In Stress Biology of Cyanobacteria, CRC, 2013

2 Water Oxidation and Water-Oxidizing Complex in Cyanobacteria

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CONTENTS

2.1 INTRODUCTION

Cyanobacteria, or blue-green algae as they were called, are a group of bacteria that obtain their energy through oxygenic photosynthesis (for a perspective, see [1]; for evolution, see [2]).Cyanobacteria converted the early reducing atmosphere into an oxidizing one and changed the composition of life forms on Earth. The consensus is that chloroplasts in plants and eukaryotic algae have evolved from cyanobacterial ancestors via endosymbiosis [3]. In this chapter, we will discuss the structure and function of the water-oxidizing complex (WOC) in cyanobacteria [4,5].

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Edited by A.K. Srivastava, A.N. Rai and B.A. Neilan

Using the energy from sunlight, photosynthesis converts CO_2 into organic compounds [6,7]. In plants, algae, and cyanobacteria, photosynthesis uses CO_2 and water, and releases oxygen as a waste product. In these oxygenic photosynthetic organisms, a linear electron-transport system is used for the conversion of nicotinamide adenine dinucleotide phosphate ($NADP^+$) to its reduced form (NADPH); water is the ultimate source of electrons and is oxidized to oxygen in the process [8]. Oxygenic photosynthetic organisms catalyze photosynthetic water oxidation, and are therefore responsible for the presence of oxygen in the earth's atmosphere. This process requires two photosystems—photosystem I (PSI) and photosystem II (PSII)—and two light reactions (I and II), working in series, using what is commonly known as the Z-Scheme [9] (see Chapter 1 for a description of the overall steps in oxygenic photosynthesis.). PSII (water–plastoquinone oxido-reductase) uses light (photons) to energize specific reaction center chlorophyll molecules; this leads to electron transfer from water, through several intermediates (coenzymes and cofactors), to plastoquinone [10]; water is oxidized to hydronium ions and molecular oxygen [11,12]. The resulting protons generated by the oxidation of water are used to create a proton gradient that is used by ATP synthase to generate ATP [13]. The reduced plastoquinone (plastoquinol) transfers its electrons to PSI [14] via a cytochrome b_6f (Cyt b_6f) complex [15] where, again, protons are released into the lumen and a proton gradient is produced across the thylakoid membrane and used for ATP synthesis. The electrons (from PSII) transferred to plastoquinone are ultimately used, by PSI, to reduce $NADP^+$ to NADPH or are used in cyclic photophosphorylation around PSI [13]. In Cyt b_6f complex, electrons pass through several intermediates (cytochrome f, Rieske iron center) to plastocyanin (or cytochrome c_6 in some cyanobacteria), which is the electron donor to PSI, in its reduced form.

The WOC, also referred to as oxygen-evolving complex (OEC), in PSII is the protein complex that oxidizes water [3,16–19]. PSII may serve as a model to split water by sunlight, which is a prerequisite for a sustainable hydrogen economy [18]. In this chapter, we will review water oxidation and the WOC in natural photosynthesis (see Wydrzynski and Hillier [19] for reviews that deal with both natural and artificial photosynthesis and their relationship to "Solar Fuels").

2.2 A BIT OF HISTORY OF PHOTOSYNTHESIS

Joseph Priestley (1733–1804) described the ability of plants to generate "phlogiston" (the power to store the air which had been injured by the burning of candles); this was the discovery of oxygen evolution by plants [6,20]. During this period of "New Chemistry," Carle Wilhelm Scheele (1742–1786) and Antoine Laurent Lavoisier (1743–1794) identified this gas as oxygen. Jan Ingenhousz (1730–1799) discovered the role of light and the importance of the green color (later established as chlorophyll) of plants, and Jean Senebier (1742–1809) discovered the role of CO_2 in photosynthesis. Nicholas Theodore de Saussure (1767–1845) established the role of water, and finally Julius Robert Mayer (1814–1878) provided the concept that in photosynthesis light energy is converted into chemical energy. Robert Hill (1899–1991) discovered that when "chloroplasts" were exposed to light in the presence of an artificial electron acceptor, oxygen evolution was observed; this "Hill reaction" shows that carbon assimilation and oxygen evolution are not obligatorily linked and two distinct systems may exist [21]. (For a timeline of photosynthesis see [22].)

There are two parts to photosynthesis (Figure 2.1) [7]:

1. The reactions that depend directly on light take place in specific pigment–protein complexes in the thylakoid membranes; they are called the "light reactions." Here, light energy is converted into chemical energy. The end product of this set of reactions, which includes many dark reactions as well, is the production of oxygen, of the reducing power (NADPH) and of the ATP. Production of oxygen is the focus of this chapter.
2. The so-called *dark reactions* that do not depend directly on light take place in the stroma or cytoplasmic region; here CO_2 is converted to sugars. The dark reactions involve a cycle called the Calvin–Benson cycle, in which CO_2 and energy from NADPH and ATP are used to form sugars.

