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Spin-driven activation of dioxygen in various metalloenzymes and their inspired models

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The need for green, profitable, and highly selective catalytic processes is becoming increasingly acute. When targeting oxygenation and/or oxidation of saturated compounds, one appealing route is to employ molecular oxygen, readily available, as the oxidant. In its ground-state free dioxygen molecule is however a spin-polarized triplet and as such is inert toward substrate oxidation. On the other hand, the singlet states are more reactive even if they in general lie higher in energy. Catalysts are thus required to promote the spin-forbidden triplet to singlet transition to use dioxygen as an oxidizing agent. This strategy has proven to be very promising for palladium-catalyzed aerobic oxidation, for example.1 More generally, this approach is legitimized by the ubiquity of metalloenzymes in aerobic life that activate dioxygen and exploit its oxidative power.2 Numerous studies have been undertaken in the last decades to understand the chemical strategies leading to O2 activation. One of the most remarkable lessons has been the identification of a broad range of chemical mechanisms that enzymes may follow to produce the oxidative species they need, depending on their particular chemical structure. In the recent past, a seemingly simple strategy has emerged from biochemical studies. Various enzymes have been found to make direct use of metal-dioxygen adducts (M\(\text{O}_2\)) to oxidize their substrates. Within such adducts, and depending on the chemical nature of the active site, the dioxygen moiety generally undergoes a partial reduction towards a superoxide (\(\text{O}_2^-\)) or a peroxide (\(\text{O}_2^=\)) form. Among the enzymes that use this strategy, Tyrosinase (Tyr),3 Catechol Oxidase (CO),4 Tyramine β-Monoxygenase (TβM),5 Peptidyldiglycine α-Hydroxylating Monooxygenase (PHM), and Dopamine β-Hydroxylase (DBH)6 are six ubiquitous cuproenzymes involved respectively in the metabolism of phenols, tyramine, neuropeptides and neurotransmitters. Some non-haem iron enzymes have also been respectively in the metabolism of phenols, tyramine, neuropeptides and neurotransmitters. Some non-haem iron enzymes have also been found to engage in their singlet state. This strategy has been implemented with success in several cases. For example, in the P450 monooxygenases (P450),7 the non-haem iron dioxygenase complex is in the singlet state and uses the dioxygen complex as an oxidant to oxygenate substrates.8,9

In this report, we provide an unprecedented description of the electronic properties of such adducts based on state-of-the-art calculations. Five inorganic complexes were retained which are representative of the various strategies followed by enzymes to produce reactive M\(\text{O}_2\) adducts (Figure 1). The topological analysis of the Electron Localization Function (ELF)10–12 coupled to Density Functional Theory (DFT) provides a powerful way to elucidate the electronic structures of molecules of biological interest (See Methods Section).13 It is applied here to trace the shape of the electron pair density around the oxygen atoms within M\(\text{O}_2\) complexes, which is shown to be connected to the spin multiplicity of the adducts. We suggest that enzymes could resort to spin state control to tune the regioselectivity of substrate oxidations.

We began this study with the binuclear copper complex ([\(\text{ImH}_2\)Cu(O\(\text{O}_2\)])\(^{1+}\) which is an adequate model of the active sites of Tyrosinase and Catechol oxidases. It contains a Cu\(\text{O}/(\mu-\eta^2: \eta^-\text{O}_2)\) core with an unusual organization consisting of a three-centre Cu-O-Cu bond.16 The second adduct, ([\(\text{Mim}\text{H}_2\)Cu(O\(\text{O}_2\)])\(^{1+}\), is a biomimicking model of the Cu\(\text{O}\) active site found in the non-coupled dicopper enzymes PHM, DβM, and TβM.17,18 These systems have been studied in their singlet and triplet spin states through extensive use of Molecular Orbitals (MO), see for example ref. 19. The ELF isosurfaces (Figure 2) reveal a particular spatial polarization of the valence basins V(O) related to the oxygen atoms. Such basins, which cannot be distinguished when looking at MOs, are identified with the oxygen lone pairs, keeping in mind that such non-bonding densities are considered here in a larger picture that in the usual formal Lewis theory: an ELF lone pair can hold an electronic population larger than 2 (Table 1). Interestingly, a particular spatial orientation of these V(O) basins is found to be spin-dependent. They are included within the Cu\(\text{O}_2\) plane in the case of the triplet adducts but are perpendicular to it for the singlet adducts. In other words, a 90° rotation of the dioxygen lone pairs is observed, as...
confirmed by the values of the Cu-O-O-V(O) dihedral angles gathered in Table 1. It is worth mentioning that similar patterns are recovered for the Cu$_2$/[μ-η$^3$: η$^2$O$_2^2$] singlet core using alternative approaches such as the topological analysis of the electrostatic potential,	extsuperscript{xxiv} or the direct statistical sampling of the electron positions obtained by means of Quantum Monte-Carlo (QMC) based electron pair localization function schemes (see Supp. Mat.), attesting thus to the robustness of the observed ELF patterns.	extsuperscript{xxv,xxvi} Figure 1. Chemical structures of the five complexes investigated in this study with their total charge and the spin states considered.

As for the Cu-O-O-V(O) angles, the volumes of the valence oxygen basins also appear to be spin dependent and thus offer some complementary quantitative elements. Overall, the oxygen lone pairs contain mostly the same total number of electrons in both spin states. On the other hand, their spatial extensions, and hence their accessibility for an exogenous substrate, are different. In the singlet states, the two valence basins at one oxygen exhibit equal volumes, leading to similar electronic expansion on the two sides of the Cu$_2$O$_2$ averaged plane. In contrast, in the triplet state, the different basins exhibit very different volumes, the basins lying between copper and oxygen being much smaller than those lying on the outside.

