



High-valent metal-oxo intermediates in energy demanding processes: from dioxygen reduction to water splitting

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Four-electron reduction of dioxygen to water and splitting of water to dioxygen are extremely important processes in the context of attaining clean renewable energy sources. High-valent metal-oxo cores are proposed as reactive intermediates in these vital processes, although they have only been isolated in extremely rare cases in the biological systems thereby making the mechanism ambiguous. Recent biomimetic studies have, however, aided in our understanding of the fundamental reactivity of the high-valent metal-oxo species in various reactions relevant to energy conversion. All these studies are summarized in the present review.

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Current Opinion in Chemical Biology 2015, 25:159–171

This review comes from a themed issue on **Bioinorganic chemistry**

Edited by **Mi Hee Lim** and **Yi Lu**

<http://dx.doi.org/10.1016/j.cbpa.2015.01.014>

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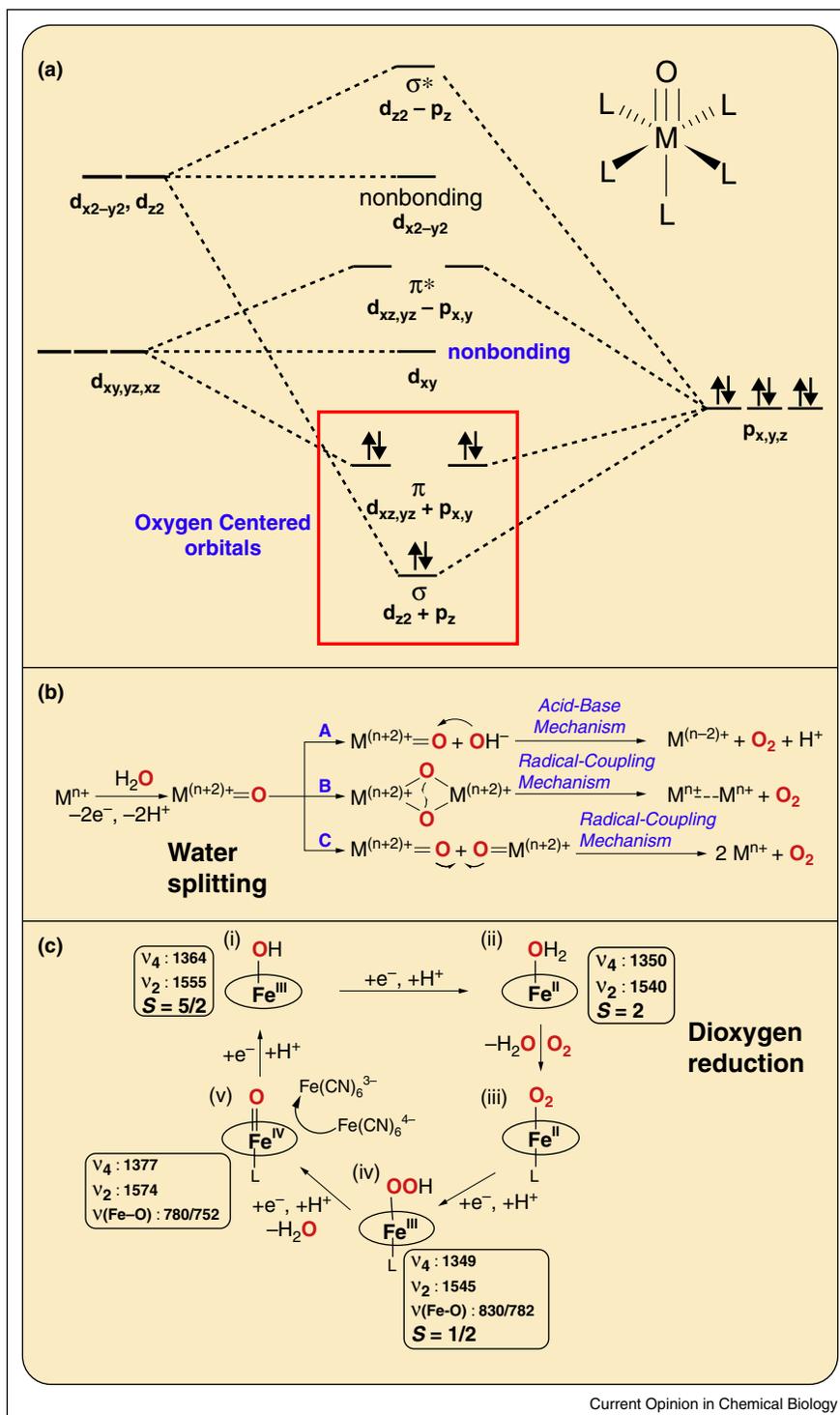
Introduction

The demand for fuel cell technology has increased sharply over the last three decades, as development has been driven by a growing awareness of issues related to anthropogenic climate change and an increase in global energy demand [1]. The most commonly used hydrogen fuel cell involves the oxidation of hydrogen to protons at a platinum anode and the four-electron reduction of O₂ to water at the cathode by Pt impregnated in carbon. The high loadings of this precious metal that are required to achieve appreciable activity have prompted the development of H₂ oxidation [2] and O₂ reduction catalysts [3] based on nonprecious metals. Furthermore, owing to issues of compression and storage, research has been

on-going into alternative ‘hydrogen-storage’ compounds [4], that can guarantee similar performance in a more convenient form. Water is the ultimate candidate as a source for hydrogen underpinning the intense interest in creating artificial systems that use catalysts based on earth abundant elements to achieve the splitting of water into hydrogen and oxygen and their recombination to obtain clean energy in a closed-cycle fuel cell [5–7]. The oxidation of H₂O to O₂ is a four-electron, four-proton process in which O–O bond formation is the key chemical step [8–11]. In photosystem II, these proton-coupled electron transfer (PCET) reactions occur via a tyrosine that is in close proximity to the Mn₄Ca oxygen-evolving complex. Similarly, a range of other metalloenzymes achieve the challenging tasks of dioxygen reduction [12–16] and hydrogen production [17,18] to fulfill the function of energy supply systems in biology by using cheap and non-toxic metals under ambient conditions of pressure and temperature. However, the large size and relative instability under aerobic conditions of many of these enzymes, and the difficulties associated with their purification process, has led to the search for well-defined molecular complexes for O₂ reduction, water oxidation and hydrogen production.

