Why did Nature choose manganese to make oxygen?

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This paper discusses the suitability of manganese for its function in catalysing the formation of molecular oxygen from water. Manganese is an abundant element. In terms of its inherent properties, Mn has a particularly rich redox chemistry compared with other d-block elements, with several oxidizing states accessible. The most stable-state Mn^{2+} behaves like a Group 2 element—it is mobile, weakly complexing, easily taken up by cells and redox-inactive in simple aqueous media. Only in the presence of suitable ligands does Mn^{3+} become oxidized, so it provides an uncomplicated building unit for the oxygen-evolving centre (OEC). The intermediate oxidation states Mn(III) and Mn(IV) are strongly complexed by O^{2−} and form robust mixed-valence poly-oxo clusters in which the Mn(IV)/Mn(III) ratio can be elevated, one electron at a time, accumulating oxidizing potential and capacity. The OEC is a Mn_{6}CaO_{4} cluster that undergoes sequential oxidations by P680^{+} at potentials above 1 V, ultimately to a super-oxidized level that includes one Mn(V) or a Mn(IV)-oxyl radical. The latter is powerfully oxidizing and provides the crucial ‘power stroke’ necessary to generate an O–O bond. This leaves a centre still rich in Mn(IV), ensuring a rapid follow-through to O_{2}.

Keywords: manganese; oxygen; catalyst; evolution; water oxidation

1. BACKGROUND AND GOALS

The 21% oxygen (O_{2}) in our atmosphere results from the action of a single catalyst, the O_{2}-evolving complex of photosystem II, for which important structural details are now emerging (Ferreira et al. 2004; McEvoy & Brudvig 2006; Yano et al. 2006; Pushkar et al. 2007). Oxidation of H_{2}O in the so-called S-cycle occurs at a unique active site, the ‘oxygen-evolving complex’ (OEC) that contains 4Mn and 1Ca, and this process has continued, very likely with little alteration, since the advent of cyanobacteria more than 2.5 Gyr ago. This uniqueness and the fact that O_{2} is essential to and electro-catalysts for H_{2}O oxidation, not because we need more O_{2} but because it is highly desirable to produce hydrogen (H_{2}) by artificial water splitting through photolysis or electrolysis, and a half an electron becomes oxidized, so it provides an uncomplicated building unit for the oxygen-evolving centre (OEC). The intermediate oxidation states Mn(III) and Mn(IV) are strongly complexed by O^{2−} and form robust mixed-valence poly-oxo clusters in which the Mn(IV)/Mn(III) ratio can be elevated, one electron at a time, accumulating oxidizing potential and capacity. The OEC is a Mn_{6}CaO_{4} cluster that undergoes sequential oxidations by P680^{+} at potentials above 1 V, ultimately to a super-oxidized level that includes one Mn(V) or a Mn(IV)-oxyl radical. The latter is powerfully oxidizing and provides the crucial ‘power stroke’ necessary to generate an O–O bond. This leaves a centre still rich in Mn(IV), ensuring a rapid follow-through to O_{2}.

So why was Mn chosen for this task? The presence of Ca is not quite so specific as it can be replaced by Sr, but Mn is somehow indispensable. This paper summarizes the properties of Mn that make it special.

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One contribution of 20 to a Discussion Meeting Issue ‘Revealing how nature uses sunlight to split water’.

We start by considering the reactions involved and derive what we can from ‘textbook knowledge’ that is available to any undergraduate.

