RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

ARTICLE TYPE

Kinetics and mechanism of PPh₃ oxygenation with ³O₂ catalyzed by a 1,3,2-oxazaphosphole as flavin mimic

I. Bors, J. Kaizer and G. Speier∗

An 1,3,2-oxazaphosphole picks up triplet dioxygen in 1:1 stoichiometry like flavin organic co-factors. It catalyzes the oxygenation of triphenylphosphine to triphenyl
10 **phosphine oxide. The reaction obeys an overall third order rate equation. In a radical pathway organic hydroperoxide is formed from the catalyst and ³O₂, which oxygenates PPh₃ similar as flavin cofactors.**

The oxygenation/oxidation of organic substrates with triplet
15 dioxygen, as a primary oxidant, is a desirable way for economical and environmental[1] reasons. However, spin restriction[2] and thermodynamic[3] burden hampers its reactivity. In order to circumvent these problems transition metal complexes[4] and energy-rich organic compounds[5] (co-factors such as pterins[6] and
20 flavins[7] in biology) are necessary to activate dioxygen for these reactions.

We found earlier that 1,3,2-oxazaphospholes can easily be prepared reacting quinone monoimines with triphenylphosphine
25 in a [4+1] electrocyclic reaction, or quinones with triphenylphosphine in the presence of ammonia in a sealed tube in good yield.[8] Later to our surprise we observed that 1,3,2-oxaza phospholes react with triplet dioxygen in a stoichiometry of 1:1 (SFig. 1). In different solvents the same amount of O₂ was taken
30 up with various velocities (SFig. 2). The peroxide formed is not stable at room temperature. Iodometric titration of the oxygenated solutions of **3** resulted in peroxide content 10-30% after immediate titration. This O₂-uptake is very similar to flavin models in which *N,N,N*,-3,5,10-trialkylated flavins (**1**) were used
35 and it was demonstrated that in their reaction with ³O₂ flavin hydroperoxides (**2**) can be generated.[9] We assumed that 2,2-dihydro-2,2,2-triphenylphenanthro[9,10d]1,3,2λ⁵-oxaza phospholes (**3**) give in a similar manner alkylhydroperoxides (**4**) (Scheme 1), which can oxygenate/oxidase various singlet organic
40 compounds.
Kinetic studies resulted in an overall third order rate equation, reaction rate = k_{obs}[catalyst][PPh₃][O₂] with a k_{obs} value of

$39.10 \pm 0.82 \times 10^{-2}$ $M^{-2}s^{-1}$. Time course of the reaction is shown in Fig. 1, which was measured by UV/Vis spectroscopy[10] at 260 nm
45 (SFig. 3). The dependence on the triphenylphosphine and dioxygen concentrations showed also first order using reaction rate *vs.* initial concentrations of PPh₃, catalyst (**3**) and O₂ plots (SFig. 4, 5 and 6).
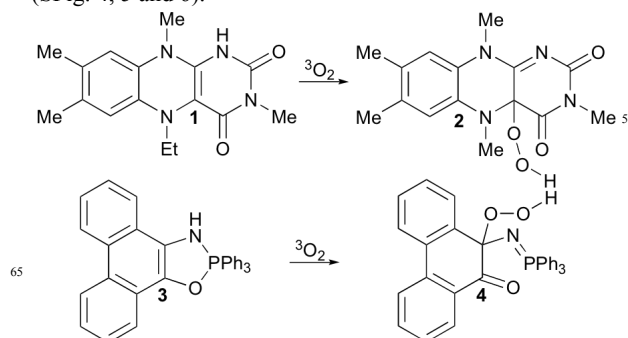
Scheme 1. Similarities in flavin models (**1**) and 2,2-dihydro-2,2,2-triphenylphenanthro[9,10d]1,3,2λ⁵-oxazaphosphole (**3**) reactions with ³O₂
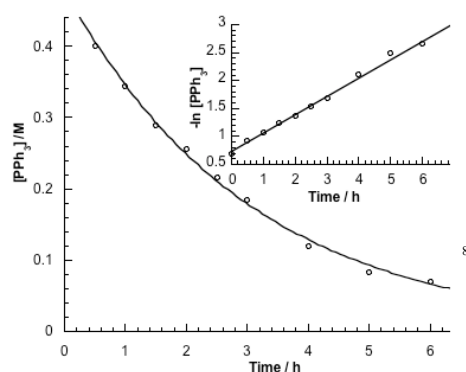75 to give hydroperoxides **2** and the hypothetical hydroperoxide **4**.

90 **Figure 1.** Time course of the oxygenation of PPh₃ catalyzed by **3**. Temperature 80°C and 1 bar O₂ pressure, [PPh₃]ₒ = 0.5 M, [**3**] = 2.5×10⁻³ M, 20 mL DMF. TON = 160, TOF = 5.7 h⁻¹.

