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Chapter
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Abstract

Oxygen, that supports all aerobic life, is abundant in the atmosphere because of its constant regeneration by photosynthetic water oxidation, which is catalyzed by a Mn_4CaO_5 cluster in photosystem II (PS II), a multi subunit membrane protein complex. X-ray and other spectroscopy studies of the electronic and geometric structure of the Mn_4CaO_5 cluster as it advances through the intermediate states have been important for understanding the mechanism of water oxidation. The results and interpretations, especially from X-ray spectroscopy studies, regarding the geometric and electronic structure and the changes as the system proceeds through the catalytic cycle will be summarized in this review. This review will also include newer methodologies in time-resolved X-ray diffraction and spectroscopy that have become available since the commissioning of the X-ray free electron laser (XFEL) and are being applied to study the oxygen-evolving complex (OEC). The femtosecond X-ray pulses of the XFEL allows us to outrun X-ray damage at room temperature, and the time-evolution of the photo-induced reaction can be probed using a visible laser-pump followed by the X-ray-probe pulse. XFELs can be used to simultaneously determine the light-induced protein dynamics using crystallography and the local chemistry that occurs at the catalytic center using X-

ray spectroscopy under functional conditions. Membrane inlet mass spectrometry has been important for providing direct information about the exchange of substrate water molecules, which has a direct bearing on the mechanism of water oxidation. Moreover, it has been indispensable for the time-resolved X-ray diffraction and spectroscopy studies and will be briefly reviewed in this chapter. Given the role of PS II in maintaining life in the biosphere and the future vision of a renewable energy economy, understanding the structure and mechanism of the photosynthetic water oxidation catalyst is an important goal for the future.

Keywords

calcium manganese oxygen-evolving complex membrane-inlet mass spectrometry photosystem II X-ray crystallography X-ray emission spectroscopy X-ray free electron laser

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1 Introduction

Most of the dioxygen in the atmosphere that aerobic life depends on is generated by plants, algae, and cyanobacteria by the light-induced oxidation of water in photosystem II (PS II) (reviewed in [1]). PS II is a multi-peptide membrane protein complex embedded in the thylakoid membranes. Photosynthetic water oxidation and dioxygen evolution is one of the most important, life-sustaining chemical processes occurring in the biosphere. PS II is usually found in a dimeric form in nature with each monomer comprised of more than 20 peptides and about 100 cofactors, which include chlorophylls (Chl), quinones, carotenoids, and lipids. The primary light-driven charge separation takes place in the PS II reaction center, P_{680}, where 4 Chls, 2 pheophytins, and 2 quinone molecules are symmetrically arranged in the two branches of PS II. After the light-induced formation of P_{680}^{+}, a redox-active tyrosine (Y_Z) is oxidized, which in turn oxidizes the oxygen evolving complex (OEC) on the lumenal side of the protein complex.

The OEC in PS II contains a heteronuclear Mn_4CaO_5 cluster (Figure 1, inset) which catalyzes the water oxidation reaction (equation 1),

$$2\ H_2O \rightarrow O_2 + 4\ e^{--} + 4\ H^{+} \quad (1)$$

that couples the four-electron oxidation of water with the one-electron photochemistry occurring at the PS II reaction center, P_{680}. The OEC cycles through five intermediate S states (S_0 to S_4, known as the Kok cycle) that corresponds to the abstraction of four successive electrons from the OEC (Figure 1) [2, 3]. The dark stable S_1 state is the first oxidized state and subsequent illumination leads to the formation of the S_2 and S_3 states. Once four oxidizing equivalents are accumulated (S_4 state), a spontaneous reaction occurs that results in the release of O_2 and the formation of the most reduced state, the

S_0 state. Upon further light excitation, the initial S_1 state is formed once again, and the catalytic cycle is resumed.