2. H_{2}O TO O_{2}

The energetics of O_{2} formation from H_{2}O have been considered by Krishtalik (1986) and I will outline his conclusions. The half-cell reaction equation (2.1), involves transfer of four electrons and four protons, and the reduction potential has a pH dependence of approximately −0.06 V per pH unit.

\[
O_{2(g)} + 4e^{-} + 4H^{+} + (aq) \leftrightarrow 2H_{2}O(l), \quad (2.1)
\]

\[
E^{°} = 1.23 \text{ V and } E^{+} (pH 7) = 0.82 \text{ V.}
\]

At pH 7, formation of a free molecule of O_{2} requires an energy input equivalent to 0.82 V per electron, that is 3.68 eV or approximately 350 kJ mol^{−1}. In photosystem II this compares with an available energy of approximately 1.25 V per electron, the driving force provided by P680^{+} (Grabolle & Dau 2005). Outside biology, in laboratory experiments, it is relevant to note that no reversible electrochemistry of the four-electron O_{2}/H_{2}O couple has been reported. Reduction of O_{2} to H_{2}O requires a sizeable overpotential, even at a Pt electrode, and the sluggish kinetics of this reaction are a major concern in the performance of fuel cells (contrast with 2H^{+}/H_{2} which is reversible at Pt and some enzyme electrodes; Anderson & Albu 2000). Electro-chemically, the reverse reaction, electrochemical oxidation of H_{2}O to O_{2}, is at least as difficult.

Krishtalik’s analysis of the O_{2} evolution problem was more sophisticated than I outline here, as he corrected reduction potentials for transfer of species between the catalytic active site and the environment. I will present
only the simple acid–base and electrochemistry considerations that are most familiar to all chemists. The substrate H2O is present at approximately 55 M and although the products of deprotonation, OH− and O2−, are much easier to oxidize, they are present only at tiny or immeasurable amounts. One function of the catalyst is therefore to generate these minority species in the active site by abstracting H+ and stabilizing OH−/O2− by coordination to a metal ion M. Since OH− and particularly O2− are strong π-donor ligands, they coordinate preferentially to transition metal ions having a high availability of suitable acceptor orbitals, most notably metals to the left side of the d-block and increasingly upon oxidation, since removing electrons from a metal ion releases H+ from coordinated H2O. Taking simple Mn species as examples, the pK of a coordinated H2O molecule is approximately 10.5 for Mn(II), approximately 0 for Mn(III) and even the remaining proton is lost upon oxidation to Mn(IV) which therefore coordinates (and stabilizes) O2− (Wiberg 2001). Transition metals coordinated by O2− ligands are commonly written as [M=O] units, although the ‘double bond’ is just a notation to indicate additional π-bonding that can vary in its extent. As the formal oxidation state of M increases, so does the likelihood that the electron is removed instead from the O2− ligand so it becomes an oxyl radical O−.

The aim of this article is not to discuss detailed mechanism; several recent articles have discussed the different possibilities that could apply given the latest refinements in structure (Messinger 2004; McEvoy et al. 2005; Siegbahn 2006, 2007). The defining property of the OEC is perhaps not so much that it produces O2 (catalases also do this) but that it makes an O−O bond. It is the only example in biology in which an O−O bond is formed from two H2O molecules, yet no long-lived intermediates (such as H2O2) are released. The single O−O bond, as occurs in a compound like hydrogen peroxide (H2O2, O−O bond energy 142 kJ mol−1) is very much weaker than the double bond of O2 (O=O bond energy 494 kJ mol−1) so that once an O−O bond is formed, completion through to O2 is comparatively easy if further oxidizing capacity is available (Emsley 1998; Wiberg 2001). Indeed there is recent evidence that the latter stages of O2 production may be reversible (Clausen & Junge 2004).

To picture the general energy profile for water oxidation, an oxidation state diagram for O is shown in figure 1. The gradients between selected intermediates show the corresponding reduction potentials for that stage (Atkins et al. 2006). I have used pH = 7 because this condition is familiar to biochemists and the features are qualitatively similar regardless of pH and even using Krishtalik’s corrected potentials. The graph shows why Krishtalik argued that any mechanism involving four one-electron reactions would encounter a particularly steep climb at H2O → OH and be energetically very unfavourable compared with two sequential two-electron transfers or a reaction in which all four electrons are transferred in a single step. Looked at in another way, formation of 'OH (or any form of oxygen in the 1-state) should occur in pairs, so that most of the energy cost is recouped by simultaneous O−O bond formation.