Labeling experiments using $^{18}O_2$ clearly demonstrated that the *O*-atom of triphenyphosphine oxide originates from O_2. The $\nu(P=O)$ frequences being 1190 and 1153 cm^{-1} for $^{16}OPPh_3$ and $^{18}OPPh_3$ (SFig. 7).[11] The activation parameters of $E_a = 31.6\pm2.9$ kJ mol^{-1} $\Delta H^{\ddagger} = 28.7\pm2.9$ kJ mol^{-1}, $\Delta S^{\ddagger} = -174\pm8$ J mol^{-1} K^{-1} of the catalytic reaction suggest that the transition state is very crowded and the small value for the activation energy indicates the easiness of the reaction.

In order to clear some points of the reaction mechanism we mesaured possible radicals formed during the catalytic reaction. Fig. 2 shows that a well-resolved spectrum of the organic radical
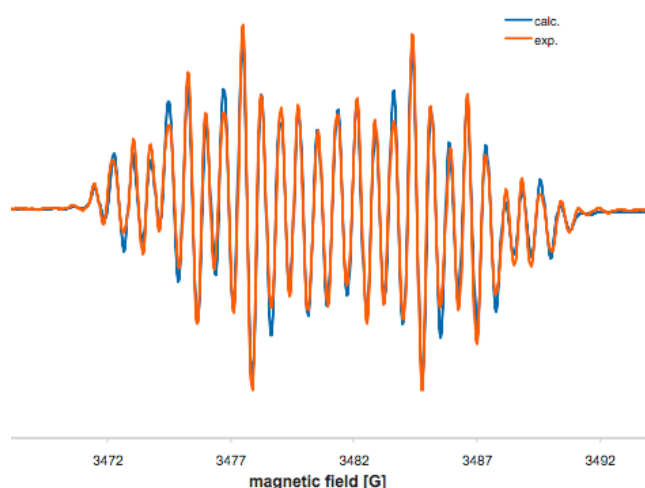

Figure 2. The EPR spectrum of **7**. Blue = measured, red = simulated, g = 2.0032, $a_P = 6.90$, $a_N = 1.10$, $a_{H1-7} = 2.35, 2.26, 2.11, 0.85, 0.79, 0.73, 0.67$ G.[12]

7 could be found. This red-colored, persistent radical could also be generated from the reaction of the 1,3,2-oxazaphosphole (**3**) and TEMPO (2,2,6,6-tetramethylpyperidin-1-yl)oxyl). It is non-reactive against dioxygen at room temperature for days. However, it reacts fast with KO_2 with diminishing red color giving a greenish solution (SFig. 8). On the other hand added triethylamine accelerated the reaction rate (SFig. 9), which suggest that deprotonation accelerates the reaction. According to these kinetic data and spectroscopic findings we propose a mechanism as shown in Scheme 2. According to that the 1,3,2-oxazaphosphole (**3**) is in equilibrium with the iminophosphorane tautomer **5**. This is then deprotonated either by triphenylphosphine or added triethylamine resulting in the deprotonated iminophosphorane (**6**). Triethylamine added in 1:1 molar ratio to the catalyst makes the reaction faster within the margin of error as fast as by a triethylamine:catalyst ratio 5:1. That means that in a 1:1 ratio the iminophosphorane is almoust completely deprotonated. The phenolate anion, which has a high energy HOMO orbital and is very energy-rich[13] easily donates an electron in a SET (Single Electron Transfer) reaction to the dioxygen resulting in the radical **7** and superoxide anion. Unfortunately the superoxide anion could not be proved with any spin traps[14] due to its consecutive reactions, short life time of the adduct and superposition in the EPR spectra, but NBT (nitroblue

tetrazolium chloride)[15] tests were positive. The organic radical **7**
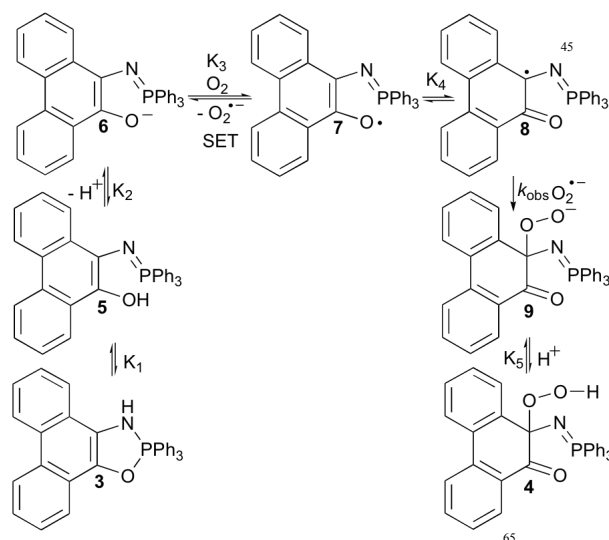
Scheme 2. Proposed mechanism of hydroperoxide (**10**) formation.

