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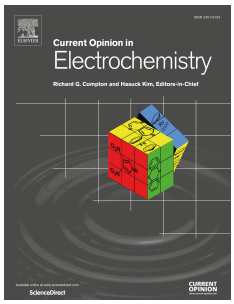

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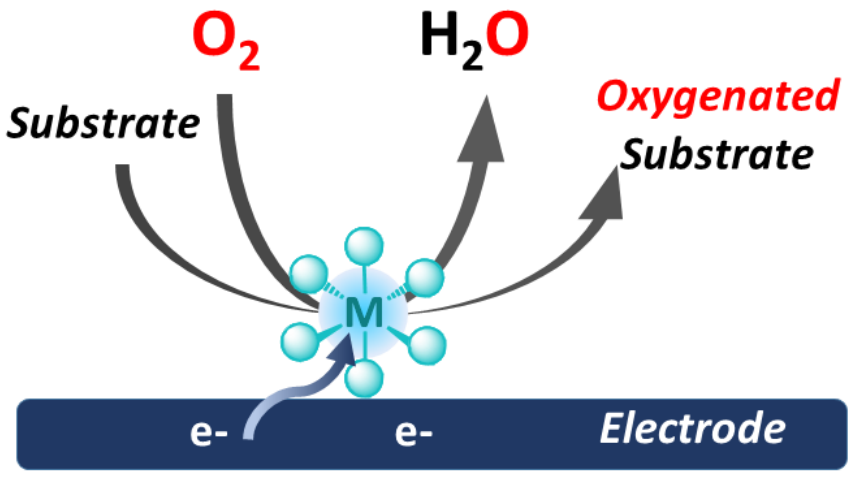

Bioinspired molecular catalysts for homogenous electrochemical activation of dioxygen

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Highlights

We describe the fundamental concept of the electrochemical reductive activation of O_2 for substrate oxidation taking inspiration from metalloenzymes. High valent metal-oxo species with potential oxidizing power are obtained from partial and controlled reduction of O_2 at a metal active site (mono or di-nuclear) *via* electron and proton transfers to achieve O-O bond cleavage. Such an approach provides new perspectives for the development of catalytic oxidation processes under mild conditions.

Key words

O_2 electrochemical reductive activation; bioinspired metal catalyst; electrochemical artificial oxygenase

Abstract

O_2, which is abundant and environmentally benign, is the ideal green oxidant for oxidation reactions, which are key transformations in the chemical industry. Still, O_2 needs to be activated and this can be achieved through the so-called reductive activation of O_2 paradigm. Taking inspiration from metalloenzymes where a non-noble redox active metal (iron, copper) controls the partial reduction of O_2 *via* electron and proton transfers, metal based synthetic systems can been developed in order to reproduce oxygenase activity. In the present article we focus on fundamental aspects that serve as support for the development of 2 electron activation of O_2 and generation of highly oxidizing metal-oxo species, thus paving the road for the development of electrocatalytic systems for organic substrate oxygenation. Scarce examples known in the literature capable of such reactivity and possible future developments are described.

Introduction

In the chemical industry, oxidation reactions are widely implemented for the preparation of many commodities from abundant hydrocarbon feedstock. Nonetheless, these transformations frequently resort to stoichiometric potent oxidizing reagents, such as Cl_2, HClO, HNO_3, which obviously poses environmental problems.[1] Dioxygen (or air) is alternatively used but high temperature and pression are required to activate this triplet (S=1) spin state molecule in order to overcome the kinetic barrier of its reaction with singlet (S=0) spin state organic molecules.[2] Due to the inherent conditions under which aerobic oxidations are carried out, they are energy consuming and frequently non selective at the same time.