A variety of options arise for achieving two- and four-electron transfers from metals to O-species that avoid one-electron intermediates, and some of these are sketched in figure 2. The two-electron intermediate is a peroxide, retained in the OEC, which can be formed either (a) by simultaneous oxidations of two adjacent coordinated H2O (OH−), via combination of the corresponding oxyl radicals, or (b) by attack by H2O (or OH−) on a ‘hot’ electrophilic oxygen atom on a highly oxidized [M=O] group (Lamburg et al. 1999; Messinger 2004). As stated above, formation of the O−O bond alone provides approximately 142 kJ stabilization relative to two separate OH− radicals. Figure 2 shows two further scenarios: (c) that two adjacent ‘hot-O’ species, terminal [M=O] or bridging O (µ-O) could rearrange to form O2 (this would also form the basis of a concerted four-electron reaction (−4 to 0) in figure 1; Vincent & Christou 1987) and (d) attack by a cluster (bridging) O2− (or a radical-like O) on an oxyl radical attached to a high-valent metal (Siegbahn 2006, 2007).

3. THE REDOX CHEMISTRY OF Mn

Biology required a catalyst capable of removing four electrons and four protons from two H2O in stages that mostly involve highly oxidizing species, with retention of all intermediates during the process. In addition to successive electron transfers, protons must be removed and transferred away rapidly and efficiently, states must exist that permit rapid binding of substrate H2O/OH− and the whole structure must be sufficiently robust to survive tens of thousands of turnovers before subunit D1 is replaced (Aro et al. 1993; Ananyev & Dismukes 2005; Cady et al. 2008). The ‘hot’ O species underlying the mechanistic ideas in figure 2 are optimized by metal ions M able to balance the ability to form an oxy species [M=O] from H2O in the first place, yet, with little further provocation, transfer O as an atom or radical and return to reduced M.
Figure 2. Sketches of skeletal mechanisms for formation of an O₂ molecule from two molecules of H₂O. Elevations in oxidation state of M are indicated by ‘+’, etc. Boxes indicate the crucial stages in each mechanism. (a,b) Ways of making an O–O bond (peroxo intermediate) that is relatively easy to oxidize further to give O₂. (a) Formation of peroxo intermediate by homonuclear combination from adjacent M⁺–OH units deprotonated and rearranged as two oxyl radicals. (b) Formation of peroxo intermediate by attack of H₂O on an electrophilic ‘O’ of [M=O]⁺⁺⁺ group. (c) Interconversion between two O₂⁺ that are either terminal ([M=O]⁺⁺⁺) or bridging ([μ-O] between two M⁺⁺), an O₂⁺ bridged between two M⁺⁺, and O₂ bound (weakly) between two M. (d) Attack of a bridging O₂⁺ on an oxyl radical.

Figure 3. Oxidation state diagram for Mn aqua species at pH 0 and 14, and the stabilization afforded as Mn species are transferred from pH 0 to 14. Inset shows ionization energies (IE) for Mn (black bars) and Fe (white bars). Reduction potentials for Mn(V) and Mn (VI) aqua species in acidic solutions are subject to large uncertainties; hence the large spread in volt-equivalent values for these species at pH 0.

Phil. Trans. R. Soc. B (2008)
The underlying redox chemistry of Mn is appreciated from the stabilities of simple compounds with oxygen and water. These stabilities are portrayed in the oxidation state diagram given in figure 3, where the inset compares ionization energies (IEs) of Mn and Fe. The diagram reveals a rich redox chemistry in which all states above Mn(II) are strongly oxidizing under some conditions. Most obviously Mn(II) sits in a local recession and is thus inherently stable under all conditions, Mn(III) is inherently unstable under acid conditions and Mn(V) is unstable under all conditions. I will return to this diagram after reviewing possibilities that are offered by other d-block metals.