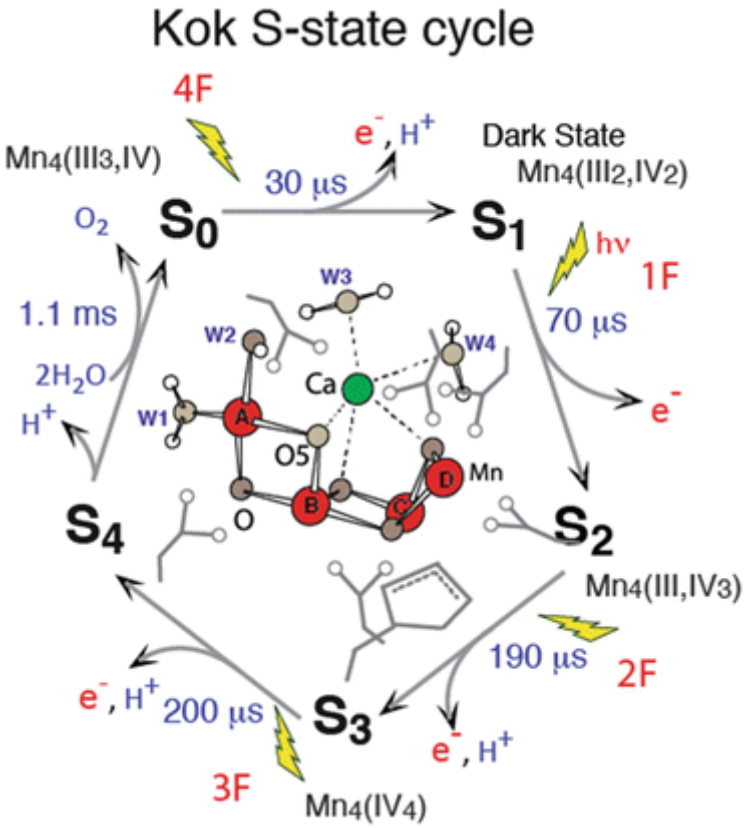

Figure 1

The Kok S state cycle for photosynthetic water oxidation and oxygen evolution. Proposed structure for the Mn_4CaO_5 cluster derived from the 1.9 Å X-ray structure modified using information from single-crystal polarized X-ray spectroscopy and EPR studies is in the inset. The proposed oxidation states for the Mn in the cluster in the various S state intermediates are shown.

Given the importance of PS II in maintaining life and the anticipated role of light-induced water-splitting for building a renewable energy economy, understanding the structure of the Mn_4CaO_5 catalyst and the mechanism of the water oxidation reaction is considered to be one of science's grand challenges [4]. Although details of the chemistry involved in water oxidation are slowly emerging, the mechanism of the reaction is not yet clear. In this chapter, we describe results from X-ray spectroscopy and diffraction studies, especially the use of time-resolved X-ray methods for room temperature studies using the recently introduced X-ray lasers. We will also describe the use of membrane inlet mass spectrometry for the elucidation of the mechanism of water-oxidation and its utility for time-resolved X-ray spectroscopy and diffraction measurements.

2 Geometric and Electronic Structure of the Mn_4CaO_5 Cluster

X-ray diffraction (XRD) [5, 6, 7, 8, 9, 10], X-ray absorption spectroscopy (XAS) [11, 12, 13, 19], electron paramagnetic resonance (EPR) [14, 15, 16], infrared spectroscopy (IR) [17], and UV-vis [18] studies of PS II have provided valuable insights into the structure and mechanism of the Mn_4CaO_5 cluster (Figure 2).


Figure 2
Figure 2

The structural models for the Mn_4CaO_5 cluster from (**left**) the polarized EXAFS and Sr EXAFS studies, (**middle**) the 1.9 Å resolution XRD study, and (**right**) derived from EPR and EXAFS spectroscopic studies. The Mn-Mn and Mn-O/N ligand distances from the EXAFS and XRD studies are summarized below the respective structural model (adapted from [20, 23, 45]).