Advances in our understanding of the mechanism of biological systems may allow vital insights into the prerequisites necessary for the design of efficient catalysts for O₂ reduction and water oxidation by using cheap and readily available first row transition-metals under ambient conditions. High-valent metal-oxo cores have been proposed, and in few cases isolated, as the common reactive intermediates in these biological reactions relevant to renewable energy formation (Figure 1), thereby making them attractive targets for biomimetic synthetic studies. Recent synthetic advances have led to the isolation and characterization of several well-described metal-oxo model complexes, and detailed reactivity studies in conjunction with spectroscopy and theory have helped to understand how the steric and electronic properties of the metal centers modulate their reactivity [19–27]. Although the synthetic metal-oxo complexes have been found to be reactive toward substrates containing weak C–H bonds, in most cases the exhibited reactions are moderate and non-catalytic, with activities falling far short of the activity of the biological catalysts. Moreover, only in extremely rare cases they are found to be efficient in initiating O–O bond formation reactions. Similarly, evidences for the involvement of metal-oxo cores in

Figure 1



(a) Molecular orbital scheme for a $[M(L)_5O]$ complex in tetragonal symmetry. (b) Different possibilities for the metal-oxo mediated O–O bond formation reactions. (c) General mechanism for the four-electron reduction of dioxygen to water; the marker bands of the individual intermediate species are given in boxes, with the $\nu(Fe-O)$ values ($^{16}O_2/^{18}O_2$) corresponding to those observed for $FeEs_4$ [28**].

artificial systems that perform catalytic dioxygen reduction have only been obtained in a limited number of cases.

In this review, we summarize some of the recent advances in bioinorganic chemistry that strengthen the proposed involvement of metal-oxo cores in transition metal mediated transformations related to energy conversion and conservation processes. In our discussion we focus on the sparse literature existing on the detailed mechanistic studies of bio-relevant transition metal complexes, where the involvement of metal-oxo cores as active intermediates has been conclusively evidenced based on spectroscopic and kinetic studies during biomimetic dioxygen reduction and water oxidation reactions.

Nucleophilic versus electrophilic oxo

It is important to understand the electronic structure of the metal-oxo unit in order to rationalize the diversity of redox processes it can perform in biology. Gray and others [29] have shown that the oxo ligand in mono-oxo complexes with d^0 – d^2 electron configurations in a tetragonal environment, is considered to be electrophilic because of π bonding between the oxygen lone pairs and the $d(xz)$ and $d(yz)$ orbitals on the metal center (Figure 1a). In d^2 complexes, the two d-electrons occupy the $d(xy)$ nonbonding orbital and the bond order for the metal-oxo bond is three. Increasing population of the π antibonding levels should lead to decrease in the metal-oxo bond order, and hence increase in the nucleophilicity of the oxo group. The orbital energy level diagram depicted in Figure 1a can be perturbed however by the judicious choice of ancillary ligands. For example, the electronic character of the terminal oxo may be altered by incorporating ligands that can change the energy of the $\sigma(dz^2 + p_z)$ and $\pi(dyz, xz + p_{x,y})$ orbitals (red box Figure 1a). This can lead to novel reactions like the reported ambiphilic reactivity of a rhenium-oxo species [30]. While the electrophilic nature of terminal oxo ligands can be used to explain the O–O bond formation mechanism (relevant to biological dioxygen formation; Figure 1b) by an acid-base (AB) mechanism [31], a nucleophilic oxo should be amenable to protonation leading to water generation (relevant to the reduction of dioxygen to water; Figure 1c). Furthermore, depending on the ligand-field of the metal ion in the $M^{n+}=\text{O}$ complexes, an oxo-to-metal charge transfer excited state with $M^{(n-1)+}-\text{O}^\bullet$ character can be low-lying in energy, which may result in radical reactions like hydrogen atom abstraction from an unactivated C–H bond [32] or O–O bond formation by a radical-coupling (RC) mechanism (Figure 1b) [31]. Thus subtle electronic changes can have drastic effect on the reactivity of metal-oxo cores.

Metal-oxo mediated O–O bond cleavage and O–O bond formation reactions

Dioxygen reduction

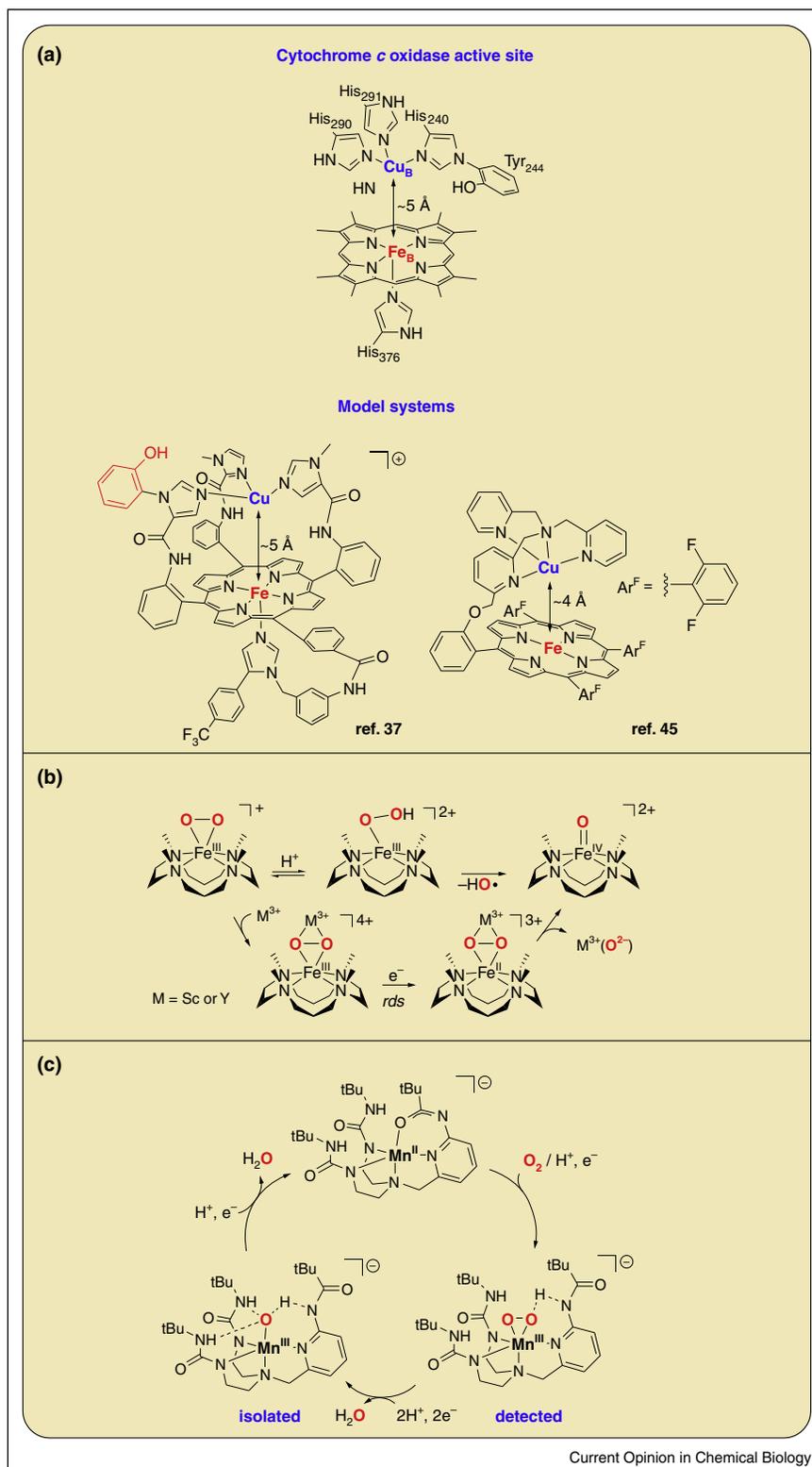
Cytochrome *c* oxidase (CcO) and related heme/copper terminal oxidases are the fuel cells of aerobic organisms.