Biology uses many first-row d-block elements, V, Mn, Fe, Co, Ni, Cu and Zn, but not Ti nor to any certain degree Cr. As we move across the 3d row, the highest accessible oxidation states as well as the number of accessible oxidation states increase up to Mn then decrease to Zn where only the 2+ state is observed (Atkins et al. 2006). This is chiefly a function of IEs which increase across the row and for each electron removed. Not only does Mn display a greater range of oxidation states than other 3d metals, but all the simple higher states, from Mn(III) upwards, are hydroxo- or oxo-species with reduction potentials in the ranges of the O-transformation reactions we have just outlined. Both V and Cr have several oxidation states available; however, V(V) (\([V(O)2]^{3+}\)) is only moderately oxidizing and although Cr(V) and Cr(VI) are strongly oxidizing, Cr(II) is powerfully reducing and the most stable-state Cr(III) is immobilized because it undergoes ligand exchange too slowly to be incorporated into a protein as a metal cofactor. Hence these metals are inherently unsuitable.

Beyond Mn, the chemistry of Fe most resembles that of Mn. The ferryl entity [FeO]2+ is well known as an intermediate in the reductive activation of \(O_2\) and it can even be generated as an anion species by reacting Fe(II) with ozone (Pestovsky et al. 2005). Of the higher oxidation states, Fe(V) has proved elusive but a complex has recently been reported (Tiago de Oliveira et al. 2007), and Fe(VI) exists as the ferrate ion \(FeO_2^-\) that is produced by oxidation in concentrated alkali (Wiberg 2001). For the later 3d elements, complexes in the higher oxidation states tend to be binuclear, consisting of a diamond-shaped core with two bridging oxo ligands \([M_2(\mu-O)_2]^{2+}\) that resemble sections of the OEC (Que & Tolman 2002). A particularly interesting example of these diamond-core complexes is found for Cu, for which isomerism exists between species formulated as \([\mu-\eta^2-\eta^2\text{-peroxo} Cu(I)]\) and bis\{\(\mu\text{-oxo}\) Cu(III)}]. This chemistry is relevant as Cu(III) is expected to be powerfully oxidizing; yet, in the common reversible \(O_2\)-binding protein haemocyanin, the incoming \(O_2\) molecule is coordinated centrally between two Cu(I) giving an adduct that is formulated as \([\mu-\eta^2-\eta^2\text{-peroxo} Cu(II)]\) (Atkins et al. 2006). A plausible transformation from bis\{\(\mu\text{-oxo}\) Cu(III)}] to \(2Cu(\text{I})+O_2\) would resemble the mechanism in figure 2c.

Of the second and third row d-block elements, only Mo and W are used in biology and neither of these is sufficiently oxidizing even in the VI state \([M(O)_2]^{2+}\). In studies to identify artificial catalysts for water splitting the best metal so far has appeared to be Ru, which is functional in compounds featuring the oxidation states III, IV and V (Meyer & Huynh 2003; Alstrum-Acevedo et al. 2005; Liu et al. 2007). But there is no evidence that Ru is used by biology. Clearly, efforts to make catalysts based on Mn (or Fe) are highly desirable because Ru is much rarer and more expensive than Mn.

The inherent stability of Mn(II) arises from the electron configuration 3ds2 in which the d-shell is half-filled—a favoured configuration due to optimal exchange energy. (The fact that a free Mn atom has the electron configuration 4s23d5, again with a stable half-filled d-shell, is one reason why metallic Mn has an unusually low heat of atomization and electropositive character among the d-block elements; Atkins et al. 2006.) The exchange energy makes it difficult to remove the fifth d-electron, so Mn(III) compounds are oxidizing—Mn3+ particularly so:

\[Mn^{3+} + e^- \rightarrow Mn^{2+}\]  

The oxidation state diagram in figure 3 is shown for pH 0 and pH 14, and the difference between the two datasets indicates the stabilization afforded by \(OH^-/O_2^-\) coordination. There is clearly a shortage of data for Mn species that are unstable in crude aqueous media but could be stabilized in special environments.