Following the study of mono and dinuclear copper centres, similar spin-dependencies are found for the \([\text{(HTt}^5\text{Im})\text{Cu}^2\text{(O}_2\text{)}_2]\), \([\text{NHCl}^2\text{Pd}(\text{O}_2)]\), and \([(\text{ImMe})_2(\text{C}_2\text{H}_4\text{COO})(4\text{NC})\text{Fe}(\text{O}_2)]\) adducts, although different spin states are to be considered depending on the nature of the metal ion (see Supp. Information.). This is, for example, the case for the nickel complex which is associated with either a doublet or a quartet state. Strikingly, the rotation of the dioxygen lone pairs appears to be a shared characteristic of M$_2$O$_2$ complexes.

A rationalization of these trends is achievable using a MO analysis of the complexes. Upon interaction with a metallic complex, the dioxygen π$^*$ antibonding MO undergoes a mixing with a symmetry-adapted d orbital of the metal ion, whereas the π$^*$ MO, interacting in δ symmetry with the metal, is generally considered as unperturbed. This is evidenced in Figure 3 in the case of \([(\text{ImN}_{2}\text{S})\text{Cu}(\text{O}_2)]\), an adduct relevant to the Cu$_{50}$ centre of PHM, DβM, and TβM.

As the symmetries of the dioxygen π and π$^*$ orbitals match those observed for the dioxygen lone pairs (Figure 2), the respective occupations of the MOs can be connected to the topology of the ELF basins. In the case of a closed-shell singlet configuration \((1)^2(2)^2\), the symmetry of the dioxygen valence basins is obtained by superimposing the three electron pairs at the oxygen, namely the two dioxygen π orbitals (resulting in a cylindrical symmetry) and the dioxygen lowest energy MO 1, i.e. π$^*$: the resulting basin will thus be mostly oriented along the y direction, namely, perpendicular to the Cu$_2$O$_2$ plane. In the triplet configuration \((1)^2(2)^2\), no electron pairing can result from the singly occupied π$^*$ system and the resulting orientation of the V(O) basins reflects the small participation of π$^*$ to the mostly metal centred d$_{xy}$/π$^*$ bonding orbital (Figure 3, bottom orbital), which justifies both the small polarization and the alternative symmetry with respect to the singlet system.

This suggests a possible relationship between the spin density of the M$_2$O$_2$ core and the topology of the ELF function. This hypothesis is tested more in depth using the introduced numerical constrained-DFT (CDFT) approach\textsuperscript{xxvii} consisting of the progressive reduction by one electron of the previous singlet complex together with the examination of the evolution of the ELF basins (Figure 3). To this end, a remote hydrogen atom, the electronic charge of which is constrained, acts as the reductive species (see Methods section). Starting from a total charge of +1 on the complex and a low-spin density on the Cu$_2$O$_2$ core, the successive injections of fractions of an electron to the complex leads to a progressive reduction of the Cu$_2$O$_2$V(O)$_{3\text{c}}$ angles and to the increase of the V(O)$_{3\text{c}}$ basin volumes. Three main conclusions can be drawn from this numerical experiment. First, it confirms the previous MO analysis stating that the respective populations of the frontier orbitals (that generate the two limit symmetries) determine the symmetry of the ELF basins.
Second, these results account for the changes of symmetry described above regarding the adduct spin state, as the singlet and the triplet states involve different populations of the MOs. Finally it shows that symmetry does not change sharply but rather smoothly upon variation of the $n^*$ orbital populations. This latter point implies that intermediate situations with particular spatial polarization and extensions of the oxygen lone pairs are, in principle, possible. In biological or bio-inspired systems, the electron reservoir currently used in the CDFT computation could consist in protein residues, enzymatic substrates or organic substituents. This hypothesis is examined in the discussion part, altogether with an analysis of the control of the bio-inspired oxidation reactions relying on the orientation patterns described above.

| MOs resulting from the interaction between the substrate and the dioxygen | Reference source not found and suggest a non-fortuitous orientation of all interacting intervening molecules. The last enzymatic example is the family of non-iron extradiol ring-cleaving dioxygenases. Recent X-Ray structures have brought decisive information about their catalytic mechanisms. | Error: Reference source not found. Using a slow aromatic substrate (4-Nitrocatechol, 4NC), it has been possible to trap an intermediate in which the dioxygen moiety is partly reduced to a superoxide radical. 

Table 1: Positions and characteristics (volume/population) of the monosynaptic valence attractors of the oxygen atoms in the [(MimH)Cu(O_2)]^+ and [(ImH)Cu(O_2)]^+ complexes (the numbering is defined on Figure 2).

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Figure 3. Left: MOs resulting from the interaction between the substrate and the dioxygen. Right: evolution of the average $CuO_2V(O_3)$ dihedral angles as a function of the spin density at the CuO_2 core upon progressive injection of one electron (constrained DFT computations) at a frozen geometry.
Attack Conformers) theory or related approaches (see ref [xxxv] for a detailed review).

Details about theoretical procedures are available in the Supporting Information. 

Abbreviations: NHC: N-heterocyclic carbenes.; HTtna: (tris-(methylthio)methyl)hydroborate.; ImH: imidazole.; ImMe: methylimidazole.; 4NC: 4-Nitrocatechol

MOs resulting from the interaction between the dioxygen $\pi_x$ and $\pi_y$ molecular orbitals and the copper $d_{xz}$ orbital for the case of the $[(\text{Mim}^\text{N2S})\text{Cu}(\text{O}_2)]^+$ complex. Right: evolution of the average CuO$_1$O$_2$V(O)$_{1/3}$ dihedral angles as a function of the spin density at the CuO$_2$ core upon progressive injection of one electron (constrained DFT computations) at a frozen geometry.