, we wish to report oxygen insertion, under mild conditions, into a P-C bond via a mechanism that resembles Baever-Villiger (BV) oxidations.<sup>[6]</sup> Identification of a key intermediate, that could be considered as a heavy analogue of the elusive Criegee intermediate,<sup>[7]</sup> was also achieved.

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**Scheme 1.** Typical (but simplified) examples of stained phosphorus heterocycles undergoing P-C bond oxidation (see ref.<sup>[5]</sup>).

Recent work in our group has been focused on the reactivity of nucleophilic carbone molecules towards various phosphine precursors.<sup>[8]</sup> The highlight of this work was the synthesis of twocoordinate phosphenium dication [(PPh<sub>3</sub>)<sub>2</sub>C-P-NiPr<sub>2</sub>]<sup>2+</sup> (1<sup>2+</sup>, Scheme 2a) which was also shown to insert into O-H bonds. [8a,b] These particular results indicated that 12+ was quite oxophilic and, thus, we decided to examine its reactivity towards pyridine N-oxide (O-py). As it occurred with the presence of other oxygen donors<sup>[8b]</sup> (e.g.  $H_2O$ , MeOH), the usual yellow color of  $1^{2+}$  in DCM instantaneously disappeared upon addition of O-py. Even though the crude reaction mixture contained at least three different products (according to <sup>31</sup>P NMR spectroscopy), we managed to crystalize the major product (this product represents about 50% of all species detected in the initial reaction mixture), identified by  $\delta_{P}$ signals at ~ 42 and 24 ppm, by layering the reaction mixture with hexane. Single crystal X-ray analysis of this sample revealed that, predictably, we have obtained an oxophosphonium dication  $(2^{2+},$ Scheme 2a).<sup>[9]</sup> However, we were somewhat surprised that this dicatacion was stabilized by a molecule of O-py<sup>[10]</sup> and not pyridine (py) that was produced with oxidation of the phosphorus centre. This observation was quite unusual considering that (i) a similar reaction involving cycling phosphenium cation [(CH<sub>2</sub>)<sub>2</sub>(N- $Dip)2P]^{\star}$  ,4  $^{\star}$  , (Dip = 2,6- $^{i}Pr_{2}\text{-}C_{6}H_{4})$  yielded pyridine-stabilized oxophosphenium cation 5<sup>+</sup> (Scheme 2b)<sup>[11]</sup> and (ii) py ( $pK_a = 5.2$ ) is much more basic than O-pv ( $pK_a = 0.79$ ). It is plausible that steric factors and/or oxophilic nature of the hypothetically "naked" oxophophonium dication  $[(PPh_3)_2C(NiPr_2)P=O]^{2+}$ , 2a<sup>2+</sup>, prevented the coordination of pv and/or favoured the coordination of a less sterically demanding and oxygen-containing O-py ligand. Nevertheless, the formation of  $2^{2+}$  is another example that reactivity of dication 1<sup>2+</sup> towards O-donors is different with respect to its analogous phosphenium monocations.<sup>[10b]</sup>



Scheme 2. Reactivity of (a) phosphenium dication  $1^{2*}$  and (b) monocation 4\* towards pyridine N-oxide (O-py) leading to oxygen insertion into a P-C bond in the former case.

The molecular structure of 2<sup>2+</sup> (Figure 1) appears to be the first example of cyrstallographically elucidated phosphorus compound that contains an O-py ligand.<sup>[12]</sup> The P1-O2 dative bond nature was supported by its distance (1.711(11) Å) and the value for the Wiberg bond index (0.46) obtained by Density Functional Theory (DFT) caluclations.<sup>[13]</sup> Computational analysis was also performed on the hypothetical O-py-free analogue of 2<sup>2+</sup> i.e. 2a<sup>2+</sup>. The removal of the O-py ligand resulted in expected shortening of all the bond distances that the central P forms with the neighbouring atoms.<sup>[14]</sup> The same observation was also described for 5<sup>+</sup> and its base-free analogue.<sup>[11]</sup> Even though the formal charge of  $2^{2+}$  is greater than in the case of 5<sup>+</sup>, it did not translate in vastly different values for the NBO partial charges observed for the central P=O fragment of these species. In fact, the P=O fragment for 5<sup>+</sup> carries a slightly more positive (+ 1.332) partial charge than the same fragment for  $2^{2+}$  (+ 1.257). This could be due to electron density overcompensation by the carbone ligand and/or difference in the electronegativity among the atoms in these two molecules that surround the central P.