In mammals and bacteria, many metabolic transformations correspond to the selective oxidation of an organic substrate by dioxygen. Thus, Nature has devised synthetic strategies to perform this class of reactions under mild conditions, which are sources of inspiration for the development of sustainable oxidations by chemists. Often, these reactions are catalyzed by metalloenzymes where a non noble redox active metal center (generally iron or copper) activates dioxygen following the so-called reductive activation of O_2.[3] This activation corresponds to a partial and controlled reduction of the oxidant to generate oxidizing reaction intermediates such as metal-superoxo, metal-peroxo or metal-oxo species along a catalytic cycle whose finality is the oxidation of the organic substrate, as written in Equation 1 in which RH is the substrate.[4-7]

$$RH + O_2 + 2\ e^- + 2\ H^+ \rightarrow ROH + H_2O \qquad \text{(Equation 1)}$$

Dioxygen activation is illustrated in Figure 1 for the iron enzymes cytochromes P450[8,9] and soluble Methane Monooxygenase (sMMO).[8,9] In an effort to mimick this type of reactions, it is necessary to timely and spatially orchestrate the consumption of the different cosubstrates, *i. e.* the terminal oxidant O_2 and the metabolized organic molecule but also the source of reducing equivalents. This condition is required to ensure the formation of the oxidizing reaction intermediates in the presence of the target substrate while preventing their direct reduction by the electron source (futile cycle). This latter reaction is deleterious and leads to an electron waste and side reactions such as the 4 e^- reduction of O_2 into H_2O. In metalloenzymes, the electrons can be either directly provided to the metal center in the active site by a sacrificial or a recyclable cofactor[5,10,11] or mediated from a terminal reductant (such as NAD(P)H) through a reductase.[6,8,10] Both P450s and sMMO use the two electrons of NAD(P)H for a turnover. Nonetheless, while in MMO these two electrons are transferred at the same time to the diiron core in the active site which stores them for dioxygen activation, they are transferred one after the other at two different steps in the P450s catalytic cycle.

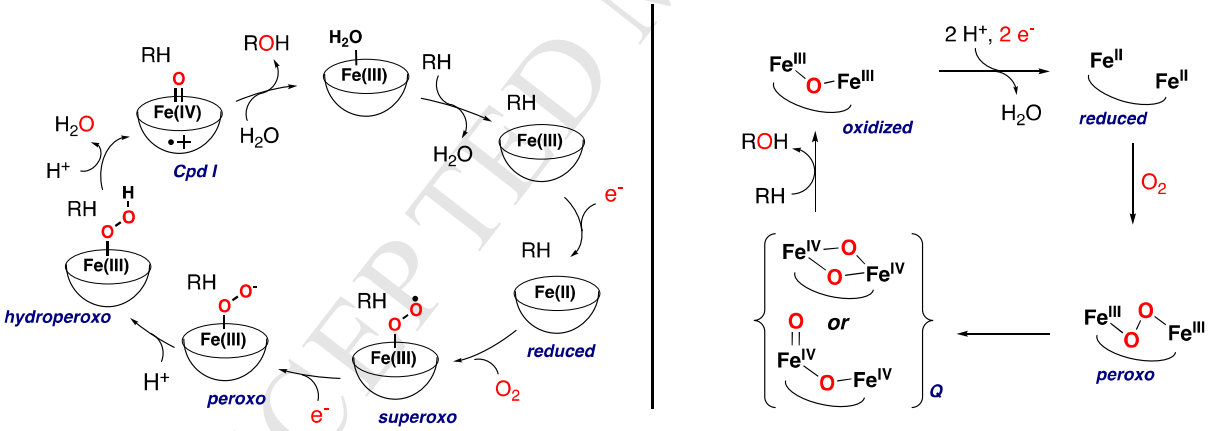

Figure 1. Left and right panels describe the catalytic cycles of P450 and sMMO, respectively (RH designates a substrate). The comparison between the two mechanisms evidences that the electrons are consumed in two different steps in P450, whereas there is only one reductive step in sMMO.

In a synthetic perspective, the first case, *i.e.* electrons directly shuttled from a reducing cofactor to the active site, is of outstanding interest if, in addition to the substrate, the reductant itself yields value added products or can be recycled. Efforts dedicated to mimick the catalytic activity of α-ketoglutarate-dependent enzymes with simple synthetic systems are currently developed.[12] The second approach, inspired by reductase dependent enzymes, has been mainly explored for the stoichiometric generation of oxidizing metal-oxygen intermediates or stoichiometric oxidation of substrates.[13] In these reports, the source of electrons was generally a sacrificial chemical reductant or a H-atom donor. Much fewer studies have been dedicated to the development of catalytic reactions following this reductive active of O_2 strategy. Most of these investigations were performed