Among them, the information regarding the geometric structural changes has come largely from extended X-ray absorption fine structure (EXAFS) studies (reviewed in [12, 13, 19]). EXAFS has provided Mn-Mn and Mn-Ca and Mn-O/N ligand distances with an accuracy of ~0.02 Å and resolution of ~0.1 Å. An important feature of EXAFS is that one can control the X-ray dose used by monitoring the Mn K-edge spectra, thus preventing the reduction of Mn and the concurrent disruption of the cluster, which occurs when PS II is exposed to the high X-ray dose used in protein crystallography (see below). EXAFS studies, including solution EXAFS [20], range-extended EXAFS [21, 22], and single crystal polarized EXAFS [23], have shown that in the S_1 state there are three short Mn-Mn distances at ~2.7 Å, one long Mn-Mn distance at ~3.3 Å, and three to four Mn-Ca distances [24, 25] at around 3.4–3.9 Å (based on Sr XAS studies [26, 27, 28]). The combination of polarized EXAFS data from single crystals of PS II with XRD led to three proposed models for the Mn_4CaO_5 cluster, one of which is shown in Figure 2 (left) [23].

X-ray diffraction (XRD) studies using synchrotron radiation (SR) have been used over the last decade to study the structure of PS II [5, 6, 7, 8, 9, 10]. However, the X-ray radiation damage to the redox active Mn_4CaO_5 cluster has been an issue, and the damage to the cluster precedes the loss of diffractivity of the crystals by about two orders of magnitude in dose in synchrotron-based crystallography (Figure 3) [29, 30]. This is accompanied by the disruption of the cluster as shown in Figure 4 [29, 30]. The recent study by Umena et al. at 1.9 Å [10], which has revealed the geometry of the Mn_4CaO_5 cluster (Figure 2, middle), however, used a significantly lower X-ray dose (X-ray dose of ~25 % Mn reduction level) and reported the atomic resolution structure of PS II (1.9 Å) in which four Mn and one Ca positions can be determined from the electron density map for the first time.

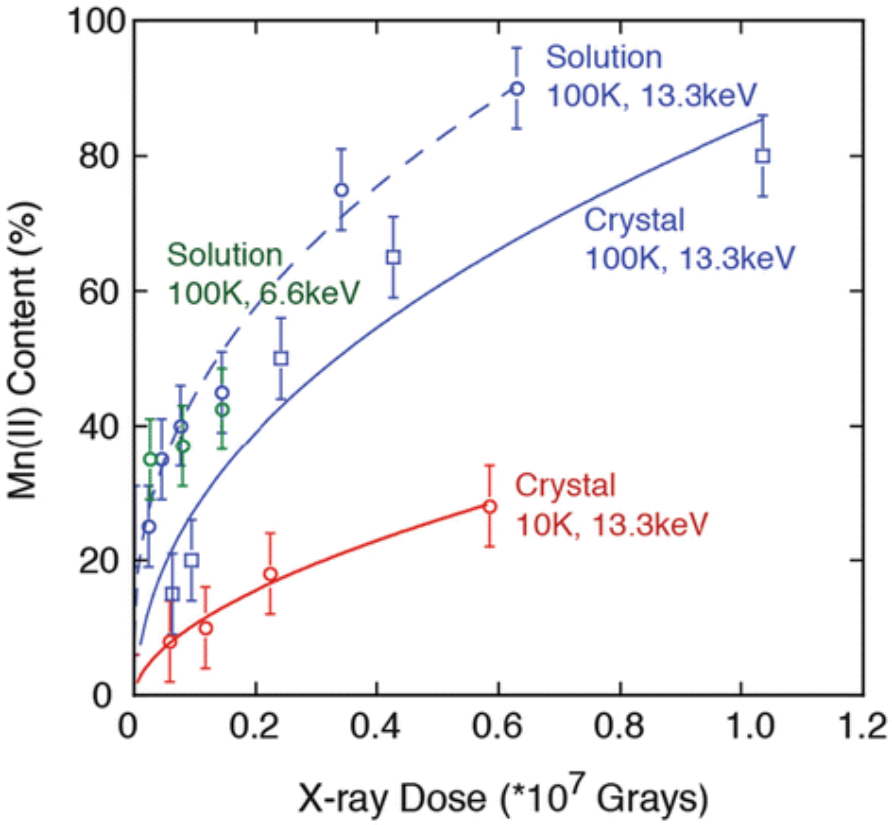

Figure 3

Radiation damage to PS II solutions and crystals as a function of X-ray dose. Dashed blue line is for PS II solutions illuminated at 100 K. The green circles are data from 6.6 keV illumination, while the blue squares are for 13.3 keV illumination. The blue solid line and blue circles are for crystals illuminated at 13.3 keV. The red solid line and red circles are for crystals illuminated at 10 K (adapted from [29]).