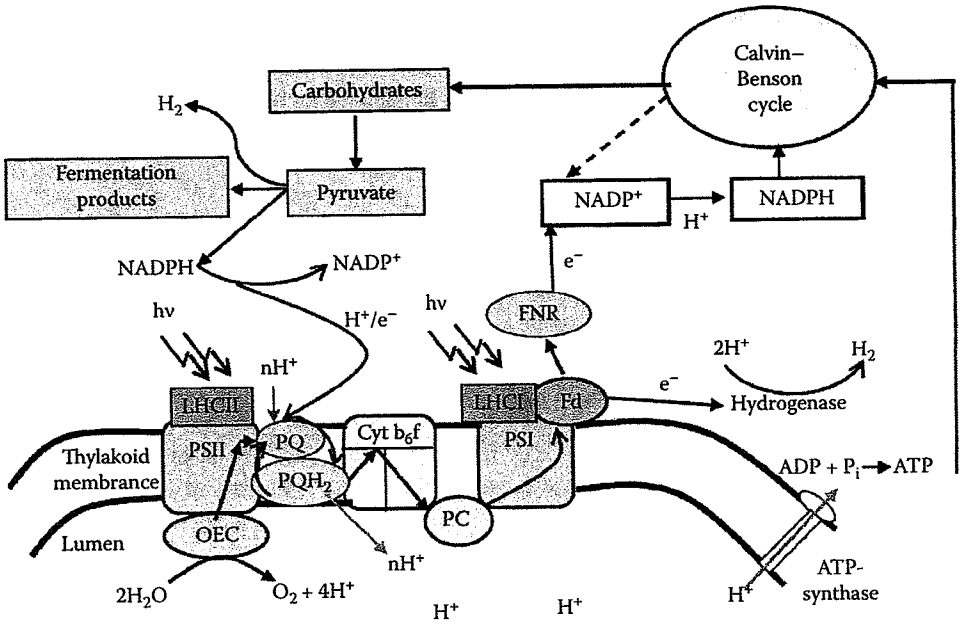


FIGURE 2.1 Carbon fixation and oxygen evolution take place in two distinct spaces in oxygenic photosynthesis. The diagram shows a schematic view of light-powered hydrogen production during oxygenic photosynthesis, as well as carbohydrate synthesis that can also be followed by hydrogen production. The photosynthetic processes are driven by light energy captured by the light-harvesting complexes (LHCII and LHCI) of PSII and PSI. Electrons are ultimately derived from H_2O by its oxidation at the water-oxidizing complex (WOC) of PSII; these electrons are passed along the photosynthetic electron-transport chain via plastoquinone (PQ), the cytochrome b_6/f complex (Cyt b_6/f), plastocyanin (PC) (or cytochrome c_6), PSI, and to ferredoxin (Fd). Then, ferredoxin–$NADP^+$ oxidoreductase (FNR) transfers the electrons to $NADP^+$ with the final production of NADPH. Protons (H^+ ions) are released into the thylakoid lumen by the WOC as water is oxidized, as well as when PQH_2 delivers electrons to Cyt b_6/f complex. The proton gradient across the thylakoid membrane is used by ATP synthase to produce ATP. The ATP and NADPH generated during the primary photosynthetic processes are consumed during CO_2 fixation in the Calvin–Benson cycle, which produces sugars and ultimately starch. Under anaerobic conditions, hydrogenase can accept electrons from the reduced Fd molecules and use them to reduce protons to molecular hydrogen. Anaerobic conditions also allow the use of starch as a source of protons and electrons for H_2 production (via NADPH, PQ, Cyt b_6/f, PC, and PSI) using a hydrogenase enzyme. (From *J. Photochem. Photobiol. B*, 104, Allakhverdiev, S.I., Recent progress in the studies of structure and function of photosystem II, 1–8, 2011, Copyright 2011, with permission from Elsevier.)

In the following sections, we describe the structure and function of the manganese–calcium cluster that performs one of the most important reactions in Nature, *water oxidation*.

2.3 WATER OXIDATION AND WATER-OXIDIZING COMPLEX IN NATURAL PHOTOSYNTHESIS

Water oxidation is one of the most important reactions on the Earth since it is the source of nearly all the atmosphere's oxygen. The WOC is a manganese–calcium cluster that oxidizes water with modest driving force and with a turnover of up to 50 molecules of O_2 released per second [23]. The structure is expected to be the same in plants, algae, and cyanobacteria. In this section, we present the available atomic level structure and the most accepted mechanism of water oxidation by the Mn–Ca cluster. (We refer the readers to a small, but wonderful, book that deals with oxygen itself, its history, and its role in the evolution of life [24].)

2.3.1 Structure of the Water-Oxidizing Complex

The first pioneering paper dealing with the structure of PSII was on the cyanobacterium *Synechococcus elongatus* from the research groups of Horst Witt and Horst Saenger [25], which was followed by structural analysis of PSII from *Thermosynechococcus vulcanus* by Kamiya and Shen [26]. The first clear evidence for the cubane model came from the laboratories of James Barber and So Iwata in 2004 [27]. These authors also provided, for the first time, information on Ca in the WOC: here was a Mn_3Ca-cubane with the fourth Mn attached a bit far away [27].

The atomic level structure of the Mn_4Ca cluster is important for the understanding of the mechanism of water oxidation. Both extended x-ray absorption fine structure (EXAFS) and x-ray diffraction (XRD) studies have been successfully used to determine the structure of the WOC in PSII, particularly from cyanobacteria [25–30].

The most accepted model based on XRD, EXAFS, hyperfine splitting, and other physical constraints is the *dangler model*, where three Mn ions are strongly coupled and one "dangling" Mn interacts with the trimer [25–30]. These XRD, EXAFS, and other methods provided the arrangement of all of the protein subunits and the location of the chlorophylls and other cofactors, and formed a basis for further investigations on PSII [25–30]. However, the early investigations did not provide enough details for the structure of the Mn_4Ca cluster, the location of the substrate water molecules, or the precise arrangement of the amino acid side chains and cofactors that may have significant mechanistic consequences in water oxidation.

In 2011, the research groups of Jian-Ren Shen and Nobuo Kamiya significantly improved the resolution of the PSII crystals from the thermophilic cyanobacterium *T. vulcanus* down to a high resolution of 1.9 Å; further, the authors analyzed their structure in details [29,30]. Their investigation has provided many more details of the structure of the WOC containing the number and location of the bridged oxygen, the location of substrate water molecules, and the precise arrangement of the amino acid side chains [29,30] (for a historical account, see [31]).

In this latest structure of the WOC, Umena et al. [29,30] found four manganese ions, one calcium ion, and five oxygen atoms that serve as oxo bridges linking the five metal ions (four manganese and one calcium ion) (Figure 2.2). In addition, four terminal water ligands were found, two of which were coordinated to Ca and two to the dangling Mn(Mn(4)).

The aforementioned structure suggests that the manganese–calcium cluster could be described as $Mn_4CaO_5(H_2O)_4$. Of these five metal ions and five oxygen atoms, the calcium and three manganese ions occupy four corners and four oxygen atoms form the other four corners of the cubane-like structure. Regarding the Ca–O and Mn–O bond lengths, the cubane-like structure is not an ideal and symmetric one. Another manganese ion is located outside the cubane and is linked to two manganese ions within the cubane by one oxygen of the cubane and the fifth oxygen by a di-μ-oxo bridge (an oxygen atom bridged between two or three metal ions) [29,30]. The location of possible substrate water molecules is very important for the understanding of the mechanism of water oxidation by the WOC.

A few amino acids with carboxylate and imidazole groups are coordinated to the $Mn_4CaO_5(H_2O)_4$ cluster (Table 2.1) [29,30]. Generally, the carboxylate ion may coordinate to a metal ion in different modes (Figure 2.3). In the WOC, only one monodentate mode of carboxylate is observed and other carboxylate groups serve as bidentate modes [29,30]. Each of the four manganese ions has six ligands, whereas the calcium has seven ligands (Table 2.1).

In the following sections, we describe the detailed structure of the WOC revealed at a resolution of 1.9 Å.