with Mn and Fe porphyrins and sacrificial reductants such as Zn powder or amalgam, NADH analogs or hydrides.[14] In a few cases, nonheme iron complexes were implemented under similar conditions[15] and suffered from similar drawbacks, *i.e.* overconsumption of the electrons due to an uncontrolled delivery of the reducing equivalents. In order to tackle this latter issue, as early as in the 1980's, Mansuy et al. and Creager and Murray independently used an electrochemical approach to achieve the epoxidation of olefin by dioxygen. Using Mn porphyrin or Mn Schiff-base catalysts, they demonstrated the potentiality of their methodology to form oxygenated products while avoiding undesired reactions responsible for low faradaic efficiency.[16-19] Surprisingly, these pioneering studies did not further encourage the development of oxidation reactions where the reductive activation of dioxygen is achieved by a molecular catalyst under the controlled assistance of electrochemistry.

The objectives of this review are to describe a few recent examples where metal-based molecular complexes have been implemented for the electrochemical activation of dioxygen. Learning from these examples, possible methods for the development of mild oxidation catalytic reactions will also be raised.

Many studies have been devoted to the 4-electrons 4-protons reduction of O_2 into water (ORR) and an excellent and detailed literature can be found.[20-22] Although this perspective will not focus on ORR, the reported mechanistic studies can certainly serve as support for the achievement of the 2-electrons activation of O_2 written in Equation 1.

1. Dinuclear complexes

Using an unsymmetrical binucleating ligand, Le Poul, Karlin et al. showed the formation of different Cu_2:O_2 intermediates (Figure 2).[23] They prepared the dinuclear Cu^I complex $\mathbf{1}^+$ which could be reversibly oxidized into the mixed-valent Cu^ICu^{II} $\mathbf{1}^{2+}$ at E°'(1) = 0.07 V *vs* SCE, following a monoelectronic process. Reaction of the precursor $\mathbf{1}^+$ with O_2 yielded the μ-1,2-peroxo bridged $diCu^{II}$ complex $\mathbf{3}^+$ whereas oxygenation of $\mathbf{1}^{2+}$ gave the superoxo bridged $diCu^{II}$ intermediate $\mathbf{2}^{2+}$. Interestingly, both of these Cu_2:O_2 species could be electrochemically interconverted at E°'(2) = 0.02 V *vs* SCE. Copper intermediates are known to display a versatile reactivity that partly depends on the core structure.[24] In particular, superoxo bridged $diCu^{II}$ have been reported to perform the abstraction of H atom from organic substrates.[25]

Even though this was not investigated by the authors, this dicopper system is of potential interest for catalytic oxidation by O_2 with the assistance of electrochemistry. Indeed, it is expected that the formation of the peroxo bridged complex $\mathbf{3}^+$ or of the superoxo bridged $diCu^{II}$ intermediate $\mathbf{2}^{2+}$ can be controlled upon polarization of the oxygenated solution at E < 0.02 V or E > 0.07 V, respectively. In the presence of a convenient substrate, the selected intermediate could then engage in a catalytic loop whose starting point is its $diCu^I$ or Cu^ICu^{II} precursor (Figure 2). The reduction of O_2 into $O_2^{\bullet-}$ occurs at a much lower potential (*ca.* -0.8 V vs SCE) in CH_2Cl_2, the solvent used in this study. If productive, this catalytic reaction would lie on an efficient reductive activation of O_2.