In contrast to the inherent instability of simple Mn(III) compounds, simple Mn(IV) chemistry is represented under all aqueous conditions as the insoluble compound MnO2, which has a high lattice energy and is effectively a thermodynamic sink. Mn(III) aqua species tend to disproportionate to Mn(II) and Mn(IV). This happens naturally in solution and would be predicted to occur in multi-nuclear O-type structure that Mn(III) complexes or in Mn(III) minerals, although it need not occur if single Mn(III) species are isolated. This tendency contrasts with Fe where the ‘rust-like’ [Fe-O-Fe] entity with Fe(III) ions bridged by \(O_2^-\) is very stable (Frajstova da Silva & Williams 2001). An example of where this prediction holds is the mixed-valence oxide Mn3O8, which contains Mn(II) and Mn(IV), rather than Mn(III) (Wiberg 2001).

A major gap in our knowledge of how the OEC works is the complete lack of electrochemical data for any stage of the S-cycle. Despite our ignorance in this area, it is now widely accepted that state S2, the source of the most characteristic electron paramagnetic resonance (EPR) signature during catalysis, should be formulated as \([\text{Mn}(\text{III}) : 3\text{Mn}(\text{IV})]\) rather than \([\text{Mn}(\text{III}) : 1\text{Mn}(\text{IV})]\) as favoured earlier (McEvoy & Brudvig 2006). The elevated-oxidation-level assignment is supported by reductive titration of the OEC with hydroxylamine, during which states S 0 and S 2 were formed and characterized (Kuntzleman & Yocum 2005). State S0 is formulated as \([3\text{Mn}(\text{III}), \text{Mn}(\text{IV})]\) and there is spectroscopic evidence that it does not contain Mn(II) (so disproportionation of two Mn(III) has not occurred; Kulik et al. 2005). It follows that the ‘power stroke’ driving O-O bond formation does not stem from reduction of Mn(III), which is instead stabilized in the OEC. We look instead to higher

\[E^0 = 1.51 \text{ V.}\]
oxygenation states and note that state $S_4$, from which $O_2$ is released, must be at a level one equivalent above $4\text{Mn(IV)}$; consequently, the crucial species for O–O bond formation is likely to include Mn(V) (or Mn(IV)-oxyl radical) (Shimazaki et al. 2004).

Of the highest oxidation states, only Mn(VII) is important in everyday chemistry. The familiar purple MnO$_4^-$ ion, which exemplifies the stabilizing effect of O$^2-$ as an anionic, strong $\pi$-donor ligand, liberates $O_2$ from H$_2$O in a slow process. The anhydrous oxide Mn$_3$O$_5$ ($O_3$MnOMnO$_3$) is extremely reactive and decomposes at 0°C (explosively at 95°C) yielding $O_2$ and MnO$_2$ (Wiberg 2001). However, it is very difficult to consider how a single metal ion could be harnessed catalytically to carry out a demanding four-electron reaction, and biology's use of a metal-oxo cluster to provide the necessary capacity to do this 'made good sense'. The data given in figure 3 for Mn(V) and Mn(VI) are reliable only for pH 14, because the aqua species are unstable in acid (Carrington & Symons 1956; Zordan & Hepler 1968). The simple aqua species are unstable in acid (Carrington & Symons 1956; Zordan & Hepler 1968). The simple aqua species are unstable in acid (Carrington & Symons 1956; Zordan & Hepler 1968).