These enzymes catalyze the selective and complete four-proton, four-electron conversion of dioxygen to water without releasing partially reduced peroxide (or superoxide) intermediates that are toxic to cells [13,15,16,33]. CcO is distinguished structurally from other heme-dependent proteins of O_2 metabolism, owing to the presence of an essential copper metal center proximate to the heme cofactor (heme copper separation is ~ 5 Å; Figure 2a) [34]. Three electrons involved in the reduction process originate from the $\text{Fe}_B^{\text{II}}/\text{Cu}_B^{\text{I}}$ centers present at the active site. The fourth electron and a proton are provided either by a tyrosine-244 moiety present in the active site or from the Fe_A/Cu_A redox cofactor. Even though its catalytic site is bimetallic, the reduction of O_2 by CcO (Figure 1c) appears to proceed via intermediates that are similar, with respect to the binding modes of O_2 and its derivatives, to those observed in monometallic heme and nonheme enzymes [19–24]. Iron-superoxo, iron-oxo and iron-hydroxo intermediates have been observed spectroscopically, thus supporting the proposed mechanism shown in Figure 1c. The precise role for the second metal center (Cu_B in Figure 2a) in mediating O_2 reduction is therefore not clear and has been controversially discussed in the literature. Although once proposed to be part of the catalytic cycle of CcO, spectroscopic evidence no longer supports $\text{Fe}_B\text{-O}_2\text{-Cu}_B$ (μ -peroxo) intermediates in CcO [35,36].

Biomimetic studies have proved to be a fruitful strategy to address questions that cannot be answered by working with the enzyme itself [37–40]. For example, based on detailed mechanistic studies on catalytic O_2 reduction on a series of functional heme/Cu model complexes (one such complex from Collman and coworkers is shown in Figure 2a; Model systems) [37], a non-redox contribution from Cu_B^{I} to the thermodynamic and decomposition stabilization of a heme/Cu dioxygen adduct has been concluded. Additionally, the copper center as well as the tyrosine moiety is discussed to be crucial in severely limiting the release of partially reduced dioxygen species during steady state turnover under a rate-limiting electron flux in CcO. Notably, the proposed role of Cu_B^{I} mainly as an $1e^-$ storage site apparently without providing a lower-energy pathway relative to O_2 reduction at a mononuclear Fe-porphyrinic unit alone contrasts with the computational studies [41] of the O–O bond cleavage at the heme/Cu site of CcO that identified the energetically preferred pathway as hydrogen atom transfer from Cu_B^{I} -coordinated H_2O to form the ferric-hydroperoxo intermediate.

Although the proposed hydroperoxo intermediate on the way to the generation of the iron-oxo intermediate from the iron-superoxo species could not be trapped in CcO or in related heme/copper model complexes [13,15,16,33,37–40,42], it has been recently identified as a reactive intermediate during the electrocatalytic O_2 reduction by a mononuclear iron α_4 -tetra-2-(4-carboxymethyl-1,2,3-triazolyl)-phenylporphyrin (FeEs_4) complex [28^{••}]. In this

Figure 2



(a) Active site structure of cytochrome C oxidase and its structural/functional models. **(b)** Scheme showing the stoichiometric conversion of a non-heme metal-peroxo core to an iron(IV)-oxo complex upon addition of proton or binding of Lewis-acidic metal ions and reduction. **(c)** Mechanism of four-electron reduction of dioxygen to water by a homogeneous manganese based catalyst.

study Dey and coworkers elegantly applied a modified surface enhanced resonance Raman spectroscopic setup to accommodate a conventional rotating disk electrochemical (RDE) system bearing the FeEs₄ catalyst and studied the steady-state electrocatalytic O₂ reduction. This approach, which combined dynamic electrochemistry with *in situ* Raman spectroscopy, allowed direct identification of intermediates involved in O₂ reduction; the oxidation and spin-state marker bands (Figure 1c) helped to identify species having the Fe in different oxidation and spin states. On the basis of this study, the dioxygen was shown to move progressively through hydroperoxo, oxo and hydroxo states, before it was completely reduced to water. Notably, the identification of the iron(III)-hydroperoxo species on the way to the generation of an iron(IV)-oxo species in the mononuclear heme system, in contrast to the transient nature of the same intermediate in heme/copper systems, may stress the importance of the distal copper center in CcO and heme/copper model complexes to minimize the steady-state concentration of the hydroperoxo intermediate whose decomposition would release partially reduced dioxygen species.