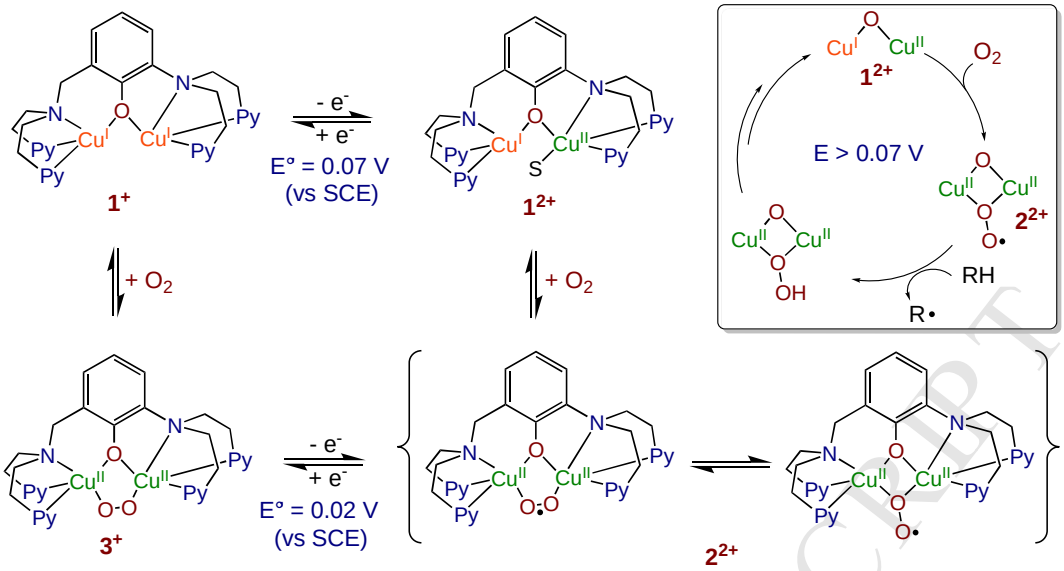

Figure 2. Generation of peroxo and superoxo bridged diCu^{II} intermediates upon oxygenation of the Cu^{I}Cu^{I} or Cu^{I}Cu^{II} precursors (adapted from reference [23]). The scheme in the frame depicts a possible strategy for the catalytic oxidation of a substrate RH.

Le Poul, Kodera et al. reported on the O-O bond cleavage of a μ-η^2:η^2 peroxo complex upon electrochemical reduction.[26] This reduction was shown to be bielectronic and was located on the peroxo group and not on the metal centers. The electron transfers thus resulted in the cleavage of the O-O product and the release of H_2O.

Depending on the ligand structural influence, μ-η^2:η^2 peroxo diCu^{II} complexes can be interconverted into bis(μ-oxo)diCu^{III} species.[24] Monoelectronic reduction of both of these Cu_2:O_2 intermediates could afford bis(μ-oxo)Cu^{II}Cu^{III}, which have been proposed to be the species responsible for CH_4 into CH_3OH oxidation in particulate Methane MonoOxygenase.[27] The quest for single electron reduction of the widely disseminated Cu_2:O_2 adducts may pave the way for the development of electro-assisted oxidations by O_2 catalyzed by diCu complexes. Note that (μ-oxo)Cu^{II}Cu^{II}, which could be obtained *via* 2 electron reduction, has also been suggested as the possible reactive species in pMMO.[23] However, the thermodynamic properties of such a synthetic model indicate that it is probably too basic to drive the cleavage of strong C-H bonds.[28] Hence, the precise control of electron injection is of prime importance.

With a combination of terpyridine and bis(pyridyl)pyrazolate ligands, Llobet, Nam and Fukuzumi reported a μ-1,2-peroxo Co^{III}Co^{III} complex for the catalytic four-electron reduction of O_2.[29] The first electron transfer to this μ-1,2-peroxo Co^{III}Co^{III} was shown to be unfavoured thermodynamically. It became possible in the presence of protons, thus yielding a putative Co^{III}(OH)Co^{III}(O$^{\bullet}$) radical species which could serve as oxidant towards organic substrates. This latter example stresses the importance of the proton delivery in the process of the O_2 activation. However, the radical species did not accumulate because its formation was shown to be rate determining.

2. Mononuclear metal complexes.

Cu^{II}(OOH) intermediates can be obtained by H^+/e^- transfer to 1:1 Cu:O_2 adduct. These species are active by themselves or can generate the highly fleeting copper-oxyl (Cu^{III}(O) ↔ Cu^{II}(O$^{\bullet}$)).[23] The protonated form of these latter species, Cu^{III}(OH), have also been shown to be capable of strong C-H bond cleavage.[30] Undoubtly, dioxygen activation by mononuclear Cu complexes under electrochemical reductive conditions is a field of investigations that should deserve a great attention in the next future.