**Figure 1.** Molecular structures for  $2^{2+}$  and  $3^{2+}$ . Apart from the Ph rings on the carbone substituent all atoms have been drawn at 50% probability. Hydrogen atoms, solvent molecules and counterions (SbF<sub>6</sub>) for both molecules while the second molecule in the asymmetric unit for only  $2^{2+}$  have been omitted for clarity.

It was not immediately evident but  $2^{2*}$  was in fact a key intermediate for the formation of a product that could be detected in the original reaction mixture after few hours. In fact, after isolation of  $2^{2*}$  it was possible to follow its conversion to this new product by <sup>31</sup>P NMR spectroscopy. Although it takes several days at room temperature, the full conversion could be achieved in about four hours if a DCM solution containing **2**<sup>2+</sup> was heated to 50°C (Figure 2). Intriguingly, the set of  $\delta_P$  signals at ~ 22 and 6 ppm assigned to this new product did not show the usual P-P coupling observed in all the compounds that contain a P-C<sub>(carbone)</sub> bond.<sup>[8]</sup> This implied the absence of this particular bonding interaction presumably caused by insertion of an atom or a group of atoms into the bond. Indeed, the single crystal X-ray analysis (Figure 1) of this new product revealed that an oxygen atom inserted into the P1-C1 bond of **2**<sup>2+</sup> to form **3**<sup>2+</sup> (Scheme 1a) which also contained a py instead of an O-py ligand.



Figure 2. Conversion of 2<sup>2+</sup> into 3<sup>2+</sup> at 50°C as followed by <sup>31</sup>P NMR spectroscopy.

Computational studies<sup>[13]</sup> were undertaken to determine the most probable mechanism for this transformation. A transition state ( $E_a = 24$  kcal/mol, Figure 3) has been identified suggesting that (i) the mechanism is concerted and (ii) the overall process could be analogous to Baeyer-Villiger (BV) oxidations.<sup>[8]</sup> The correct mechanism for Beayer-Villiger oxidations, proposed by Criegee<sup>[15]</sup>, was established by the reaction of O<sup>18</sup>-labelled benzophenone and perbenzoic acid.<sup>[16]</sup> In the proposed mechanism the peroxy acid attacks the carbonyl group and after intramolecular proton shift it forms the Criegee intermediate (Scheme 3b). Then, in a quasi-concerted step the initial carbonyl group is re-formed, "one substituent migrates from the carbonyl carbon atom to the partially positive charged oxygen atom" <sup>[6a]</sup> and the peroxy acid's O-O bond is heterolytically cleaved.<sup>[6,16]</sup>



Figure 3. Computationally determined transition state for transformation of  $2^{2\star}$  into  $3^{2\star}.$ 

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Scheme 3. (a) Established mechanism for the Bayer-Villiger oxydations; (b)



computationally determined mechanism for transformation of 22+ to 32+.

According to the computational studies a very similar mechanism can be proposed for the formation of  $3^{2+}$  (Scheme 3b). Apart from having a phosphine oxide instead of a carbonyl group, the major differences between the Criegee intermediate and 22+ are protonation of this carbonyl group and the nature of the migratory groups. The absence of the phosphine oxide protonation is not surprising considering the non-protic nature of the O-py oxidant. On the other hand, the electronic (ylide) and steric (see below) nature of the migratory group in  $2^{2+}$  seems to be crucial for the overall P-C bond oxidation. According to the NBO analysis it is possible to locate a lone pair (confined within a p orbital <sup>[14]</sup>) on C1 which is expectedly a bit delocalized over the surrounding atoms/bonds as its electron population is 1.74e. The absence of this lone pair in the transition state implied its involvement in the formation of the initial C1-O2 bonding interaction. Indeed, according to the NBO analysis this initial interaction is formed by a p-p atomic orbital overlap. In other words, the lone pair on C1 attacks O2 resulting in the C1-O2 bond formation and heterolytic cleavage of the O2-N1 bond (Scheme 3b). The initial  $C1 \rightarrow O2$ attack seems possible as O2 should be more electrophilic when coordinated to the electron deficient P atom in  $2^{2+}$  with respect to the free molecule. Thus, the presence of a lone pair in  $2^{2+}$ , which actually "re-forms" in the final product, [14] seems to be one of the key reasons for the observed facile O insertion into P1-C1. Furthermore, as required by the BV mechanism the carbone/yilde substituent (the migrating group in this case) is positioned antiperiplanar to the O-N bond in the transition state.<sup>[6b]</sup> It is also noteworthy that the mechanism for the P-C bond oxidation for bicyclic compounds included in Scheme 1 is virtually identical to the BV oxidations of lactones and ketones.<sup>[5]</sup>