Figure 4
Figure 4

(**a**) Mn K-edge shift of PS II as a function of X-ray dose at 13.3 keV and 100 K. The spectrum at the highest inflection point energy is from an undamaged PS II crystal (in red). Light-blue to black lines are at increasing X-ray dose from 0.14, 0.21, 0.25, 0.54, 0.95, 2.3, and 5.0×10^{10} photons/μm^2. The exposure was at 100 K, and all XANES was collected at 10 K at low dose ($1 \times 10^7/\mu m^2$). XANES shows that the increase in amplitude at ~6552 eV provides evidence for the photo-reduction to Mn^{II} in PS II crystals by exposure to X-rays. (**b**) A comparison of Mn K-edge spectra from two tetranuclear complexes, $[Mn_4O_3(OAc)_4(dbm)_3]$ and $[(Mn_2O_2)_2(tphpn)_2](ClO_4)_4$, in oxidation states Mn_3(III)Mn(IV) and Mn_2(III)Mn_2(IV) similar to those in intact PS II, and from Mn(II) in aqueous solution. (**c**) Fourier transforms of Mn EXAFS of PS II as a function of radiation dose. The Fourier transform of the EXAFS spectrum from an intact PS II solution sample is on the bottom (red). The three Fourier peaks are characteristic of a bridged Mn_4Ca complex, with peak I

from bridging Mn-oxo and Mn-terminal ligand atoms, peak II is from Mn-Mn distances at 2.7 Å characteristic of di-μ-oxo bridged moieties and peak III is from mono-μ-oxo bridged Mn-Mn distances at 3.3 Å and Mn-Ca distances at 3.4 Å. The Fourier transforms from PS II samples exposed to radiation at 13.3 keV and 100 K, and containing 5 (blue), 10 (black), 25 (green), and 90 % (gray) photo-reduced Mn(II) centers. The Fourier peaks exhibit drastic changes, as the percent of Mn(II) increases, even at very low levels of X-ray dose. Peak II and peak III (vertical lines) that are characteristic of Mn-Mn distances at 2.7, 3.3, and 3.4 Å decrease and disappear along with peak I that is due to Mn-oxo bridging atoms. Peak I characteristic of bridging Mn-O distances is replaced by a longer Mn-O distance characteristic of Mn(II)-O terminal distances (adapted from [29]).

Although, the similarities in the number of Mn-Mn and Mn-Ca vectors is striking between the XRD and EXAFS structural models, noticeable changes still exist between the crystal structure and the EXAFS results in which the data was collected at much lower X-ray dose and the integrity of the sample was maintained (summarized in Figure 2). The Mn-ligand and Mn-Mn distances are longer in the 1.9 Å crystal structure than those determined using EXAFS by 0.1–0.2 Å for the Mn-Mn and ~0.3 Å for the Mn-O distances (Figure 2) [20]. These differences in distances could be caused by radiation damage during the XRD data collection and thus lead to some of the differences in the proposed models for the clusters.

2.1 Geometric and Electronic Structural Changes During S State Transitions

The 1.9 Å structure of PS II [10], nevertheless, serves as the current basis to relate spectroscopic data with the structural changes that occur during the catalytic S_i state transitions. Figure 2 (right) shows the structural model of the cluster modified from that shown in Figure 2 (left) taking into consideration the newest data from XRD and input from XAS [20] and EPR [14] studies. Based on this structure, possible changes that the Mn_4CaO_5 cluster undergoes during the S state transitions has been proposed as shown below in Figure 6. This model incorporates the ligands and basic structure of Mn found in the 1.9 Å crystal structure and builds upon this using EXAFS distances, FTIR, and EPR results and the changes in distances determined using Mn and Sr EXAFS of all the S states (Figure 5). The oxidation states assigned for the Mn atoms are based on both XANES and XES [31, 32] and EPR results [14, 33, 34].