2.3.1.1 Manganese Ions

Manganese is a trace mineral that participates in many enzymes [33]. It is found widely in *Nature*, but occurs only in trace amounts in human tissues. Mn(II) or (III) ions function as cofactors for a number

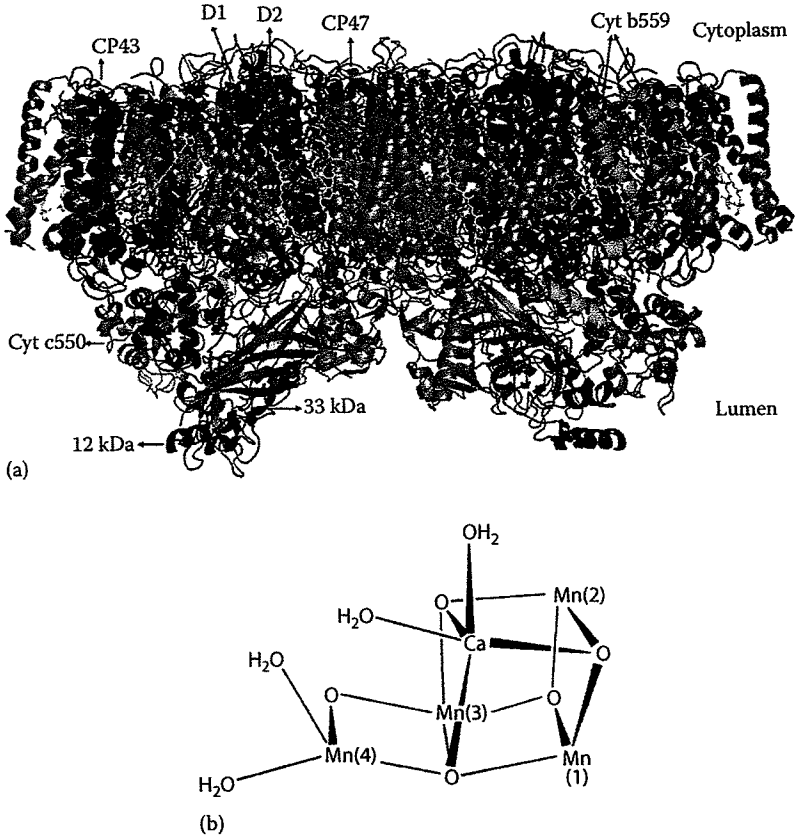


FIGURE 2.2 **(See color insert.)** (a) Structure of a cyanobacterial PSII dimer [29]. View from a direction perpendicular to the membrane normal. Molecules in green, yellow, and blue represent chlorophylls, β-carotenes, lipids, and detergent molecules, respectively. Red and yellow balls at the lumenal surface represent Mn and Ca ions, respectively. Protein subunits are labeled in the figure. For clarity, water molecules are omitted. (b) The entire structure of the Mn_4CaO_5 cluster resembles a distorted chair, with the asymmetric cubane. (From Umena, Y. et al., *Nature*, 473, 55–60, 2011; Kawakami, K. et al., *J. Photochem. Photobiol. B*, 104, 9–18, 2011.)

TABLE 2.1
Ligands for Manganese and Calcium Ions in the WOC

Ion	Ligands
Mn(1)	3(μ_3-O), 1(monodentate COO^-), 1(bridging COO^-), 1(imidazole)
Mn(2)	3(μ_3-O), 3 (bridging COO^-)
Mn(3)	3(μ_3-O), 1(μ_2-O), 2 (bridging COO^-)
Mn(4)	1(μ_4-O), 1(μ_2-O), 2 (bridging COO^-), 2(H_2O)
Ca	3(μ_3-O), 2 (bridging COO^-), 2(H_2O)

Sources: From Umena, Y. et al., *Nature*, 473, 55–60, 2011; Kawakami, K. et al., *J. Photochem. Photobiol. B*, 104, 9–18, 2011.

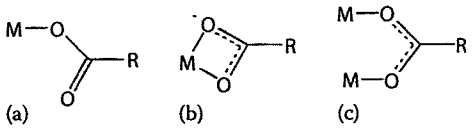


FIGURE 2.3 Unidentate (a), bidentate (b), and bridging carboxylate modes (c) [32]. In the structure of the WOC, one monodentate mode of carboxylate is observed and other carboxylate groups serve as bidentate modes.

of enzymes in higher organisms, where they are essential for detoxification of free radicals [33]. This element is required as a trace mineral for all known living organisms. The human body contains a total of 15–20 mg of manganese, most of which is located in the bones, with the remainder found in the kidneys, liver, pancreas, pituitary glands, and adrenal glands. In larger amounts, manganese can cause a poisoning syndrome in mammals, with neurological damage, which is sometimes irreversible. The most common oxidation states of manganese in biological systems are (II), (III), and (IV). Mn(II) often competes with Mg(II) in biological systems. Manganese compounds with oxidation states V, VI, and VII are strong oxidizing agents and are vulnerable to undergo disproportionation reactions. The most stable oxidation state for manganese in many mononuclear manganese enzymes and also manganese catalase is (II). In water, Mn(III) ion is unstable and prone to disproportionate to Mn(II) and Mn(IV), but this oxidation state could be stabilized with many "hard" ("hard" applies to chemical species that are small, have high charge states, and are weakly polarizable [34]) ligands in enzymes [34]. Mn(IV) is a usual oxidation state in minerals and could be stabilized by many hard ligands in biological systems. As shown in Figure 2.2b, there are four manganese ions in the WOC in PSII. In this section, we discuss the details of coordination chemistry of metal ions and a few important groups near the manganese–calcium cluster. However, it is worth mentioning that in the manganese–calcium cluster, there is charge distribution and charge on each ion is lower than suggested by its oxidation state. In other words, the $Mn_4CaO_5(H_2O)_4$ cluster is a delocalized system and each ion should not be studied completely separately, but rather in an integrated manner.

We describe next what is known about the four individual Mn atoms.

2.3.1.1.1 Manganese(1)

The ligands around Mn(1) are similar to one of the manganese ions in manganese catalase enzymes (Figure 2.4a). As usual, the coordination number for Mn(III) or (IV) is 6. Three μ_3-O as hard ligands and two carboxylate and one imidazole group as a borderline ligand could stabilize the oxidation state of III or IV for the manganese ion. As shown in Table 2.1 and in Figure 2.4a, in the WOC of PSII, Mn(1) has six ligands: two μ_3-O, one μ_4-O (μ_n-O means an oxo bridge linking n atoms together), one monodentate carboxylate, one bridging carboxylate, and one imidazole ligand [29,30].

2.3.1.1.2 Manganese(2)

The six ligands around this ion are three μ_3-O and three bridging COO^- [29,30] (Figure 2.4b). These ligands could stabilize oxidation state of III or IV for the ion. The coordination number of the ion is 6. The ion is connected to calcium and two manganese ions with a bridging carboxylate and three oxo groups.

2.3.1.1.3 Manganese(3)

The six ligands around this ion are two μ_3-O, one μ_4-O, one μ_2-O, and two bridging COO^-. Four hard μ-O could stabilize Mn(IV) than Mn(III) (Figure 2.4c).

2.3.1.1.4 Manganese(4)

The ligands around this ion are one μ_4-O, one μ_2-O, two bridging COO^-, and two H_2O (Figure 2.4d) [29,30]. These two water molecules are very important and one of them may serve as one of the substrates for water oxidation [29,30].