4. THE AQUEOUS COORDINATION CHEMISTRY OF Mn SPECIES

In aqueous solution, the chemistry of Mn is dominated by the aqua ion Mn(H$_2$O)$_6^{2+}$ which remains unhydroylysed up to pH 9. Owing to its lack of ligand field stabilization, Mn(II) forms weaker complexes than other divalent $d$-block metals and it behaves more like Group 2 metal ions for which the only truly stable complexes in water are those with chelating ligands (Tagore et al. 1994). These complexes are quite stable and do not react with H$_2$O.

5. AVAILABILITY OF Mn IN BIOLOGY

Manganese is the twelfth most abundant element in the Earth's crust (approx. 950 ppm), the third most abundant transition element, and it occurs in seawater as the Mn$^{2+}$ aqua ion at a concentration of approximately $10^{-4}$ ppm (Wiberg 2001). It is likely that in the archaean Earth there would have been extensive complexation by bicarbonate ions (HCO$_3^-$) due to the very high level of $CO_2$ existing at that time, and Mn(II)-bicarbonate clusters of the type $[\text{Mn(HCO}_3\text{)}_2]_n$ would have existed (Dismukes et al. 2003). In minerals, Mn is almost entirely found as oxides, or with other $O$-containing anions such as silicates. The most common sources are Mn$_2$O$_3$ (pyrolusite), Mn$_3$O$_4$ (hausmannite) and MnCO$_3$ (rhodochrosite). Other naturally occurring oxides include manganite (MnO(OH)) and MnO (manganosite; Wiberg 2001). Rich deposits of manganese are found as 'manganese nodules' on the ocean floor: compacted colloidal particles of Mn/Fe oxides containing 15–20% Mn. Thus, manganese is a plentiful and freely available resource.

The difficulty in stabilizing Mn(III) starts to recede once we improve the complexing power of the aqueous solvent, either by increasing the pH or introducing ligands with good donor properties. An important example (see below) is the stabilization of Mn(III) by bicarbonate (HCO$_3^-$), a ubiquitous ligand in natural waters, which lowers the IV/III reduction potential from 1.5 to 0.6 V (Kozlov et al. 2004; Dasgupta et al. 2006). Owing to its $d^3$ configuration the coordination sphere of Mn(III) is subject to Jahn–Teller distortion, which allows Mn(III) to have fast rates of ligand exchange, like Cu(II) or Cr(II), for monodentate ligands like H$_2$O.

Mn(IV) complexes are mainly found with bridging or terminal oxo-ligands, and polynuclear Mn–O clusters of mixed valency are common. Of these, compounds of the type $[\text{Mn}_n\text{O}_4\text{L}_m]$, based on a $\text{Mn}_4\text{O}_4$ cubane cluster and containing both Mn(III) and Mn(IV), have attracted interest as structural and functional models for the OEC (Rüttinger & Dismukes 1997). These clusters assemble spontaneously when L is a suitable ligand like phosphinate (RRP$_2^-$), which resembles bicarbonate in the arrangement of its donor orbitals. A relevant note here is that the oxidation levels of polynuclear Mn–O clusters, including the OEC, are usually considered in terms of localized Mn oxidation states, although this may be a mistaken generality (Glatzel et al. 2004). Owing to its $d^3$ configuration, Mn(IV) should favour octahedral geometry and this is observed for each subsite of Mn$_4$O$_8^{2+}$ (Wu et al. 2006). Normally we would expect simple Mn(IV) complexes to display much slower rates of ligand exchange than Mn(III), a property that is well established for another $d^3$ ion Cr(III) (Atkins et al. 2006). Studies on model $\mu$-oxo dimanganese complexes have suggested that this is the case when considering exchange of bridging oxo-ligands (Tagore et al. 2006). However, for terminal ligands, the strong $\pi$-donor ability of terminal or bridging O is expected to labilize a trans position, thus terminal water exchange at Mn(IV) could be fast.