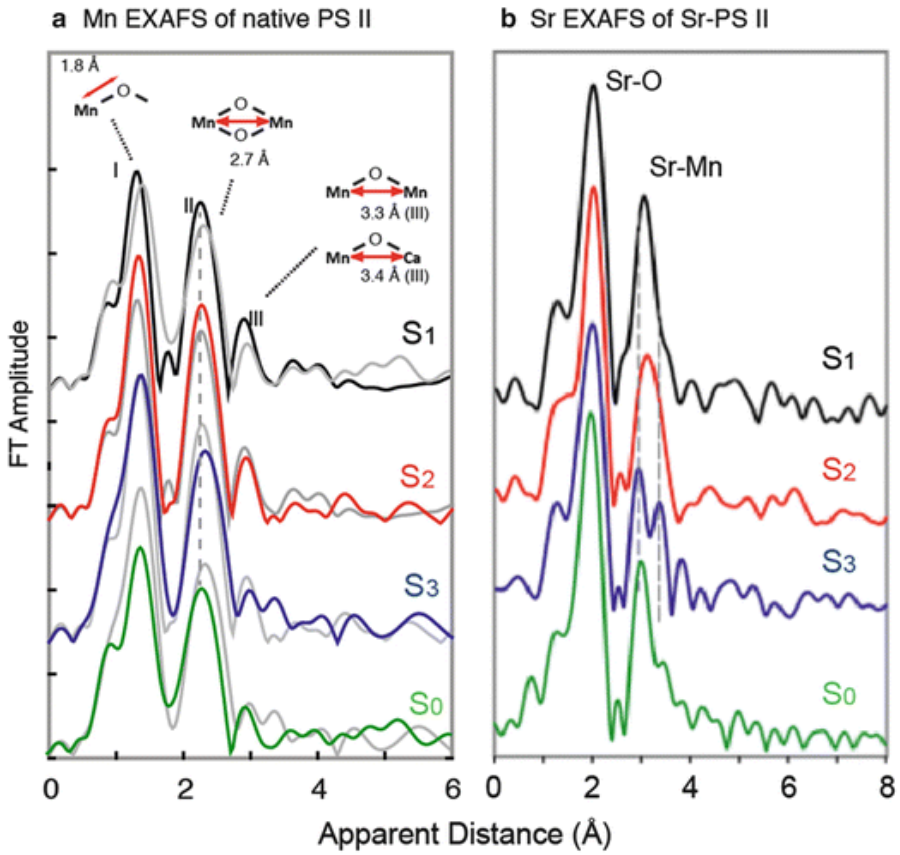

Figure 5

(a) The Mn EXAFS Fourier transforms from all the S states. The Mn-ligand, Mn-Mn, and Mn-Ca distances are characterized by the Fourier transforms peaks I, II, and III (adapted from [20]). (**b**) Sr EXAFS Fourier transforms of PS II from all the S states, showing the Sr-O and Sr-Mn distances (adapted from [28]). The significant changes in the distances during the S_2 and S_3 state, and the S_3 to S_0 transitions are seen. The vertical lines show the changes in the distances in the Mn-Mn and Mn-Sr distances.

The main topological difference between the structure proposed on the basis of EXAFS (in addition to the differences in the distances) [20, 23], EPR [14], and theoretical studies [35, 36] and the 1.9 Å XRD structure [10] is the position of the bridging oxygen atom O5 as shown in Figure 1 (inset), leading to a more open-cubane like structure. The open-cubane like structure for the S_1 and S_2 states is supported not only by polarized EXAFS of single crystals of PS II [20, 23], but has also been suggested by Siegbahn on the basis of theoretical studies [35], and by the Neese/Lubitz/Messinger groups on the basis of EPR studies for the S_2 state [14, 33, 34]. In the S_2 state a formal oxidation state distribution of (IV,IV,IV,III) for manganese atoms Mn1,2,3,4 (Figure 6) was assigned based on Mn K-edge XANES and Kβ emission spectroscopy [31], ^{55}Mn ENDOR measurements [34], and theoretical calculations [35], with one Mn being oxidized from Mn(III) to (IV) during the S_1 to S_2 transition.