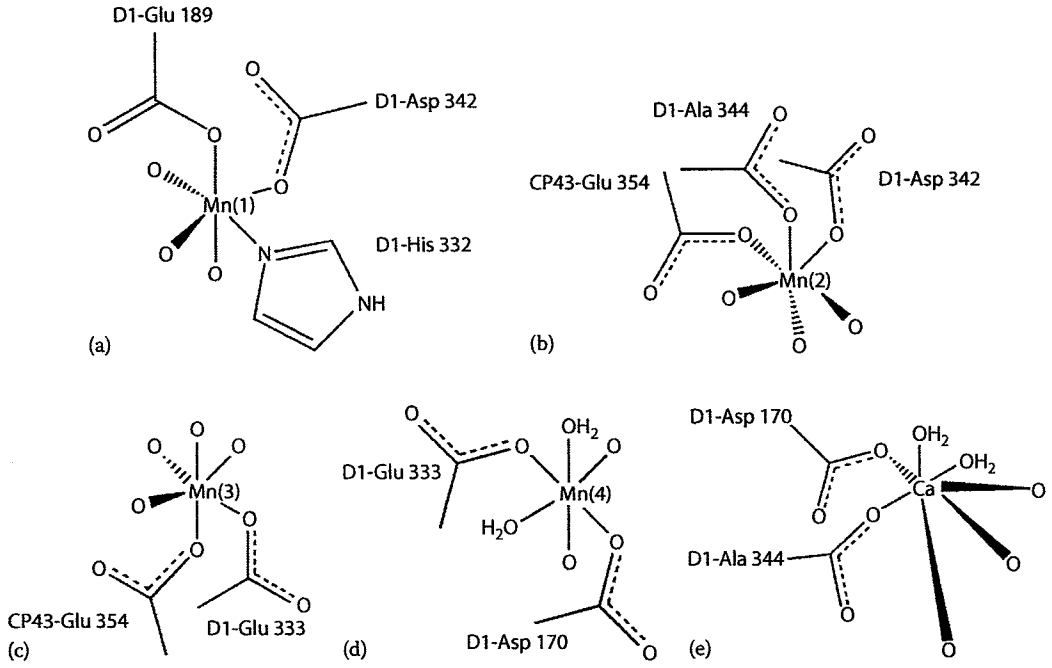


FIGURE 2.4 Mn(1) (a), Mn(2) (b), Mn (3) (c), Mn(4) (d), and Ca (e) and their surrounding ligands. (From Umena, Y. et al., *Nature*, 473, 55–60, 2011; Kawakami, K. et al., *J. Photochem. Photobiol. B*, 104, 9–18, 2011.)

Regarding these ligands, the oxidation state of Mn(III) could be stabilized for the ion, but deprotonation of water molecules could stabilize the oxidation state of Mn(IV) as well as higher oxidation states (e.g., Mn(V)).

2.3.1.2 Calcium Ion

Calcium is an essential ion for many organisms, particularly in cell physiology, where the movement of the calcium ion into and out of the cytoplasm functions as a signal for many cellular processes. Calcium is also a major structural element in bones and teeth. The usual role of this ion is structural and it is important for the stabilization of a number of proteins and enzymes. Calcium has been identified as an essential cofactor in water oxidation, and the calcium-binding sites in PSII have been previously studied by several methods. Strontium (II) is the only cation that can functionally substitute for calcium in the WOC [35]. In the 1.9 Å structure of the WOC, calcium has seven ligands, two μ_3-O, one μ_4-O, two bridging COO^-, and two H_2O molecules (Figure 2.4e) [29,30]. Similar to water molecules coordinated to Mn(4), these two water molecules are very important and one of them may serve as the substrate for water oxidation. The *coordination number of calcium* ions varies from 6 to 10 in different compounds. Thus, a ligand may coordinate to or decoordinate from this ion in different states of water oxidation.

2.3.1.3 Water

The location of the substrate water binding sites on the inorganic Mn_4Ca core has been an important question in the study of the mechanism of water oxidation. Hillier and Wydrzynski [36] used ^{18}O exchange kinetics of the substrate water molecules in PSII to examine the interactions of calcium and strontium with substrate water and to probe a number of point mutations surrounding the catalytic site. The most direct approach to follow water ligand exchange is by using mass spectrometry. This involves the addition of ^{18}O water followed by time-dependent sampling of the products. In this technique, two kinetic phases at m/e = 34, representing separate ^{18}O exchange rates

for the two substrate water molecules, were detected [36]: the slow and fast phases that show the exchange of the two nonequivalent substrate sites. Since four water molecules are coordinated in the structure of the WOC, two of them may serve as the substrate for water oxidation [29,30]. Other suggested substrates for water oxidation are μ-O groups [29,30]. Another water molecule, also found around WOC, is hydrogen-bonded to one of the μ-O and one carboxylate group in this structure. This water molecule, although less likely, could also serve as a substrate for water oxidation (Figure 2.5) [29,30].

In PSII, there are three types of channels: for oxygen, water, and protons [29,30,37–39]; they lead from the WOC to the lumenal side of PSII. The functional assignment of these channels has been based on electrostatic, structural, and orientation grounds. This strategy of having separate specific channels is expected to avoid the interaction of unwanted chemicals with the WOC and to increase the catalytic activity of the enzyme (Figure 2.5).

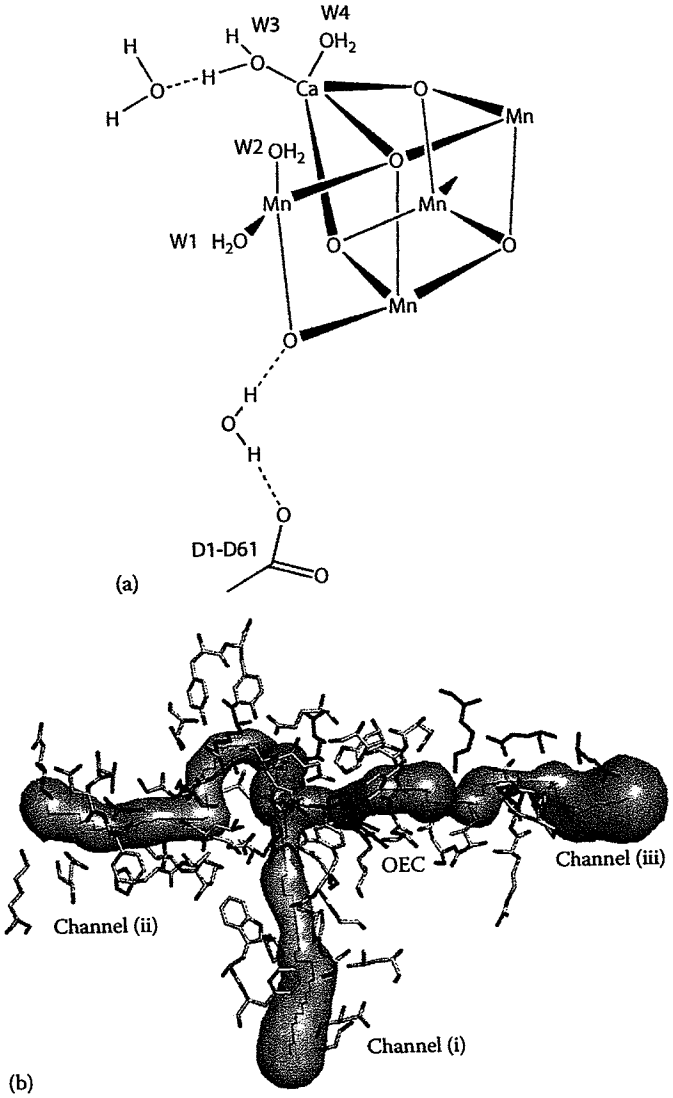


FIGURE 2.5 (a) The location of the substrate water binding sites (labeled as W1, W2, W3 and W4) on the WOC [29,30]. (b) The figure shows channels for hydrophobic oxygen (i), water (ii), and protons (iii), all leading to the catalytic Mn_4Ca cluster of PSII. OEC stands for oxygen-evolving complex. (Reproduced from Barber, J., *Inorg. Chem.*, 47(6), 1700, 2008.)