Advancement in the understanding of the chemistry of mononuclear nonheme metal-oxo intermediates has also provided vital insights into the mechanism of dioxygen reduction in CcO. In one study Cho *et al.* [43] demonstrated the formation of a structurally well characterized [Fe^{IV}(O)(TMC)]²⁺ complex by protonation of an iron(III)-peroxo complex [Fe^{III}(TMC)(O₂)]⁺ via the intermediate generation of an iron(III)-hydroperoxo core. This reaction is essentially isoelectronic to the proposed reaction of the heme iron(III)-superoxo intermediate with Tyr244 (a H-atom donor) and therefore provides a synthetic precedent of the H-atom assisted conversion of a metal-superoxo species to a high-valent metal-oxo species, which is considered as a key step in the dioxygen activation mechanism of CcO. Furthermore, the reduction of [Fe^{III}(TMC)(O₂)]⁺ by ferrocene (Fc) in presence of redox-innocent metal ions, such as Sc³⁺ and Y³⁺ ions, also led to the near-quantitative formation of [Fe^I(O)(TMC)]²⁺ [44*]; a proposed mechanism involves the initial binding of the metal ions to the peroxo unit of [Fe^{III}(TMC)(O₂)]⁺, followed by reduction and O–O bond heterolysis steps. In support of this mechanism, the iron(III)-peroxo complexes bound to Sc³⁺ and Y³⁺ ions were characterized by various spectroscopic methods and unambiguously assigned as heterodinuclear Fe(III)–O₂–M(III) (M = Sc³⁺ and Y³⁺) complexes containing a peroxo ligand in a side-on fashion between two metal ions. Moreover, the conversion of Fe(III)–O₂–M(III) to the iron(IV)-oxo species could be monitored by UV–vis spectroscopy, and the rate of the reaction was shown to be dependent on the Lewis acidity of the redox-inactive metal ions and the concentration and oxidation potential of the electron donors. These results indicate that the reduction of Fe(III)–O₂–M(III) by electron

donors to form the one-electron reduced species (i.e. [(TMC)Fe^{II}(O₂)–M^{III}]) is the rate-determining step (r.d.s.), followed by a rapid heterolytic O–O bond cleavage step that results in the formation of the iron(IV)-oxo complex (Figure 2b). The role of the Lewis-acidic metal ions is to increase the electrophilicity of the Fe–O₂ core, thereby assisting in the rate-determining reduction step. On the basis of this study, a similar role of Cu(II) as a Lewis acid in the one-electron reduction of the iron(III) porphyrin–O₂²⁻–Cu(II) intermediate (presumably formed by an intramolecular electron transfer process in the spectroscopically identified iron(III)superoxo Cu(I) species) at the active site of CcO to give the S = 1 Fe(IV)-oxo and Cu(II) species can be envisioned.

In a related study Karlin, Fukuzumi and coworkers [45] also reported UV–vis spectral evidences in favor of the involvement of a well characterized μ -peroxo iron copper species during the catalytic four-electron reduction of dioxygen by a heme/copper model system under homogeneous conditions; an iron(III)-hydroperoxo intermediate could also be identified before the final O–O cleavage step leading to the formation of water thereby supporting the mechanism shown in Figure 1c. It is important to note, however, that the Fe–M distances in Fe(III)–O₂–M complexes (M = Sc³⁺, Y³⁺ or Cu²⁺) are in the range of 3.5–4.0 Å [44*,46], which are significantly shorter than the observed Fe–Cu distance of ~5.0 Å in the bimetallic active site CcO [34]. Whether the formation of a similar μ -peroxo species is also involved in the catalytic cycle of CcO is now a particularly intriguing question. This would, however, warrant a significant structural distortion relative to the crystallographically characterized resting state of the enzyme [34], which may be extremely energy demanding.

The possible involvement of a metal-peroxo intermediate in the catalytic cycle of CcO has also been evidenced in the report of a monomeric [Mn^{II}H₂bupa]⁻ complex by Borovik and coworkers that catalyzed the reduction of dioxygen to water using diphenylhydrazine or hydrazine as the sacrificial reductant [47]. Two key species produced during reduction were identified: a monomeric manganese(III) peroxo complex and a hybrid Mn(III)–O/OH species that is strongly H-bonded to the supporting tripodal ligand. These observations led to a proposed catalytic cycle shown in Figure 2c that was also supported by results from product distribution studies. The ability of [Mn^{II}H₂bupa]⁻ to reduce dioxygen to water has been attributed, in part, to the carboxyamido group in the secondary coordination sphere. It is proposed to play the same role as Tyr244 in CcO, which ensures precise coupling of electron and proton transfers during the dioxygen reduction process. The carboxyamido group serves various functions: it is deprotonated in [Mn^{II}H₂bupa]⁻ and binds to the manganese(II) ion through its oxygen atom. Additionally, the carboxyamido

unit is proposed to be protonated during the initial reduction steps to produce the peroxo ligand, preventing the accumulation of the more reactive hydroperoxo species. Once protonated, the carboxyamido group adopted a different conformation — one that places its NH group within the interior of the cavity — and thus served as an additional H-bond donor to the peroxo ligand. Conversion to the manganese-oxo(hydroxo) liberated the first equivalent of water; the thermodynamic driving force is presumably provided by the large stability of the hybrid $\text{Mn}^{\text{III}}\text{-O(H)}$ unit strongly H-bonded to the carboxyamido group. Finally, additional reduction produced the second equivalent of water, causing the carboxyamido to rebind to the manganese(II) ion via the O-atom. Notably, no catalytic conversion of O_2 to H_2O is observed for analogous manganese complexes [26] lacking the carboxyamido group. These systems have been reported to reductively cleave dioxygen producing stable $\text{M}^{\text{III}}\text{-O(H)}$ complexes that cannot produce water. These results further corroborate the suggested roles of the carboxyamido group in catalytic dioxygen reduction and highlight the importance of incorporating intramolecular functional groups within the secondary coordination sphere of metal-containing catalysts.