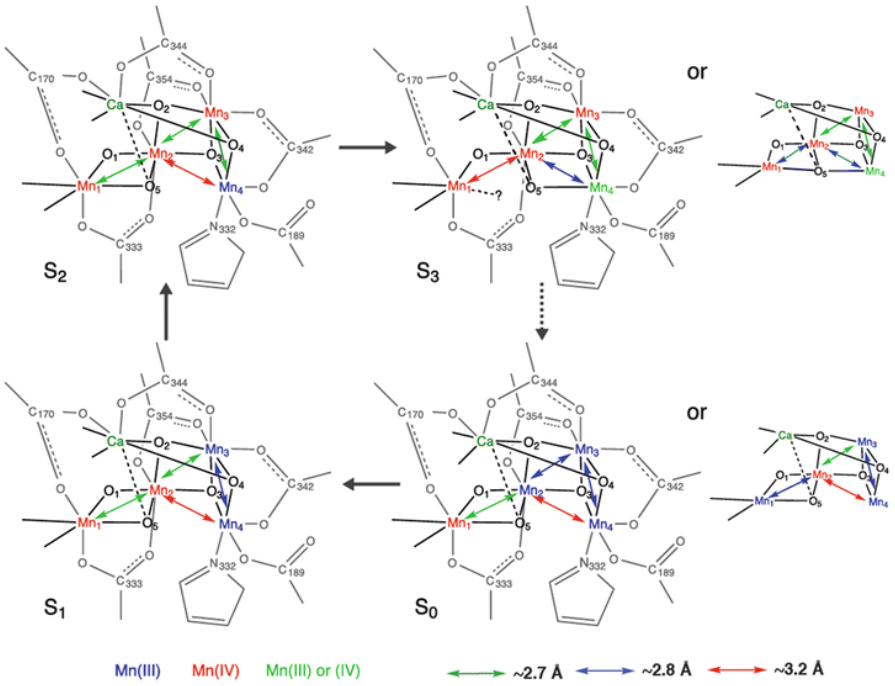

Figure 6

Proposed structural changes during the S state transitions based on the EXAFS distance changes, and possible protonation states (at oxo-bridging and terminal water molecules) or changes in the ligand environment (type of ligands and ligation modes). The Mn-Mn distances at ~2.7 Å are indicated by green arrows, ~2.8 Å by blue arrows and ~3.2 Å by red arrows. The dashed line indicates that it may not be a bond. For the S_3 and the S_0 state two possible models are shown. Mn atoms are shown in blue (Mn(III)), red (Mn(IV)) or green (Mn(III) or Mn(IV)) possible), Ca in green and the surrounding ligand environment in grey (adapted from [20]). Several different nomenclatures have been used to refer to the Mn atoms. The numbering scheme shown here is from reference [20]. Mn(1,2,3,4) here corresponds to Mn(A,B,C,D) from polarized EXAFS studies and Mn(4,3,2,1) from the 1.9 Å XRD structure. The second N atom in the His ring and other atoms are not shown for simplicity.

Different nomenclatures have been used in the literature for identifying the Mn atoms, and they are all denoted in the caption for Figure 6. The shortening of one Mn-Mn interaction (~2.79 to ~2.74 Å) during the S_1 to S_2 transition is likely due to the change in oxidation state of one Mn (formally Mn(III) to Mn(IV)). FTIR studies indicate that the Mn3 atom ligated by Ala344 undergoes oxidation in the S_1 to S_2 state transition [37], however, it is possible that other Mn atoms could be oxidized. ENDOR studies [38, 39] suggest that Mn4 is the Mn(III) moiety in the S_2 state leaving open the possibility that either Mn3 or Mn1 is oxidized during the S_1 to S_2 transition.

The recent EPR/ENDOR studies support the formal oxidation state assignment of $Mn_4(III_3,IV)$ in the S_0 state and $Mn_4(III_2,IV_2)$ in the S_1 state [33, 40]. An oxidation state change of one Mn is also supported by Mn XANES and Kβ emission spectroscopy for the S_0 to S_1 state transition. The S_0 to S_1 state transition is also accompanied by the

shortening of Mn-ligand distances as well as a Mn-Mn distance (~2.8 to ~2.7 Å) [41]. The shortening of the Mn-ligand and Mn-Mn distances could be due to the elimination of the Jahn-Teller effect at one Mn after its oxidation. An open cubane moiety in the S_0 state seems likely with either Mn2 or Mn1 being the Mn oxidized during the S_0 to S_1 state transition.