Using the commercially available [$Mn^{III}Cl(TPP)$] complex and following a cyclic voltammetry approach, Costentin and Nocera determined the mechanism of ORR promoted by this catalyst.[31] They evidenced that the rate determining step was the heterolytic O-O cleavage of the $Mn^{III}(OOH)$ intermediate (formed from Mn^{II}, O_2, e^- and H^+, mimicking the P450 reactivity, Figure 1). The resulting $Mn^{V}O$ intermediate was proposed to be readily reduced at the electrode to produce H_2O (Figure 3). Within the frame of our perspective, the challenging efforts are to find the conditions to accumulate the highly oxidizing $Mn^{V}O$. Indeed, such a situation would render possible the competition between the direct reduction and the oxygen atom transfer to an organic substrate (pathways (a) and (b) in Figure 3, respectively). Interestingly, using the same catalyst, Murray et al. reported three decades ago an efficient electrocatalytic epoxidation system.[17] They indeed showed that the reaction of the $Mn^{III}(OO^-)$ with benzoic anhydride yielded the manganese-acylperoxo intermediate that gave a $Mn^{V}O$ resulting from the O-O heterolysis favoured by 1-methyl imidazole as an axial ligand (push effect).

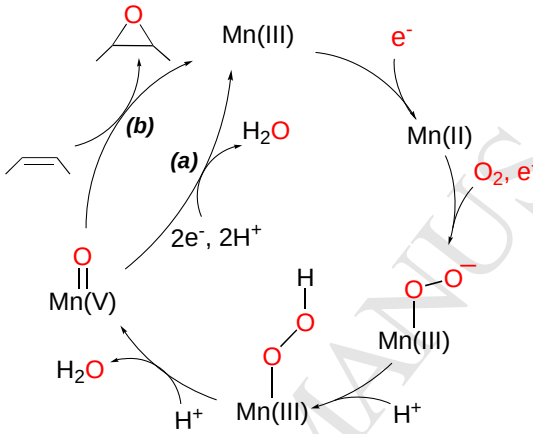

Figure 3. Generation of $Mn^{V}O$ intermediates upon electrochemical reductive activation of O_2 promoted by [$Mn^{III}Cl(TPP)$] porphyrin complex (TPP = tetraphenylporphyrin, here omitted for clarity) and example of epoxidation reaction (adapted from references [16] and [28]).

To gather mechanistic information on the reaction of Fe porphyrins with O_2 under reductive conditions, the group of Dey developed a methodology combining electrochemistry and surface enhanced resonance Raman. The studies are conducted with Fe catalysts immobilized on self-assembled monolayer on a gold electrode and evidenced the formation of high valent FeO intermediates.[32,33] Depending on the nature of the axial ligand of Fe, a totally different reactivity was observed. With thiolate bound Fe porphyrins, the catalytic oxidation of inert substrates such as cyclohexane (into cyclohexanol and cyclohexanone) and toluene (into benzyl alcohol and p-cresol) was observed. This is one of the rare examples of electrochemically driven reactivity which mirrors the one of P450. In contrast, with imidazole as axial ligand, no oxidation of the substrates occurred but the generation of partially reduced oxygen species was observed. This observation suggests that, in that latter case, the cleavage of the Fe-O occurs rather than that of the O-O bond, which underlines the importance of the axial ligand.

Using a similar electrochemical approach coupled to spectroscopies our groups have studied electrochemical activation of O_2 with tetrakis(pentafluorophenyl)porphyrinFe(III) $[Fe^{III}(F_{20}TPP)]^+$ in DMF and reported electrochemical generation of $Fe^{III}(OO^-)$ and $Fe^{III}(OOH)$ intermediates, thus mimicking the first steps of O_2 activation cycle (Figure 1, left panel).[34] The formation of the $Fe^{III}(OO^-)$ complex generated at -0.5 V vs SCE from the electrochemical reduction of the superoxo $Fe^{III}(OO^{\bullet})$ adduct (Figure 4, left panel) was confirmed by UV-vis absorption spectroscopy (Figure 4 right panel) and its oxidation was reported for the first time at +0.5 V vs SCE. The protonation of this latter complex readily afforded the unstable $Fe^{III}(OOH)$. Even though it was not demonstrated, the fate of the $Fe^{III}(OOH)$ intermediate is expected to lead to the $Fe^{V}O$ oxidizing agent.