could be proved by EPR (Fig. 2) and it reacts with superoxide anion (KO_2) to **9** (SFig. 8). The red color changes to greenish indicating the reaction of the radical to the hydroperoxide (**4**) and to its decomposition products. Similar hydroperoxide have been prepared and characterized also by x-ray measurement from 3,4,6-triisopropylcatechol with di-*tert*-butylperoxide and dioxygen.[16] The formation of the unstable hydroperoxide **4** is the rate-determining step (k_{obs}) involving also the various preequilibria and the fast protonation of **9**. The course of the catalytic reaction of the hydroperoxide **4** with the substrate PPh$_3$ (Scheme 3) may take two pathways: **a**) oxygenating the bound phosphorus as part of the iminophosphorane (**4**), a part of the catalyst, (Pathway **a**) or that of added PPh$_3$ being oxygenated to the oxide (Pathway **b**).
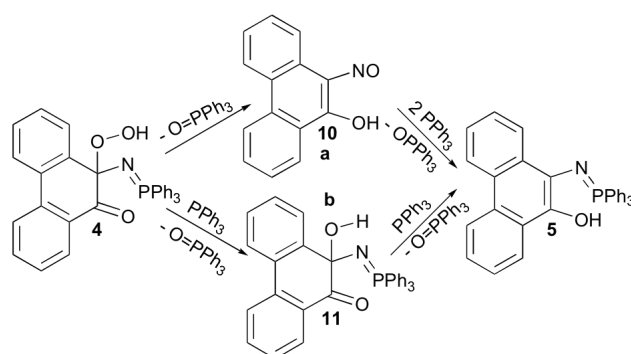
Scheme 3. Pathways **a** and **b** for the oxygenation of PPh$_3$ by the hydroperoxide **4**.

In the reaction path **a** where the iminophosphorane is oxygenated 9-nitroso-10-hydroxyphenanthrene (**10**) is formed, which is the tautomeric form of 9,10-phenanthrenequinon oxime.[17] This is also able to transfer an *O*-atom to PPh$_3$ and gives 9,10-phenanthrenequinone monoimine (SFig. 10), and with additional

triphenylphosphine the iminophosphorane (**5**) is reformed. Pathway **b** starts with the classical oxygenation of PPh₃ and **11** is formed. Triphenylphosphine thereafter abstracs an *O*-atom from **11** giving triphenylphosphine oxide and the iminophosphorane (**5**) formed just closing the catalytic cycle.

Conclusions

Although triplet dioxygen does not react with ground state, mostly singlet organic molecules its activation beside transition metal complexes can also be done with some organic molecules, possibly flavin mimics. It has been disclosed that 2,2-dihydro-2,2,2-triphenylphenanthro[9,10d]1,3,2λ⁵-oxazaphosphole reacts with $^3O_2$ under ambient condition and catalyzes the oxygenation of triphenylphosphine to its oxide. Labeling experiments proved that the source of oxygen in triphenylphosphine oxide originates from dioxygen. On the basis of kinetic and spectroscopic data a possible radical mechanism is proposed. The *O*-transfer to triphenylphosphine from the hydroperoxide differs from the usual H_2O_2[18] or hydroperoxide[19] oxygenation, since in the present case both *O*-atoms of the hydroperoxide are transferred to the triphenylphosphine. The scope of the catalytic oxidations/oxygenations however, remains to be elaborated.

Notes and references

Department of Chemistry, University of Pannonia, H-8200 Veszprém, Hungary.