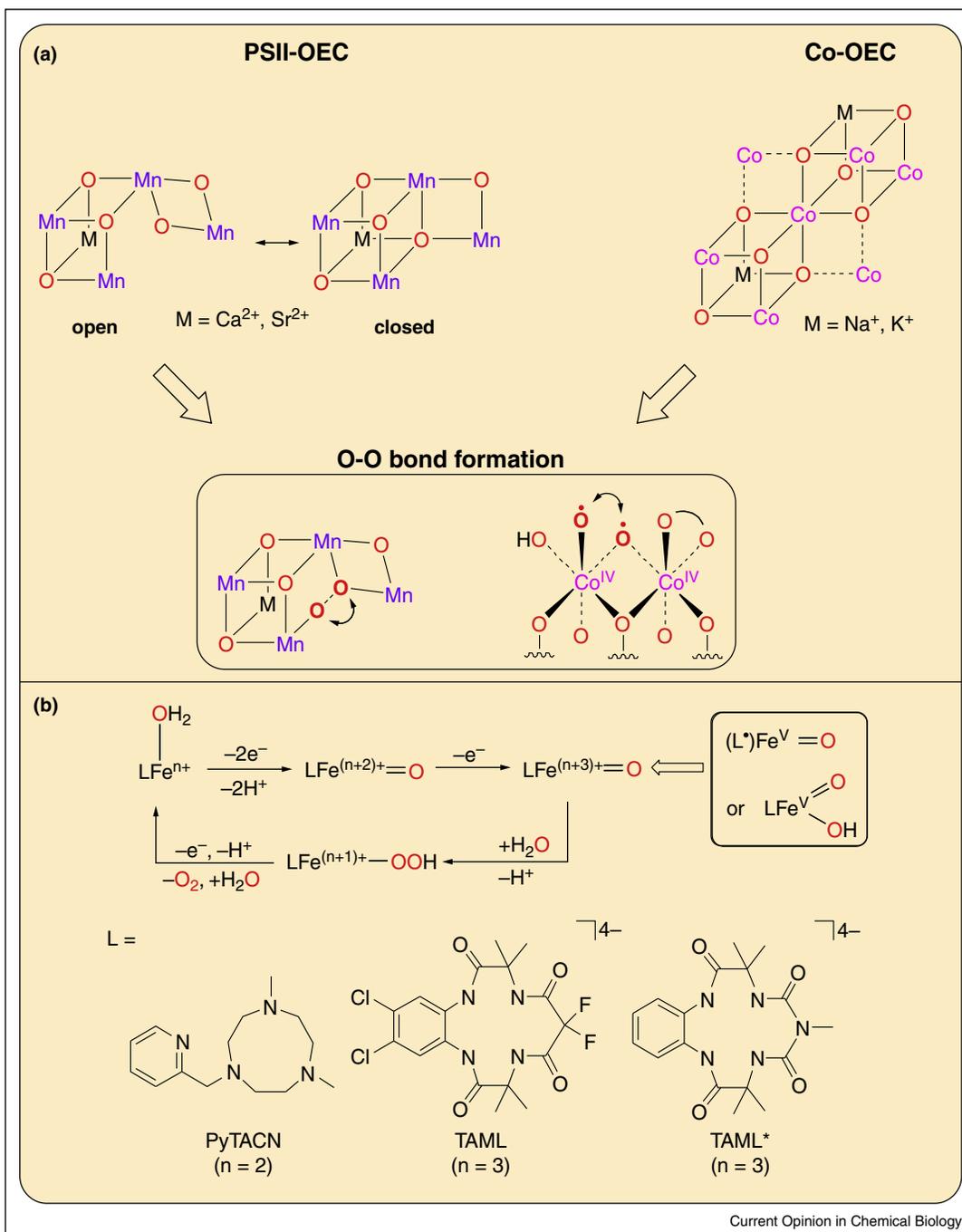
Water oxidation

Nature's water oxidizing catalyst, the oxygen evolving complex (OEC) of photosystem II (PSII), generates protons, electrons, and molecular oxygen from water and solar energy [8,9,48,49]. A recent X-ray structure [50] has provided a detailed picture of the active site of OEC with three closely spaced manganese centers, part of a heteronuclear Mn_3CaO_4 cubane, bridging via oxide or hydroxide ligands to a dangling fourth manganese ion (Figure 3a; PSII-OEC). Oxidation of two bound water molecules in PSII requires transfer of four electrons. This transfer occurs one electron at a time, starting with chlorophyll-based photooxidation of a tyrosine. The resulting tyrosine radical, Y_Z^\bullet , in turn oxidizes the Mn cluster in a series of intermediates, S0 to S4, and O_2 is released 1 ms after the highly oxidized S4 state is formed. All but the short-lived S4 state have been trapped at low temperatures, allowing detailed studies of these states [8,9,48,49]. The X-ray structure was assumed to correspond to the dark-stable S1 state of the OEC, in which the generally accepted Mn formal oxidation states are $\text{Mn}_2^{\text{III}}\text{Mn}_2^{\text{IV}}$. The net oxidation states of the four manganese (Mn) ions in the S2 state are generally considered to be IV, IV, IV, and III; however, some researchers also favor a net oxidation level two electrons lower: IV, III, III, and III [9]. Additionally, the Mn_3CaO_4 cluster in the S2 state adopts two distinct but interconvertible Mn core topologies, an open and a closed cubane motif, which differ by the reorganization of a single μ -oxo bridge rendering the Mn^{III} ion five-coordinate (Figure 3a; PSII-OEC) [51]. Notably, the closed and open cubane forms are discernible by spectroscopy; while the former exhibits an electron paramagnetic resonance

(EPR) multiline signal at approximately $g = 2.0$, indicative of a spin $S = 1/2$ ground state, the latter shows higher spin signals at $g = 4.1$ [9]. No information on the S3 state was available until very recently. Cox, Lubitz and co-workers [52**] applied high-resolution pulse EPR experiments together with computational studies on the S3 state to confirm an 'open cubane' structure for the Mn_3CaO_4 cluster with a six-coordinate Mn(IV) assignment for all the four Mn ions. The mechanism of dioxygen evolution is, however, still not fully elucidated, mainly with respect to the nature of the O–O bond coupling step. Two possibilities have been discussed in the literature [8,9,48,49]. Oxidation of one Mn atom in the S3 state would give an S4 state, generating a single Mn(V)-oxo species that could form an O–O bond with a Ca^{2+} -bound water or hydroxide (AB mechanism; Figure 1b). Alternatively, in the transient S4 state, the electron hole may be localized on a substrate O atom, that would give rise to a RC O–O bond formation mechanism between the Mn(IV)-oxyl radical and a Mn ligated μ -oxo bridge (Figure 3a; O–O bond formation). Although Cox, Lubitz and coworkers [52**] favor RC over AB mechanism, no direct experimental evidence for the involvement of manganese-oxo cores in the O–O bond formation step is presently available.