F. A. Armstrong 1267

Nature chooses manganese to make oxygen

Phil. Trans. R. Soc. B (2008)
Owing to the difficulty in oxidizing Mn$^{2+}$ in simple aqueous environments, it is almost certain that this form is the one available to organisms, although it has recently been proposed that dissolved Mn(III) species may persist in certain ‘suboxic’ marine environments where insoluble Mn(IV) oxides at the seabed are subject to reduction by inorganic sulphides like H$_2$S (Trouwborst et al. 2006). I remarked above that the Mn$^{2+}$ cation is very stable, exchanges ligands rapidly and forms soluble salts; these factors, coupled with its natural abundance and the fact that (unlike Mg) a cell’s requirement for Mn is very low, means that supply will usually exceed demand. For plants, soil acidity increases the availability of Mn and leads to toxicity, whereas alkaline environments can actually result in Mn deficiency. Once taken up by an organism, Mn will tend to remain as Mn$^{2+}$ unless it is captured by ligands that favour its oxidation to Mn(III) and Mn(IV).

The mechanisms of Mn$^{2+}$ transport and homeostasis are best understood in micro-organisms, and only recently have Mn$^{2+}$ transport pathways begun to be identified in plants (Chandler et al. 2003; Pittman 2005). These pathways include specific plasma membrane ‘Nramp’ Mn$^{2+}$ transporters, as well as broad specificity systems that transport Mn$^{2+}$ along with Ca$^{2+}$, Mg$^{2+}$ and Fe$^{2+}$. In plant cells, excess Mn$^{2+}$, which is highly toxic, accumulates in vacuoles as a result of ‘housekeeping’ mechanisms that are linked with Fe homeostasis. It is not clear how Mn is transported into chloroplasts.

6. ASSEMBLY AND MAINTENANCE OF THE OEC

How did the OEC come into existence? Dismukes and co-workers have considered this question and drawn attention to the important role that bicarbonate might have played as a Mn$^{2+}$ chaperone in the archaean period (some 3–4 Gyr ago) when atmospheric CO$_2$ levels were extremely high (Ananyev et al. 2001). The concentration of HOCO$_2$K in the oceans would have been high enough for [Mn(HOCO$_2$)]$^{+}$ and higher complexes to exist in solution (Baranov et al. 2000). It has also been argued that bicarbonate, at these high concentrations, would have been a more efficient substrate than H$_2$O for O$_2$ production (Dismukes et al. 2001). As mentioned earlier, complexes formed by reaction of Mn$^{2+}$ with HOCO$_2$K are quite easily oxidized to Mn(III) and an intermediate of this nature is proposed to be important in OEC assembly (Baranov et al. 2000). There is indeed evidence that a carbonate is retained as a ligand in the intact OEC (Ferreira et al. 2004). The indigenous protein ligands lining the Mn,CaO$_2$ binding site, mainly glutamates and aspartates, are also highly suited to coordinating a cluster of ‘hard’ metal ions, and it has been proposed that the OEC might originally have been a Ca site (Fraústo da Silva & Williams 2001). Even without much ‘chemical’ intervention, Mn$^{2+}$ ions may have become trapped in such sites by photooxidation, due to the higher solar UV intensity of the pre-oxygenic/ozonic Earth (Allen & Martin 2007).