2.3.1.4 Amino Acids in the Second Coordination Sphere (D1-His 337 and CP47-Arg 357)

The imidazole nitrogen of D1-His 337 is hydrogen-bonded to one of the μ-O. The role of this hydrogen bond may be as a stabilizer for the WOC (Figure 2.6) [29,30].

There is an arginine in the second coordination sphere of WOC, CP43-Arg 357, and this residue may have an important role in maintaining the structure of the metal cluster, in stabilizing the cubane structure, and/or in providing partial positive charges to compensate for the negative charges induced by the oxo bridges and carboxylate ligands of the WOC [29,30]. One of the guanidinium nitrogens of CP43-Arg 357 is hydrogen-bonded to both μ-O manganese-calcium clusters, whereas the other is hydrogen-bonded to the carboxylate oxygen of D1-Asp 170 and to that of D1-Ala 344 (see Figure 2.6). The structure shows that the distances between the nitrogens of the arginine side chain and Ca^{2+} are 4.2 and 4.4 Å. Also, the distances between the nitrogen atoms of the arginine side chain and Mn(4) are 4.7 and 6.0 Å. The side chain of arginine may stabilize the structure of the WOC as it is hydrogen-bonded to two μ-O bridges and one carboxylate group bridging between Ca^{2+} and Mn(2).

2.3.1.5 Chloride

The function of chloride in biology, in general, could be to contribute negative charges in the formation of membrane potentials, responsible for the regulation of osmotic pressures in cells, to halogenate aromatic amino acids or to produce reactive species that are bactericidal and to act, as a bridging ligand, between heme *a* and Cu_B in the oxidized form of cytochrome oxidase. We know that chloride ion is a native anion and is required for electron donor reactions in the WOC [29,30,40–45]. Umena et al. [29,30] have identified two chloride ions in the structure of the WOC. Both Cl^- ions are surrounded by water molecules and amino acids. Umena et al. [29,30] have suggested that the two chloride anions may function to maintain the coordination environment of the $Mn_4CaO_5(H_2O)_4$, allowing the water oxidation reaction to proceed properly (Figure 2.7) (also see [45]).

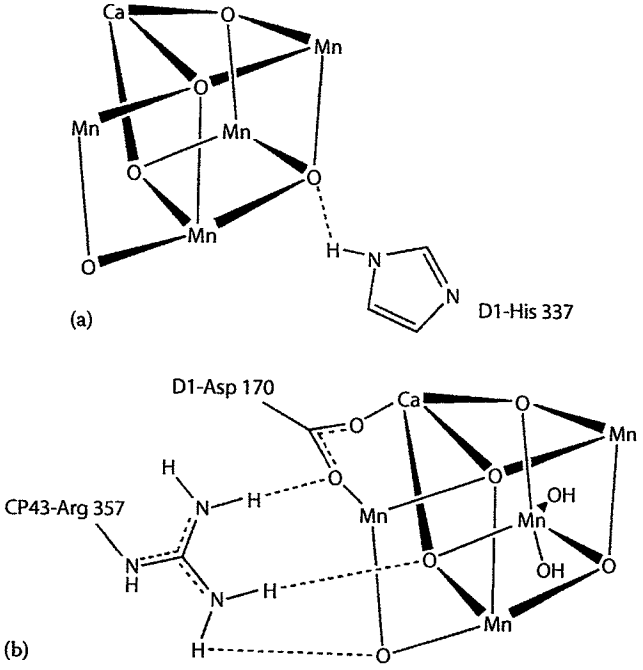


FIGURE 2.6 (a) The localization of D1-His 337 that is hydrogen-bonded to one of the μ-O in the WOC and (b) the localization of Arg 357. (From Umena, Y. et al., *Nature*, 473, 55–60, 2011; Kawakami, K. et al., *J. Photochem. Photobiol. B*, 104, 9–18, 2011.)

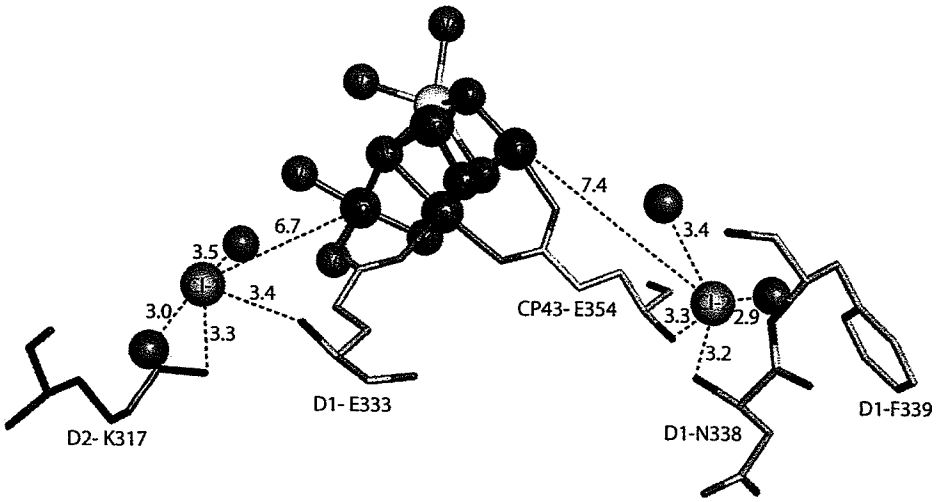


FIGURE 2.7 Structure of the two Cl^- binding sites near the $Mn_4CaO_5(H_2O)_4$ cluster. Hydrogen-bond distances are given in Å. (Reproduced from *J. Photochem. Photobiol. B*, 104, Kawakami, K. et al., Structure of the catalytic, inorganic core of oxygen-evolving photosystem II at 1.9 Å resolution, 9–18, 2011, Copyright 2011, with permission from Elsevier.)