The uncertainty related to the O–O bond formation mechanism in PSII inspired bioinorganic chemists to simulate the structural motif of the OEC and use molecular complexes for O–O bond formation reactions, so as to obtain a better understanding of the oxygen evolution mechanism [6,7,53,54]. This has led to the synthesis of a large variety of manganese based systems, some of which have provided valuable spectroscopic models for the OEC as well as insight into the reactivity of high oxidation state manganese species, including water oxidation [53,55–57]. One recent highlight is the synthesis of $[\text{Mn}_3\text{O}_4]$ cubane clusters structurally related to the CaMn_3 subsite of the OEC substituted with divalent and trivalent redox-inactive metals [58**,59]. This series of compounds allowed for the systematic study of the electrochemical effect of the Lewis acidic metal ions on the manganese reduction potentials. Varying the Lewis acidity of the capping metal from Mn^{3+} to Sr^{2+} shifted the redox potentials of these clusters by over 1 V. These results support proposals that part of the calcium's role in OEC may be to stabilize high oxidation states of its Mn neighbors (or in other words providing stability to the $\text{Mn(V)=O/Mn(IV)-O}^\bullet$ species necessary for the O–O bond formation step) presumably by modulating the redox potential of the manganese centers via the μ -oxido ligands. In another important study Gao *et al.* provided for the first time the experimental demonstration of the O–O bond formation reaction via nucleophilic attack of hydroxide on a well characterized corrole Mn(V)-oxo oxygen to generate dioxygen via a hydroperoxo intermediate, reminiscent of the AB mechanism proposed for the

Figure 3



(a) Active site structure of PSII-OEC and its structural/functional model complex. The inset shows the mechanism of the O–O bond formation reaction proposed during the biological and chemical water oxidation reactions. **(b)** Generalized mechanism for water oxidation by mononuclear iron containing water oxidation catalysts.

O–O bond formation step during biological dioxygen evolution [60].

In a related study, Nam and coworkers [61] also demonstrated reversible O–O bond cleavage and formation between high-valent Mn(V)-oxo and Mn(IV)-peroxo

units supported by a tris(3,5-trifluoromethylphenyl) corrole ligand. In this study, although dioxygen evolution was not observed, addition of hydroxide to the low spin $S = 0$ Mn(V)-oxo species afforded the high spin $S = 3/2$ Mn(IV)-peroxo compound, which reverted to the Mn(V)-oxo state upon acidification. Interestingly, experimental

evidences have also been obtained in favor of the reversible O–O bond formation step in PSII [62].

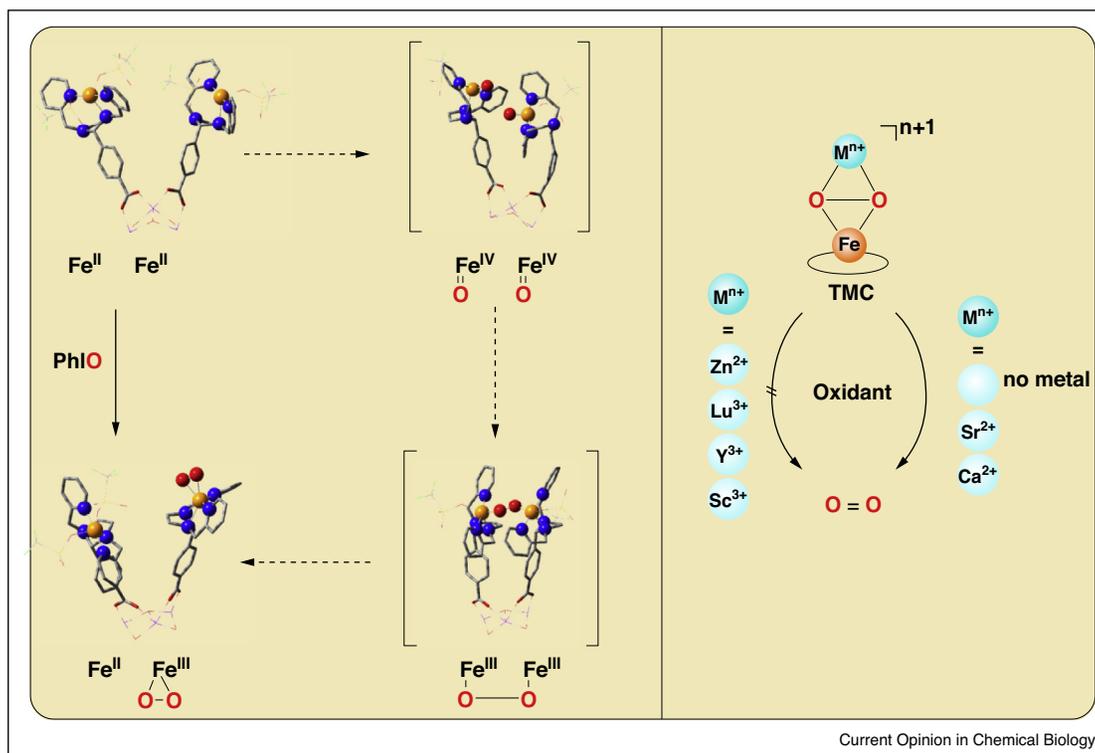
In an effort to better understand the mechanism of O–O bond formation reactions, studies have also been extended to systems involving metal centers other than manganese [6,7,53,54]. In particular, iron-based water oxidation catalysts [63] are extremely important in the context of obtaining a cheaper alternative energy source. Chemical water oxidation using iron complexes was first reported by Collins, Bernhard, and coworkers using fluorine-substituted Fe-tetraamidomacrocyclic ligands (Fe-TAML) as a catalyst and Ce(IV) as the oxidant [64]. However, the activity of the Fe-TAMLs was reported to vanish after few seconds (turnover number = 16) and also no detailed mechanistic studies were performed to understand the mechanism of the O–O bond formation step in the original publication. Recently, however, Cramer, Siegbahn and coworkers performed detailed theoretical calculations to understand the reaction mechanism of water oxidation enabled by the Fe-TAML catalyst [65,66]. They suggested that the key oxidizing species is $\text{TAML}^{+\bullet}\text{-Fe(V)=O}$, a formal Fe(VI) species, that is attacked by water to form a TAML-Fe(IV)-OOH intermediate, which then releases O_2 and regenerates the TAML-Fe(III)-OH_2 species (Figure 3b). A possible degradation pathway for the catalyst could be identified involving a nucleophilic attack of water on the ligand radical in $\text{TAML}^{+\bullet}\text{-Fe(V)=O}$ in a process that is associated with an even lower barrier than those for the desired O–O bond formation pathway. The calculations also provided insights into the design strategy for a more efficient iron-TAML based water oxidation catalyst where the ligand must be optimized with a balance of electron-donating and electron-withdrawing substituents that would significantly affect the kinetics of the formation and reactivity (stability) of the vital iron-oxo intermediates. Indeed, by substituting the $-\text{CF}_2$ group of the TAML ligand with a $-\text{NMe}$ group in TAML^* (Figure 3b), Sen Gupta, Dhar and coworkers could significantly improve the performance of the water oxidation catalyst (TON = 220) [67]. Additionally, they could experimentally demonstrate for the first time the generation of the $\text{TAML}^*\text{-Fe(V)=O}$ species as a vital intermediate (on the basis of the UV-vis and EPR spectroscopic markers established for $\text{TAML}^*\text{-Fe(V)=O}$ in a previous study [68]) during photochemical water oxidation by the modified Fe-TAML* catalyst. Involvement of redox-innocent ligands should also prevent the catalyst decomposition by nucleophilic attack of water into the oxidized ligand. Accordingly, Fillol and Costas *et al.* demonstrated that iron complexes of tetradentate neutral organic ligands were able to catalyze water oxidation at low pH with TON > 350 and >1000 using Ce(IV) and IO_4^- as oxidant, respectively [69,70]; the TON values for these catalysts are the highest reported for any homogeneous system based on first-row transition metals and are comparable to those of the most active Ru-based and Ir-based systems [6]. Screening of a large number of iron