E-mail: speier@almos.uni-pannon.hu

Fax: +36 88 624 469; Tel: +36 88 624 720

1   A. N. Campbell and S. S. Stahl, *Acc. Chem. Res.* 2012, **45**, 851-863.
2   (a) W. von E. Doering and R. M. Hains, *J. Amer. Chem. Soc.* 1954, **76**, 482-486; (b) T. Funabiki, *Dioxygenases in Catalysis by Metal Complexes, Oxygenases and Model Systems*; T. Funabiki, ed., Kluwer Academic: Dordrecht, 1997, pp. 19-89; (c) D. T. Sawyer, *Oxygen Chemistry*, Oxford University Press: New York, 1991; (d) J. P. Klinman, *J. Biol. Inorg. Chem.* 2011, **6**, 1-13.
3   (a) J. S. Valentine, *Dioxygen Reactions in Bioinorganic Chemistry*; eds. I. Bertini, H. B. Gray, S. J. Lippard and J. S. Valentine; University Science Books: Sausalito; 1994, pp. 253-258; (b) D. T. Sawyer "*The Chemistry and Activation of Dioxygen Species (O₂, O₂⁻ and H₂O₂) in Biology*" in *Oxygen Complexes and Oxygen Activation by Transition Metals*; eds. A. E. Martell and D. T. Sawyer; Plenum: New York; 1988, pp. 131-148.
4   (a) B. G. Malström, *Annu. Rev. Biochem.* 1982, **51**, 21-59; (b) L. L. Ingraham and D. L. Meyer *Biochemistry of Dioxygen*, Plenum; 1985; (c) *Molecular Mechanism of Oxygen Activation*, ed. O. Hayaishi; Academic Press: New York; 1974, pp. 405-451; (d) R. A. Sheldon and J. K. Kochi, *Metal-catalyzed Oxidations of Organic Compounds,* Academic Press: New York; 1981.
5   R. J. Schmitt, M. Bierbaum and C. H. De Puy, *J. Am. Chem. Soc.* 1979, **101**, 6443-6445.
6   (a) R. R. Mendel and R. Hänsch, *J. Exp. Bot.* 2002, **53**, 1689-1698; (b) R. R. Mendel and F. Bittner, *Biochim. Biophys. Acta* 2006, **1763**, 621-635; (c) B. Thony, G. Auerbach and N. Blau, *Biochem. J.* 2000, **347**, 1-16; (d) A. A. DiMarco, T. A. Bobik and R. S. Wolfe, *Annu. Rev. Biochem.* 1990, **59**, 355-395.
7   V. Joosten and V. J. van Berkel, *Curr. Opin. Chem. Biol.* 2007, **11**, 195-202.
8   (a) G. Speier and Z. Tyeklár, *Chem. Ber.* 1979, **112**, 389-391; (b) H. B. Stegmann, R. Haller and K. Scheffler, *Chem. Ber.* 1977, **110**, 3817-3828.
9   (a) Modern Oxidation Methods, 2ⁿᵈ ed. ; ed. J-E. Bäckwall; Wiley-VCH: Weinheim, 2010, pp. 277-314; (b) S. Ball and T. C. Bruice, *J. Am. Chem. Soc.* 1979, **101**, 4017-4019; (c) T. C. Bruice, *Acc. Chem. Res.* 1980, **13**, 256-262.
10   R. Hiatt, R. J. Smythe and C. McColeman, *Can. J. Chem.* 1971, **49**, 1707-1711.
11   L. Daasch and D. Smith, *Anal. Chem.* 1951, **23**, 853-868.
12   F. Neese, *The ORCA program system. WIREs Comput. Mol. Sci.* 2012, **2**, 73-78.
13   M. L. Mihailovic, Z. Cekovic in *The chemistry of hydroxyl group*, ed. S. Patai; Interscience Publishers London, 1971, pp. 505-592 and references therein.
14   (a) G. R. Buettner and R. P. Mason, *Spin-Trapping Methods for Detecting Superoxide and Hydroxyl Free Radicals In Vitro and In Vivo in Critical Reviews of Oxidative Stress and Aging: Advances in Basic Science, Diagnostics and Intervention,* ed. R. G. Cutler and H. Rodriguez; World Scientific: New Jersey, London, Singapore, Hong Kong, 2003, Vol. I. Chapter 2, pp 27-38; (b) F. A. Villamena, *J. Phys. Chem. A* 2010, **114**, 1153-1160.
15   B. H. J. Beilski and H. W. Richter, *J. Am. Chem. Soc.* 1988, **110**, 8085-8092.
16   G. A. Abakumov, N. N. Vavilina, Yu. A. Kurskii, V. I. Nevodchikov, V. K. Cherkasov and A. S. Shavyrin, *Russ. Chem. Bull. Internat. Ed.* 2003, **52**, 1847—1853.
17   R. V. Linko, V. A. Soldathina, B. E. Zaitsev, M. A. Ryabov and V. I. Sokol, *Russ. Chem. Bull.* 1998, **48**, 1095-1099.
18   (a) R. Noyori, M. Aoki and K. Sato, *Chem. Comm.* 2003, 1977-1986; (b) B. C. Nyamunda, F. Chigondo, M. Moyo, U. Guyo, M. Shumba and T. Nharingo, *J. Atoms and Molecules,* 2013, **3**, 23-44.
19   (a) J. Mlochowski, W. Peczynska-Czoch, M. Pietka-Ottlik and H. Wójtowicz-Mlochowska, *Open Cat. J.* **2011**, *4*, 54-82; (b) F. G. Gelalcha, *Chem. Rev.* 2007, **107**, 3338-3361.