2.3.1.6 Tyrosine 161

In PSII, photons are absorbed by light-harvesting pigment-protein complexes, and excitation energy is transferred to the reaction center chlorophyll P_{680}; here, primary charge separation occurs: oxidized P_{680} (P_{680}^+) and reduced pheophytin (Phe^-) are formed [10,46,47], for details, see Chapter 1. Then, P_{680}^+ is reduced by electron transfer from a tyrosine (Tyrosine 161) residue (Y_z), residing on the D1 protein, to form a tyrosine radical ($Y_z^{\bullet+}$) [4,5]. Electrons for the reduction of $Y_z^{\bullet+}$ are extracted from the WOC. As shown in Figure 2.8, this group forms a strong hydrogen bond with

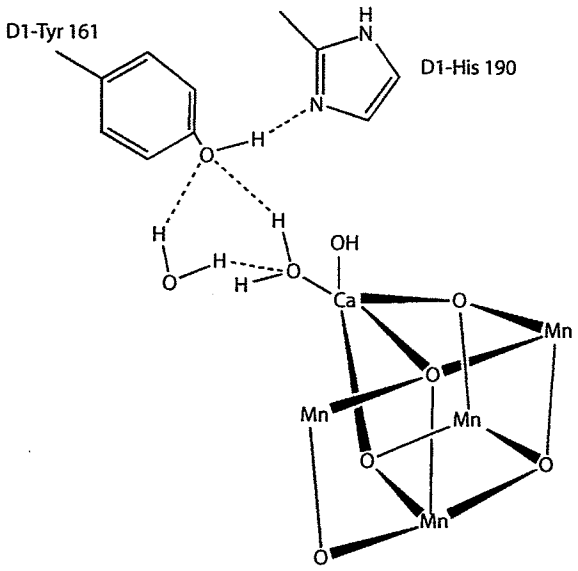


FIGURE 2.8 The location of Tyrosine 161. (From Umena, Y. et al., *Nature*, 473, 55–60, 2011; Kawakami, K. et al., *J. Photochem. Photobiol. B*, 104, 9–18, 2011.)

one water molecule coordinated to calcium [29,30]. Another hydrogen bond is observed between Y_z and the ε-nitrogen of a histidine (D1-His 190). This histidine is further hydrogen-bonded to other amino acids or water molecules to form a hydrogen-bond network suggested as an exit channel for protons [29,30].

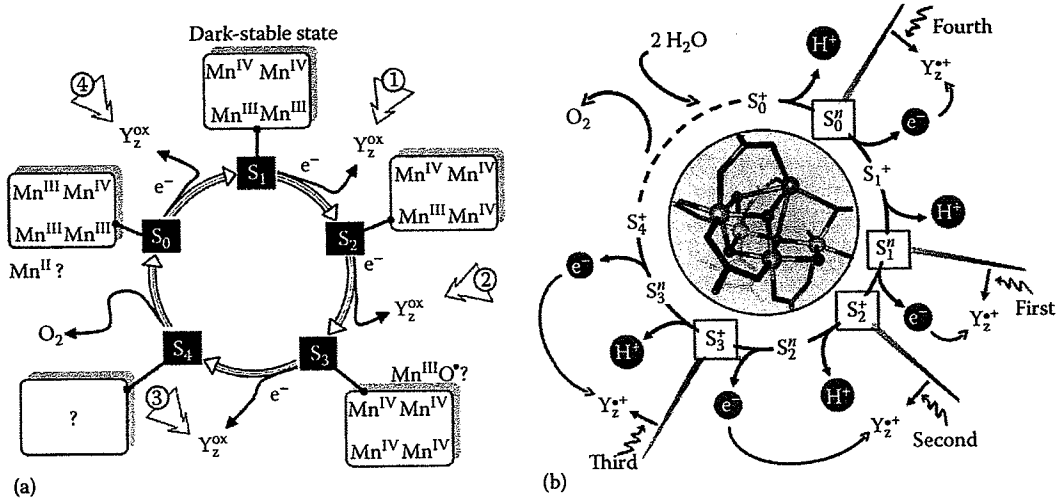
2.3.2 Mechanism of Oxygen Evolution

2.3.2.1 Four-Electron Water Oxidation

In thermodynamic terms, a four-electron water oxidation is certainly easier than four-sequential one-electron oxidation or two-sequential two-electron oxidation because in those cases the first steps (H_2O to hydrogen peroxide and hydroxyl radical) are more endergonic than the four-electron water oxidation, and result in low over-voltage for practical operations. As described later, *Nature* uses a four-electron oxidation mechanism for water oxidation with lower activation energy than other known mechanisms [5,48,49].

2.3.2.2 Flash-Induced Oxygen Evolution Pattern: The Joliot Experiment and the Kok Cycle

An elegant method to study oxygen evolution in biological systems is to activate a photosynthetic system with short and intense light flashes, with appropriate dark periods, and measure the oxygen yield on each flash. Pierre Joliot's experiments in 1969 showed that flash illumination produced an oscillating pattern in the oxygen evolution and a maximum occurred on every *fourth* flash [50–56]. These patterns are very interesting because splitting of two water molecules to produce one oxygen molecule requires the removal of *four* electrons. In 1970, Kok et al. [56] proposed an explanation for the observed oscillation of the oxygen evolution pattern. The Kok et al. [56] hypothesis was that in a cycle of water oxidation a succession of oxidizing equivalents is stored on each separate and independent WOC, and when four oxidizing equivalents accumulate one by one, an oxygen is spontaneously evolved. Each oxidation state of the WOC is known as an "S-state," with S_0 being the most reduced state and S_4 the most oxidized state in the catalytic



SCHEME 2.1 Classical S-state cycle of photosynthetic water oxidation [50–58]. Absorption of a photon causes charge separation at the reaction center P_{680} of PSII that leads to the formation of $Y_z^{\bullet+}$ (oxidized tyrosine-161 on the D1 protein) within less than 1 μs. Reduction of $Y_z^{\bullet+}$ by electron transfer (ET) from the manganese complex results in $S_i \rightarrow S_{i+1}$ transition. There are several similar S-state cycle schemes. Here, we show a plausible oxidation state of the four Mn ions in the different S-states (a). The extended S-state cycle including not only four oxidation but also four deprotonation steps is also shown in (b). (From Grundmeier, A. and Dau, H., *Biochim. Biophys. Acta*, 1817, 88, 2012.)

cycle (Scheme 2.1) [56]. It is essential to recognize that to explain the fact that the first maximum of oxygen evolution is after the 3rd flash, and then after 7th and 11th flashes, the S_1 state must be dark-stable. The $S_4 \rightarrow S_0$ transition is light independent and in this state oxygen is evolved. All other S-state transitions are initiated by the photochemical oxidation of P_{680} P_{680}^+ [56].