complexes with various structural motifs, including, for example, PyTACN derivatives (1-(2'-pyridylmethyl)-1,4,7-triazacyclononane; Figure 3b), allowed Fillol, Costas and coworkers to establish that the presence of two cis free coordination sites is a structural prerequisite for water oxidation catalysis that has been observed by others as well [71]. Detailed kinetic studies including isotopic labeling experiments as well as DFT calculations [72] led to the conclusion that an Fe(V)-oxo hydroxo species is the active species responsible for the O–O bond formation step following an AB mechanism. The proposed Fe(V)-oxo hydroxo species could, however, not be trapped on the way to oxygen generation (similar to $\text{TAML}^{+\bullet}\text{-Fe(V)=O}$); the only intermediate observed was the Fe(IV)-oxo complex, which has been proposed as the resting state and was characterized by UV-vis spectroscopy and ESI-MS. A general mechanism for the water oxidation based on iron catalysts is shown in Figure 3b. The reaction starts from two sequential PCET steps from the starting iron complex to form an iron-oxo species, followed by a rate-determining one-electron oxidation to yield a higher-valent iron-oxo species (which may either be an Fe(V)-oxo hydroxo species or an Fe(V)-oxo ligand radical) as the key oxidant responsible for the O–O bond forming step. A water molecule then performs a nucleophilic attack on the oxo group of the transient iron-oxo species to form a hydroperoxo intermediate, which then releases O_2 and regenerates the starting complex.

Notably, kinetic studies on the iron-based water oxidation catalysts suggest that the formation of O_2 is first-order, which exclude the possibility of a cooperative metal-oxo coupling mechanism. However, Kundu *et al.* demonstrated that a RC reaction involving two Fe(IV)-oxo units bound to a central stannoxane core (Figure 4 left) is also a viable route to O–O bond formation [73]. On the basis of infrared, UV/vis, kinetic and DFT studies, the formation of the O–O bond is proposed to occur in a series of electron-transfer steps with the oxygen progressing through terminal oxo, bridging peroxo, and superoxo states concomitant with a decrease in the formal iron oxidation state.

The reaction reported by Kundu *et al.* is nevertheless non-catalytic and is not accompanied by the release of dioxygen. An understanding of the factors that may lead to the eventual release of dioxygen after the O–O bond formation step is therefore also critical in the context of designing an efficient water oxidation catalyst. In a recent study, Bang *et al.* [74] provided some insight into the terminal step of dioxygen release during biological water oxidation in the OEC. They focused on a step of water-oxidation chemistry that occurs after O–O bond formation, hypothesizing that it relates to the role of calcium in the OEC: the formation/release of dioxygen from a peroxide moiety (O_2^{2-}). They added solutions of redox-inactive metal ions to a redox-active iron peroxide species, $\text{Fe}(\text{O}_2^{2-})$, and

Figure 4



Radical coupled O–O bond formation mediated by a polynuclear Fe(II) complex (only two iron centers shown for simplicity) in presence of iodobenzene. (b) Scheme showing the Lewis-acid dependent release of dioxygen from an iron-peroxo complex binding redox-innocent metal ions.

obtained complexes containing the Fe–(O₂²⁻)–M motif (M can be ions of calcium, strontium, zinc, lutetium, yttrium or scandium). Interestingly, when the Fe–(O₂²⁻)–M was oxidized by an electron acceptor, the release of O₂ occurred only for complexes involving Ca²⁺ or Sr²⁺ ions; no reaction was observed for complexes bound to stronger Lewis acids like Zn²⁺, Lu³⁺, Y³⁺ and Sc³⁺ (Figure 4 right) [74**]. The effects of calcium and strontium ions are of particular interest because they are biologically relevant: calcium is the native component of the OEC, and strontium is the only metal that can replace calcium and still generate a functional catalyst. The parallels between the biological and synthetic systems (in terms of dioxygen release only in presence of calcium and strontium) suggest that the study's conclusions may extend to the OEC — although the more complicated structure of the OEC and the different metals within it will affect the interactions with, and the chemical reactivity of, the peroxide moiety.