Our groups also reported a similar electrochemical approach coupled to spectroscopies using the non-heme $[Fe^{II}(TPEN)]^{2+}$ complex (TPEN = N,N,N',N'-tetrakis(2-pyridylmethyl)ethane-1,2-diamine).[35] In this case, analysis of the cyclic voltammetry data allowed to evidence the formation of the $Fe^{II}O_2$ adduct, a rare moiety in nonheme chemistry, and of its reduction product $Fe^{III}(OO^-)$. Nonetheless this later species was reduced at a more positive potential than the initial $Fe^{II}O_2$ adduct which prevented its accumulation. Kinetic and thermodynamic data deduced from a thorough analysis of the cyclic voltammograms revealed that the coordination of O_2 to Fe^{II} (yielding $Fe^{II}O_2$) was very unfavored, unlike in porphyrin complexes. Hence, its reduction, leading to $Fe^{III}(OO^-)$, occurred at a very negative potential, close to the one of O_2. These observations stress the necessity to develop new non-heme systems for which the formation and reduction of the $Fe^{II}O_2$ adduct is facilitated in order to accumulate the $Fe^{III}(OO^-)$, and potentially, of subsequent intermediates.

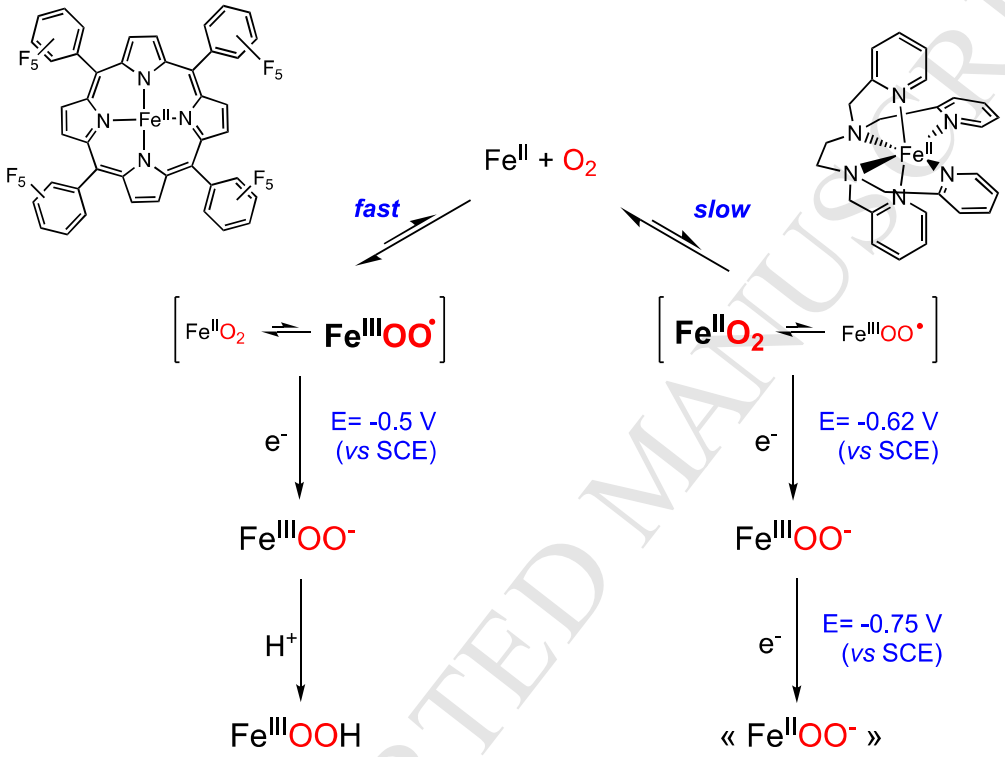

Figure 4: Electrochemical reductive activation of O_2 by a porphyrinic (left panel) or non porphyrinic (right panel) iron complex underlining basic differences between the two classes of complexes. Adapted from references [34] and [35], respectively.

Conclusions and Perspectives.