As indicated above, there is a consensus that Mn-centered oxidation occurs during the S_0 to S_1, and S_1 to S_2 transitions. However, there has been a long debate regarding the nature of the S_2 to S_3 transition [31, 32]. In the S_3 state, the question remains whether a Mn-centered oxidation occurs, $Mn_4(III,IV_3)$ to $Mn_4(IV_4)$, see above, or a ligand-centered oxidation takes place before O-O bond formation and release of O_2. Although Mn XANES studies have produced results that clearly indicate that in the S_0 to S_1 and S_1 to S_2 transitions Mn is oxidized, the S_2 to S_3 transition studies have not been conclusive, with one study suggesting that Mn may not be involved in the oxidation, while another study supports such a process [31, 32]. Mn Kβ emission spectra have indicated that the oxidizing equivalents may not be totally centered on the Mn. RIXS spectroscopy has also shown that formal oxidation states may be insufficient for describing the complex nature of the electronic structure in multinuclear clusters like the Mn_4CaO_5 cluster in PS II, and that the electrons are strongly delocalized in the Mn_4CaO_5 cluster, and that would mean that ligands may be involved in the redox chemistry [42, 43]. Mechanisms that rely on delocalization of charge on the ligands may be more relevant as discussed below.

EXAFS data show that Mn-Mn distances during the S_2 to S_3 state transition are elongated, compared to the S_0 to S_1 or S_1 to S_2 state transitions where contractions are observed. This suggests that the S_2 to S_3 step is not a simple one-oxidation state change of Mn, but is accompanied by changes in the geometry of the Mn_4CaO_5 cluster [20, 44]. Protonation of an oxo-bridge and the consequent elongation of Mn-Mn due is unlikely at the S_2 to S_3 state transition, unless protons from terminal water molecules are transferred to the bridging oxygens. A structural change that is caused by the shift of the oxygen O5 from the Mn1 side to the Mn4 side as illustrated in Figure 6 has been proposed. Such an O5 shuffling possibility has been suggested as a reason for the change from the S_2 low spin ($S = 1/2$) to S_2 high spin ($S = 7/2$), and on the basis of DFT calculations during the S_2 to S_3 state transition [45]. The motion of the oxygen O5 towards the Mn_3Ca open cubane site, generates a Mn_3CaO_4 closed cubane in the S_3 state, and such a structure is supported by Mn-Mn distances that have been seen in inorganic complexes [20]. A second possible structure for the S_3 state is also shown in Figure 6.

The 2.7 Å Mn-Mn distances on average are shown to be shortened during the S_3 to S_0 state transition via the S_4 state. This is counterintuitive as the Mn oxidation state changes from the most oxidized form in the S_3 state to the most reduced state form in the S_0 state. But such changes can be explained if the Mn_4CaO_5 geometry reverts back to a structure similar to the S_1 and S_2 states where the Mn_3Ca moiety shows open-cubane like structures, upon the S_3 to S_0 state transition.

Sr can functionally replace Ca [46, 47] in the OEC and, therefore, Sr XAS studies of Sr-substituted PS II (Mn_4SrO_5 cluster) have been used to study the structural changes of the Mn_4CaO_5 cluster [26, 27, 28]. The Mn-Sr (and by inference Mn-Ca) distance changes were observed during the S state transitions, with significant changes during the S_2 to S_3

state transition (Figure 5). These results, together with the Mn XAS data, have demonstrated that Ca (or Sr) plays an important role during the S_2 to S_3 state transition. This is in line with the fact that the OEC does not go beyond the $S_2Y_z^{\bullet}$ state when Ca (or Sr) is chemically depleted from PS II. Recent studies by Lohmiller et al. have shown that the depletion of Ca from the Mn_4CaO_5 core does not disturb the overall structure of the Mn_4 moiety or the spin states in the S_1 and S_2 states [48], as well as the geometry ([24] and unpublished data, T. Lohmiller). The fact that Ca can be removed more easily in the S_3 state (or that Ca can be more easily exchanged in the higher S states) compared to the S_1 and the S_2 states [49], together with the observations on the Ca-depleted system, implies that the Mn-Ca binding modes are changed upon the S_2 to S_3 state transition.