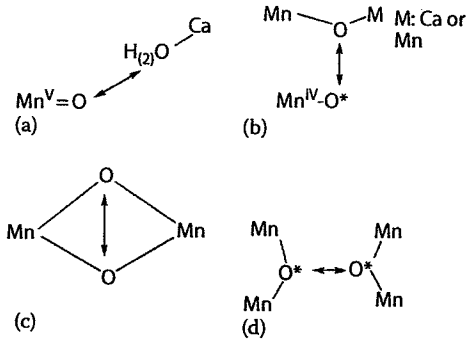
2.3.2.3 Oxidation States of Manganese Ions in the Kok Cycle

It is well known that redox changes in the $S_0 \rightarrow S_1$ and $S_1 \rightarrow S_2$ transitions for the WOC are manganese-based [48]. The $S_2 \rightarrow S_3$ and the $S_3 \rightarrow S_4$ transitions are still controversial as to whether a metal-centered or a ligand-centered oxidation occurs [48]. In the $S_4 \rightarrow S_0$ transition (Scheme 2.1), rapid oxidation of two substrate water molecules occurs [48]. Based on the experimental evidence accumulated thus far, the four Mn ions in the S_1-state are believed to be $Mn_2(III)Mn_2(IV)$, but a lower valence combination may also be possible.

2.3.2.4 Mechanism of Water Oxidation in Nature

Detailed physico-chemical mechanism of water oxidation by the WOC of PSII is still not resolved [58]. There are many proposals for the mechanism of water oxidation by the WOC in PSII [48]. The most important models are the following (Scheme 2.2):

1. *Nucleophile–electrophile reaction*: Pecoraro et al. [59] have proposed that a terminal Mn(V)=O undergoes a nucleophilic attack by a Ca^{2+} bound hydroxide ligand to form a Mn-bound hydroperoxide. Brudvig et al. [60] have proposed a mechanism in which a Ca^{2+} ion plays a role as a weak Lewis acid. In this mechanism, a water molecule bound to calcium reacts with a Mn(V)=O species to form the O=O bond through a nucleophilic attack. Lee and Brudvig [61] provided direct support for the proposal that Ca^{2+} plays a structural role in the early S-state transitions, which may also be fulfilled by other cations with similar ionic radius. Umena et al. [29,30] suggested that one of the water molecules that is coordinated with calcium, and is near Tyr 161, may serve as one of the substrate molecules, and the water molecule coordinated to Mn(4) may serve as the second substrate in the O–O formation.
2. *Coupling of an oxyl radical and a manganese-bound oxo-ligand*: Siegbahn [62], based on extensive DFT calculations by his research group, has suggested that a Mn(IV)−O$^\bullet$ may react with a manganese-bound oxo-ligand to form oxygen. In this mechanistic hypothesis, spin alignment of the reactive oxygen atoms is important [62].



SCHEME 2.2 The most important proposed mechanisms of oxygen evolution by the WOC (a–d). (From Springer Science+Business Media: Burnap, R.L. and Vermaas, W.F.J., Eds., *Advances in Photosynthesis and Respiration Functional Genomics and Evolution of Photosynthetic Systems*, Probing functional diversity of thermophilic cyanobacteria in microbial mats, Vol. 33, Chap. 2, 2012, pp. 17–46, Bhaya, D.)

3. *Reductive elimination of two bridging oxo-ligands*: Rüttinger et al. [63] in the research group of Charles Dismukes proposed that a high-valent Mn-oxo-cluster collapses to form oxygen from two bridging oxo-ligands.
4. *Radical coupling mechanism*: In this mechanism, two oxyl radicals ($O^{\bullet}$) are formed followed by a radical coupling to generate the oxygen–oxygen bond [64].

Umena et al. [29,30] suggested that one oxygen that bridges between Ca, Mn(4), Mn(3), and Mn(1) may exist as a hydroxide ion in the S_1 state and that it may provide one of the substrates for dioxygen evolution. One of the water molecules coordinated to calcium or Mn(4) may provide another substrate for oxygen evolution (Scheme 2.2).

Research on many WOC mutants has provided information on the role of specific amino acids in the mechanism of oxygen evolution (see, e.g., Ref. [48]). We need to be aware that although the basic mechanisms of oxygen evolution must be the same in all systems, it needs to be studied and checked even within different diverse groups of cyanobacteria. We already know that just even within thermophilic cyanobacteria there is functional diversity in natural populations [65].

2.4 POSSIBLE EVOLUTIONARY ORIGIN OF THE WATER-OXIDIZING COMPLEX IN PHOTOSYSTEM II

The high concentration of oxygen in Earth's atmosphere is one of the most geologically important signatures of life. Accumulation of oxygen began after the evolution of oxygenic photosynthesis in cyanobacteria around 3 billion years ago [66]. The increasing concentration of oxygen may have many biological patterns, among them the evolution of "body size" [66]. However, it is an enigma as to when and how oxygen-producing photosynthetic cyanobacteria evolved from their photosynthetic bacterial precursors [1]. It has been suggested that two of the bacterial reaction centers and PSII are evolutionarily related [67]. However, PSII must have provided a very strong oxidation potential to oxidize water because water is a stable molecule and to oxidize water a molecule must have a midpoint potential greater than ~ 0.82 V versus the standard hydrogen electrode at pH 7 [67]. P_{865}, reaction center of an anoxygenic bacteria, has only a moderate E_m (midpoint potential) value of 0.5 V and thus cannot oxidize water or even tyrosine [67] (Table 2.2).

The WOC in PSII found in cyanobacteria and in the thylakoid membranes of plant chloroplasts are believed to have evolved from a single common ancestor [68,69]. There are several hypotheses for the origin of the WOC. One hypothesis suggests that the WOC originated in binuclear manganese active sites, including ribonucleotide reductase, catalase, and arginase [70,71]. Perhaps, Mn catalase could have been a key intermediate en route to oxygenic photosynthesis [70,71]. Blankenship and Hartman [71] proposed that a primitive Mn catalase was the original template upon which the modern WOC was structured. Raymond and Blankenship [72] developed an approach for determining the optimal superposition of the atoms concentrated around the active sites of PSII and binuclear-manganese proteins. These observations support a common structural core in the WOC and in distinct manganese binuclear enzymes. It is also possible that

TABLE 2.2
Midpoint Potential at pH = 7 Relative to the Standard Hydrogen Electrode

Compound	Midpoint Potential
P_{680}/P_{680}^{+}	1.1–1.4
H_2O/O_2	0.82
Tyr/Tyr^{+}	1–1.1
P_{865}/P_{865}^{+}	0.5