The selected examples discussed in the previous paragraphs are chiefly dedicated to mechanistic studies. With the objective to run catalytic reactions, these studies are prerequisites which allow identifying how to manage the electron flux in order to properly activate O_2.

The comparison of the results reported with the $[Mn^{III}Cl(TPP)]$ complex, *i.e.* ORR[31] *vs* oxygen atom transfer[17] (Figure 3), illustrates the kinetic dilemma to resolve if one wants to drive the fate of the $M:O_2$ intermediate to a reaction or the other. This problem can *a priori* be easily addressed by using a large amount of a not too inert substrate. Nonetheless, such a strategy appears relatively limited to a few catalysts and substrates and complementary approaches are needed.

In the case of non heme Fe^{II} complexes, an obvious drawback is the unfavoured coordination of O_2 to the metal center.[35] The adduct resulting from oxygenation of the Fe^{II} precursor is better described as $Fe^{II}O_2$. This is in contrast with porphyrinic systems for which coordination of O_2 is promoted by an

electron transfer from Fe^{II} to yield a $Fe^{III}(OO^{\bullet})$ intermediate (superoxide is a much better ligand than dioxygen). Introduction of anionic or electron donating groups in the first coordination sphere of the metal would improve the interaction between Fe and O_2 by favouring an electron transfer from the metal to dioxygen. Along this line, the increase of the reduction potential of the Fe^{II}:O_2 adduct is also expected.

Second sphere interactions (H-bonding, charge / charge interactions) play a fundamental role in oxygenases, in that they modulate the reactivity of intermediates and modulate their electron transfer potentials.[3] Accordingly, it has been reported that non redox active Lewis acids can tune the redox properties (over hundreds of mV), kinetics of electron or H atom transfer in non heme $Fe^{III}(OO^{-})$ intermediates.[36,37] Additionally, the strongest Lewis acids promotes the generation of $Fe^{IV}O$ intermediates upon one electron reduction of the $Fe^{III}(OO^{-})$ species.[36] Interestingly, a recent report showed that strong Lewis acids can also enhance the oxidation potential of a nonheme $Mn^{V}O$ complex by 700 mV.[38] The use of redox inactive cations appears as one promising strategy to explore for the development of electro-assisted oxidation reactions. Furthermore, this method has the advantage to be synthetically effortless and suitable to any kind of metal complexes.

As pointed above in the case of $Fe^{III}(OO^{-})$, the use of electroreductive activation of O_2 necessitates to find the conditions to accumulate reaction intermediates, and therefore, to slow down their reduction so as it becomes rate limiting with respect to substrate oxygenation. One elegant strategy, previously illustrated in the case of O_2 reduction by a nitric oxide reductase model is to tether the complexes to the surface of the electrode *via* visely chosen linker so as to control the electron transfer rate.[39]

Acknowledgments.

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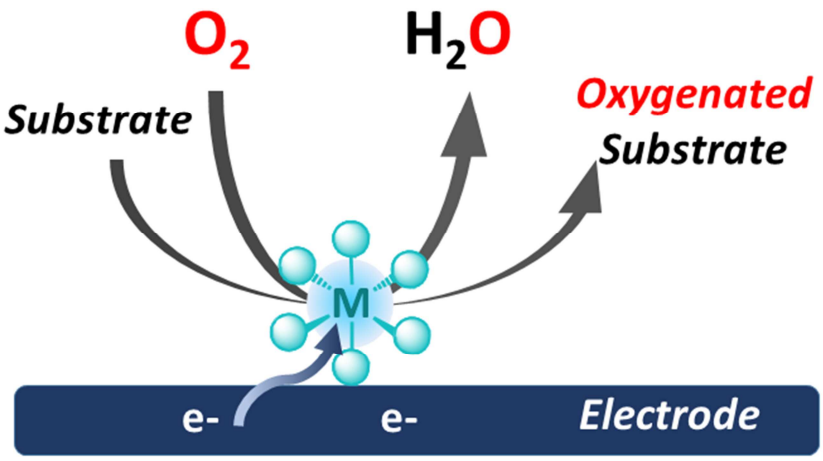
Graphical Abstract



AUTHOR DECLARATION

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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