Since the mainstay of the S-state cycle involves interconversions between Mn(III) and Mn(IV) the OEC avoids formation of the labile Mn$^{2+}$ and remains intact. The OEC is stabilized structurally by Mn(IV)–O bonding and accumulates charge over a range of Mn(III)/Mn(IV) states leading finally to Mn(IV)/Mn(V) then back to S$_0$, which does not include the labile Mn(II). An Fe–O cluster would behave differently in this respect. The binding constants for high-spin Fe(II) with O-donor ligands are only marginally higher than for Mn(II), and much less than Mn(III) (Fraústo da Silva & Williams 2001). Also, Fe(IV) is too oxidizing to provide a stable intermediate (compare the lack of Fe(IV) oxides with the abundance of Mn(IV) oxides). An Fe–O cluster equivalent of the OEC able to accumulate oxidizing power by sequential oxidations would therefore be one in which the subsites cycle between Fe(III) and Fe(II). Although similar redox cycling occurs in Fe–S clusters as part of their physiological function, it is clear that clusters consisting mainly (or entirely) of Fe(II) are more labile. An Fe–O cluster might be prone to loss of labile Fe$^{2+}$ in the same way as the Fe-storage protein ferritin releases Fe upon reduction (Atkins et al. 2006). Loss of Fe$^{2+}$ would occur particularly during darkness where a reduced, resting state would prevail. It follows that Mn(II) may not be relevant, apart from providing a source of Mn, and the oxidation of Mn(II) to

$$\text{Mn}^{2+} \rightarrow \text{Mn}^{3+} \rightarrow \text{Mn}^{4+} \rightarrow \text{Mn}^{5+}$$

**Figure 4.** Summary of the roles played by each oxidation state of Mn. The Mn(II) is an abundant mobile building unit which is taken up into the OEC and trapped by oxidation; Mn(III) and Mn(IV) provide a stable framework within which oxidizing equivalents are accumulated by increasing the Mn(IV) content; Mn(V) (or an oxyl radical) hosts the ‘hot’ O-atom generated and spent during the ‘power stroke’ of the S-cycle (S$_3$–S$_0$). No labile Mn$^{2+}$ is generated at any part of the cycle.
Mn(III) is important only for the purpose of assembling the OEC. Figure 4 summarizes and integrates the useful properties of the various oxidation states of Mn, as they are relevant to the function of the OEC. There is no single property of manganese that suits it for its role—rather there are several attributes, ranging from its elemental abundance and availability as a stable aqua-cation to its unrivalled repertoire of redox chemistry under highly oxidizing conditions.

This research is supported by the BBSRC and EPSRC. The Leverhulme Trust and St Johns College, Oxford are also gratefully acknowledged.

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Nature chooses manganese to make oxygen

F. Armstrong


Discussion

J. Barber (Imperial College London). Nature chose Mn not only due to its chemical properties but because it is an abundant transition metal in the environment. If you could choose any metal from the periodic table to replace Mn, independent of its abundance, which would it be?

F. Armstrong. From a simple angle of catalytic competence, it would be Ru, because compounds of this element are well known to have high activities in O2 evolution (see papers by T. J. Meyer). However, there is a lack of simple Ru species (labile aqua ions) that could be easily processed by a living organism. I would therefore suggest that Fe is the best alternative.

W. Junge (University of Osnabrück). You are reporting on Mn-energetics ‘in aquo’. How much are these figures affected not only by the number of ligands but also their chemical nature, in short by ‘the protein’?

F. Armstrong. The basis of energetics in coordination chemistry is the competition between a ligand and the one or more water molecules that it replaces in an interchange reaction. This competition is reflected in equilibrium constants and the change in the reduction potential of the half-cell reaction. Higher oxidation states are favoured (i.e. the reduction potential is lowered) when the ligand is a strong σ-donor, strong π-donor and negatively charged, whereas lower oxidation states are favoured by neutral ligands, particularly if they are π-acceptors. Ligands of the latter type include not only the exchangeable molecules CO and O2, but also either of the two imidazole-N atoms of a histidine side chain. In a protein, there is also a tendency for the most stable oxidation state to be the one that confers ‘lowest internal electrical charge’, although this is usually achieved by deprotonating an aqua/hydroxo ligand if one is present. Oxide (O2–) is a particularly important ligand for higher oxidation states of transition metals like manganese as it is a good π-donor and its −2 charge enables it to provide very economical coordination: for example, stabilization of Mn(VII) by F− would require at least seven F− ligands (which would be sterically unfavourable) rather than just four O2–, as in MnO42−.)