The report of an artificial catalyst showing both structural and functional resemblance to the OEC in PSII, however, comes from the group of Nocera and coworkers [75,76]. They reported an inorganic cobalt-based catalyst film (Co-OEC; Figure 3a) that is efficient at neutral pH, is very stable (self-repairing) under working conditions, operates close to

the Nernstian potentials for the H₂O/O₂ half-cell reaction, and is self-assembled from low-cost materials. The catalysts films are structurally amorphous and thus X-ray absorption spectroscopy (XAS) was used to structurally characterize Co-OEC [77,78]. The extended X-ray absorption fine structure (EXAFS) spectra of *in situ* Co-OEC during catalytic turnover and *ex situ* films are consistent with a molecular cobalt complex consisting of edge-sharing CoO₆ octahedra. The average size of the molecular cobaltate cluster is determined to involve seven cobalt atoms. Notably, the core of Co-OEC is a nearly identical structural congener of the PSII-OEC as schematically illustrated in Figure 3a. Both systems are a partial cubane with identical metal–metal (*d* = 2.82 Å) and metal–oxo (*d* = 1.89 Å) distances. Moreover, the proposed mechanism for water splitting in Co-OEC is also similar to that proposed in PSII-OEC. X-ray absorption near-edge spectral (XANES) data were found to be consistent to include an appreciable amount of a Co(IV) intermediate and *in situ* EPR studies under catalytic conditions also confirmed the appearance of an *S* = 1/2 low-spin Co(IV) species in about 3–7% yield [79].

On the basis of detailed spectroscopic studies, an active Co(III/IV) mixed valence cluster has been proposed to be the catalyst resting state. Further kinetic studies established a PCET conversion of Co(III)–OH to Co(III)–oxyl

as a key mechanistic step leading to O–O bond formation; a RC based O–O bond formation between Co(III)-oxyl radical and the Co ligated μ -oxo bridge (Figure 3a; O–O bond formation) is proposed which is also supported by a recent DFT calculation [80].

Conclusion

The production of hydrogen and oxygen from water and sunlight represents an attractive means of artificial energy conversion for a world still largely dependent on fossil fuels. A practical technology for producing solar-derived fuels remains an unachieved goal, however, and is dependent on developing a better understanding of the key step, the O–O bond formation reaction leading to the oxidation of water to dioxygen. Similarly, O–O cleavage leading to the four-electron reduction of dioxygen is another important reaction from the viewpoint of energy conversion because it is the cathodic reaction in all types of fuel cells and the reduction process in aerobic respiration. A range of metalloenzymes achieve these challenging tasks in biology under ambient conditions and with high efficiency by using cheap and abundant first-row transition metals (e.g. iron, copper and manganese). The recent results presented here from the bioinorganic chemistry community lend credence to the participation of high-valent metal-oxo complexes in the above-mentioned processes. Notably, a high-valent molybdenum-oxo catalyst has also been recently reported as an efficient photocatalyst for hydrogen evolution from water [2]. Understanding the structures, properties and reactivities of such metal-oxo species is therefore critical for obtaining mechanistic insights into water oxidation and dioxygen reduction catalysis and for developing new, selective catalytic reagents and processes. Metal-oxo model complexes have now been synthesized using dioxygen or water as the oxygen source, via mechanisms reminiscent of the O₂/H₂O activation processes proposed in biology [19]. Many of these complexes show intriguing reactivities, which in turn have provided vital insights into the modeled enzymatic reactions. Among the most significant findings of these studies is the identification of the long sought-after metal-hydroperoxo intermediate on the way to the generation of the metal-oxo species upon dioxygen activation. Detailed kinetic studies of the step leading to the conversion of the metal-hydroperoxo species to the metal-oxo core have revealed the importance of the second coordination spheres (by ensuring precise coupling of electron and proton transfers) in minimizing the steady-state concentration of the hydroperoxo intermediate during the four-electron and four-proton reduction of dioxygen without the release of partially reduced dioxygen species. These hydrogen-bonding interactions have also been found to be important for O–O bond formation. Furthermore, in water oxidation chemistry the roles of calcium/strontium in the stabilization of high-valent metal-oxo species (responsible for the O–O bond formation step) as well

as in dioxygen release have been proposed [59,74^{••}]. The former proposition is also supported by the recent synthesis of the Lewis-acid adducts of the otherwise transient cobalt(IV)-oxo [81,82^{••}] and copper(III)-imido [83] intermediates.

Unfortunately, the activities exhibited by the model complexes are found to be falling far short of the activity of the biological catalysts in many cases, which have prevented their technological applications. Moreover, the lack of any isolable metal-oxo reactive intermediates responsible for the O–O bond formation step makes the mechanism of dioxygen evolution extremely ambiguous. Evidences in favor of the participation of the [Mn^{IV}–O[•]], [Fe^V(O)(OH)]²⁺, [Fe^V(O)(TAML[•])], [Co^{III}–O[•]] or [Ni^{III}–O[•]] cores in the O–O bond formation step during chemical and biological water oxidation reactions are only limited to theoretical studies. Thus, new and innovative synthetic strategies are still needed to be sought in subduing thus far inaccessible above-mentioned metal-oxo complexes that are of interest in the context of O–O bond formation studies. In dioxygen reduction chemistry, most of the functional catalysts are presently based on solid supported state, which has precluded any spectroscopic monitoring or detection of intermediates. This problem is a major obstacle for the development of kinetics and mechanistic studies in synthetic models or to answer important mechanistic questions such as the role of the Cu_B in the four-electron reduction of O₂. Future efforts should therefore concentrate on employing the SERRS-RDE technique of Dey and co-workers [28^{••}] in probing electrochemical systems using synthetic as well as biological catalysts for dioxygen reduction and to gain first-hand information on the reaction mechanism of these electrocatalysts. These goals may eventually lead to the development of cheap and efficient bioinspired/biomimetic catalysts for dioxygen activation/reduction and water oxidation that will influence the energy landscape of our society.

Acknowledgements

The authors gratefully acknowledge research support of this work by the NRF of Korea through CRI (NRF-2012R1A3A2048842 to WN) and GRL (NRF-2010-00353 to WN), the German funding agency Deutsche Forschungsgemeinschaft (Cluster of Excellence 'Unifying Concepts in Catalysis', grant number EXC 314/1 to KR) and Cost Action (CM1305 ECOSTBio to KR).

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