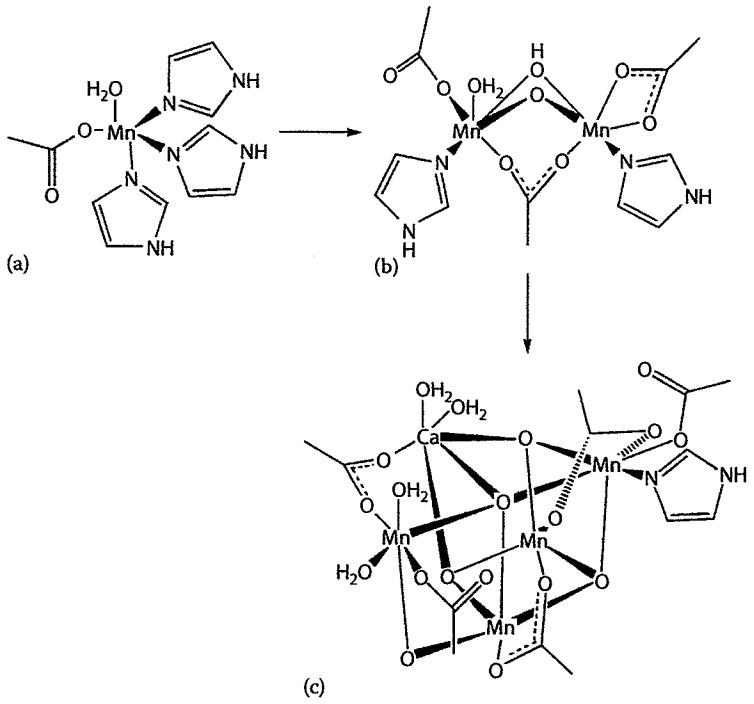


FIGURE 2.9 A mononuclear enzyme similar to manganese superoxide dismutase (a) might have served as an origin for catalase (b) and then the WOC (c). (With permission from Springer Science + Business Media: *Origins Life Evol. Biosphere*, A possible evolutionary origin for the Mn_4 cluster in photosystem II: From manganese superoxide dismutase to oxygen evolving complex, 39, 2009, 151–163, Najafpour, M.M.)

the development of oxygenic photosynthesis occurred in steps, the first of which involved only mononuclear manganese enzymes—the mononuclear manganese enzymes could have been a key intermediate en route to catalase and then to the WOC (Figure 2.9) [73].

Recently, Allen et al. [74] demonstrated that modifications of bacterial reaction centers can produce a highly oxidizing protein with a tight Mn-binding site that is redox active. Allen et al. [74] further showed that after light-induced electron transfer from the primary donor to the electron acceptors, the bound Mn is oxidized and can react with superoxide to produce molecular oxygen. This interesting system could serve as a useful model for understanding the involvement of intermediates in the evolutionary development of PSII [74].

Williamson et al. [68] have proposed that manganese ions may have replaced iron in iron-binding site of an enzyme and formed the precursor to the WOC. One of us (MMN) (see [75]) has also proposed a novel origin for the WOC from the manganese-oxidizing bacteria. The Archaean ocean may have sufficient Mn and Ca, ions with high affinity for interaction with the Mn oxide, and alkaline conditions may have enabled protocyanobacteria to assemble mineral oxides as functional compliments of early active site of PSII. Thus, those bacteria did not need to do large amount of manganese oxidation any more, since few manganese ions were enough to oxidize a large amount of water [75]. It is highly likely that those manganese-oxidizing bacteria may have changed to become the water-oxidizing bacteria. Water oxidation may have been an advantage for water-oxidizing bacteria because the amount of water on Earth was huge and water-oxidizing bacteria could reproduce and survive more easily than the other bacteria. These water-oxidizing bacteria may be the origin for cyanobacteria, and thus for algae and plants. In this regard, it is interesting that manganese oxides, in the form of dispersed powders, have been tested as catalysts for the four-electron oxidation of water to oxygen in the presence of different oxidants [76]. More interestingly, it has been shown that incorporation of

calcium into mixed-valence manganese oxides produces a structure similar to the WOC and greatly improves the water oxidation activity of these manganese oxides toward water oxidation [77–80]. Further, these manganese oxides, with calcium, but without any additional groups, show a structure similar to the WOC in PSII [77–80].

2.5 STRESS AND OXYGEN EVOLUTION

Cyanobacteria, just as algae and plants, are prone to different stresses. They have, for example, cold stress, heat stress, salt stress, water stress, and light stress. It is instructive to learn from all the systems to understand the impact of stress on cyanobacteria. We recommend the readers to consult Refs. [81–86]. Among the photosynthetic apparatus, the WOC is known to be one of the most susceptible sites of inactivation induced by various stresses. This is largely due to the unstable nature of the protein components that constitute the WOC, as well as the vulnerable structure of the distorted Mn_4CaO_5 structure. For example, heating is known to release extrinsic proteins, indispensable components for an intact WOC, of cyanobacteria and higher plant PSII, thereby inhibiting oxygen evolution [87–89]. The binding of extrinsic proteins in the WOC is weak and can also be affected by cold stress [90] and salt stress [91], leading to their dissociation from PSII and the inactivation of oxygen evolution. One of the primary targets of photoinhibition has been proposed to be the Mn site [92,93], as Mn absorbs ultraviolet light, which may cause the destruction of the WOC. Thus, engineering a system with the aim to improve stability of the WOC complex might lead to cyanobacteria and plants that can better cope with various stress conditions. In this regard, photoinhibition by visible light and UV radiation on PSII is an important issue. Hakala et al. [94] showed that the release of Mn ions to the thylakoid lumen is the earliest detectable step in both UV- and visible-light-induced photoinhibition. After Mn release from the OEC, oxidative damage to the PSII reaction center occurs because the Mn-depleted OEC cannot reduce P_{680}^+ normally. As discussed by Vass et al. [95–98], PSII has mechanisms to protect itself from photodamage by light, by nonradiative charge recombination, and repair of damaged reaction center complexes.

2.6 WATER OXIDATION IN ARTIFICIAL PHOTOSYNTHESIS

The goal of artificial photosynthesis is to make different useful material or high-energy chemicals for energy storage using sunlight [99]. Hydrogen production by water splitting may be one of the most important goals of artificial photosynthesis [99]. To evolve hydrogen efficiently in a sustainable manner, it is necessary to first synthesize a "super catalyst" for water oxidation, which is the more challenging half reaction of water splitting [100]. There is an efficient system for water oxidation in cyanobacteria, algae, and plants (see e.g. Refs. [22–27]). Published data on the Mn–Ca cluster have provided details on the mechanism and structure of the WOC [29,30]. To design an efficient WOC for artificial photosynthesis, we must learn and use wisely the knowledge about water oxidation and the WOC in the natural system [101–103].

In the end, we refer the readers to the web site of Royal Society of Chemistry for a collection of articles : A Comment on "Artificial Photosynthesis, titled "Running on sun" is online at Chemistry World, Royal Society of Chemistry: http://rsc.li/PCKq86; it is a part of a special collection http://blogs.rsc.org/cs/2012/09/25/a-centenary-for-solar-fuels/ to mark the centenary of Ciamician's paper "The Photochemistry of the Future".

ACKNOWLEDGMENTS

M.M. Najafpour and A. Nemati Moghaddamare are grateful to the Institute for Advanced Studies in Basic Sciences, in Iran, for financial support. Govindjee is grateful to the School of Life Sciences, Jawaharlal Nehru University, New Delhi, India, for support since this review was completed while he was a visiting professor there in 2012.

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