In view of the abovementioned experimental and theoretical details the analogy between this P-C bond and the usual BV oxidations is quite evident even though a yilde is the migratory group and the typical C=O group has been replaced by a P=O group. The relationship between the Creigee intermediate and  $2^{2+}$  might not be as apparent but in both cases the migratory group "attack" and simultaneous O-X (X = O for BV; X = N for our case) heterolytic cleavage steps are almost indistinguishable. The only difference, apart from protonation of the carbonyl group, seems to be that in our case the lone pair on C1 initiates the attack while this is absent in the Creigee intermediate. However, as already mentioned, the presence of a lone pair seems to contribute in lowering the activation energy of the oxygen insertion step. Therefore, compound  $2^{2+}$  could be considered as a heavy analogue of the Criegee-like intermediate<sup>[7]</sup> while the overall

process should be viewed as the first example of an oxidation reaction whose mechanism resembles a BV oxidation in which pyridine N-oxide was used as the oxidant.<sup>[6]</sup>

As previously indicated the formation of  $\mathbf{2^{2+}}$  was somewhat surprising considering that a less basic O-py ligand stabilized the oxophosphonium dication even though more basic py was present in the solution. We attributed this observation to steric factors and/or oxophilic nature of 2a2+ as O-py appeared to be less sterically encumbered than py and it contains an O-donor atom.<sup>[17]</sup> Thus, we wanted to determine whether the steric strain of 22+ played an important role in the overall transformation of 2<sup>2+</sup> to 3<sup>2+</sup>. In fact, according to the solid state analysis of these two dications the O1-P1-N1 angle increased from 112.6(7)° for 22+ to 118.6(1)° for 3<sup>2+</sup> suggesting alleviation of the steric strain after the oxygen insertion. This is further supported by the fact that (i) the P1-O1 (1.456(10) (1.454(10)) and 1.451(2) Å for 2<sup>2+</sup> and 3<sup>2+</sup>, respectively) and P1-N1 (1.617(16) (1.54(2)) and 1.611(3) Å for 2<sup>2+</sup> and 3<sup>2+</sup>, respectively) bond lengths, (ii) the orbital makeup (NBO analysis) of these bonds (iii) the electronic population of the C1 lone pair (1.70 and 1.71e for  $2^{2+}$  and  $3^{2+}$ , respectively) were virtually unchanged during the oxidation.<sup>[14]</sup> This evidence would suggest that electronic effects of the ligands surrounding the central P were highly unlikely responsible for the observed O1-P1-N1 angle widening. Thus, these observations indicated that the insertion of an O atom into P1-C1 bond of 22+ has alleviated some of the steric strain presumably because the bulky carbone ligand has been "pushed away" from the central P. To quantify the energy released by diluting the steric congestion the carbone coordinates from the optimized structures for 2<sup>2+</sup> and 3<sup>2+</sup> have been extracted and their respective energy computed without any further optimizations. The energy difference of 7.0 kcal/mol between the two fixed carbone structures has been obtained. If we assume that the carbone ligand in 2<sup>2+</sup> has been sterically strained by this amount of energy three conclusions could be formulated. The first, the steric strain does not have any effect on the outcome of the overall oxidation reaction considering it is exergonic by 31.8 kcal/mol. The second, this steric strain appears to considerably increase the reaction rate because adding 7.0 kcal/mol to the Ea would increase the activation temperature by about 25%. In other words, the reaction would not have happened at room temperature (20°C or 293K) and heating to about 90°C (or 366K) would have been required. Despite the fact there is a limited amount of information regarding the quantification of steric strain on reaction rates, many example exist in which various steric factors were identified as the main reason in enhancing the corresponding reaction rates.<sup>[18]</sup> Lastly, this steric strain could be in part responsible for preventing the coordination of a more nucleophilic but more sterically demanding py ligand to  $2a^{2+}$  in favour of O-py to form  $2^{2+}$ . However, the established oxophilicity of these cationic species might play a role in favouring the coordination of the oxygen containing ligand.

In conclusion, oxygen insertion into a P-C bond (using mild reaction conditions) has been demonstrated. According to computational analysis the mechanism for this insertion resembled Baeyer-Villiger (BV) oxidations. The key intermediate has also been identified which could be considered as a Criegee-like intermediate which is usually not observed in BV insertions. Lastly, the steric strain in this intermediate greatly lowered the activation energy but it did not influence the final outcome of the process.

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# **Keywords:** P-C bond oxidation • Baeyer-Villiger oxidation • Creigee intermediate • phosphenium dication • main-group chemistry

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### **Entry for the Table of Contents**

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