In addition to the changes to the core of the Mn_4CaO_5 cluster, terminal ligands from carboxylates, histidine, and water/hydroxo ligands could be involved in the catalytic reaction. It has been shown using site-directed mutagenesis studies that some ligands have critical roles in the OEC activity. The replacement of just one His terminal ligand by a glutamate residue (D1-His332Glu) resulted in a major change in the EXAFS and XANES spectra [50], illustrating the importance of the ligands in maintaining the active-site structure and how well-tuned the active site is by the residues surrounding the Mn_4CaO_5 cluster.

3 X-Ray Diffraction and Spectroscopy of Photosystem II at Room Temperature Using Femtosecond X-Ray Pulses

As described in the previous section, synchrotron-based XRD has been used over the last decade to study the structure of PS II using cryo-cooled crystals with improving resolution, with the most recent at a resolution of 1.9 Å. Detailed mechanistic studies are hampered by the intrinsic radiation-sensitivity of the Mn_4CaO_5 cluster to X-rays [29, 30], a problem that is common with other redox-active metalloenzymes [51, 52, 53, 54]. The higher oxidation states of Mn(III)/Mn(IV) in PS II in the native state are rapidly reduced to Mn(II) upon exposure to X-rays, resulting in structural disruption with concomitant changes in the Mn-O-Mn bridging structure, changes in metal-metal and metal-ligand bond lengths. Thus, even at cryogenic temperatures synchrotron radiation (SR)-based XRD of the Mn_4CaO_5 structure in PS II is fundamentally limited by the radiation damage to the redox active metal site. While X-ray radiation damage makes it difficult to obtain structures of the stable intermediate states of PS II or other metallo-enzymes using frozen cryo-trapped states, it is almost impossible to study the transient intermediate states involved in the catalytic reaction, which can only be generated at ambient conditions, best at room temperature (RT). Thus, it is imperative to work at RT, if one needs to determine physiologically/or biologically relevant structures and changes in the catalytic cycle.

The geometric and electronic structure of the intact Mn_4CaO_5 cluster in the stable S_0 through S_3 states has been addressed especially by X-ray absorption and emission techniques at cryogenic temperatures using a well regulated low X-ray dose (see above).

However, following the time course of the water-oxidation reaction at RT using X-ray absorption or emission spectroscopic features within the threshold of radiation damage has been unrealistic with SR sources. In particular studying the transient [S_4] state, when the O-O bond formation and the evolution of O_2 occurs, cannot be captured by traditional cryo-trapping methods and requires time-resolved detection at RT [17, 55, 56, 57]. Within ~1.3 milliseconds during the S_3-[S_4]-S_0 transition, which is initiated by the 3rd flash, the following sequence of events is proposed to occur [3]: (a) release of a proton from the $S_3Y_Z{}^{ox}$ state, (b) transfer of one electron to $Y_Z{}^{ox}$ from the Mn_4CaO_5 cluster, (c) formation of the O-O bond (peroxo intermediate) coupled with a 2-electron reduction of the Mn_4CaO_5 cluster, (d) formation and release of O_2 together with a further 2-electron reduction of the Mn_4CaO_5 cluster, (e) binding of one or two water molecules to the cluster, and (f) release of another proton during steps (c) to (e). Determining the geometric and electronic structures of intermediates of this reaction (e.g., $S_3Y_Z{}^{ox}$ and peroxo state) is pivotal for testing the many hypotheses that have been proposed for the mechanism of the water-oxidation reaction (see below).

The recent introduction of X-ray free electron laser (XFEL) sources that produce intense and ultra-short X-ray pulses provide an opportunity to overcome the above described limitations of SR sources for both crystallography and spectroscopy of biological samples with the “collect before destroy” approach [58, 59, 60], which entails measuring the response of the system before the manifestation of radiation-induced changes. Unlike cryogenic conditions required at synchrotron sources, the experiments with XFELs can be carried out at RT, making it possible to obtain molecular movies of the catalyst at work by recording snapshots at different time points in the catalytic cycle. In such a study crystallography and spectroscopy can give complementary information: spectroscopy provides detailed information about changes in the Mn oxidation states and the chemical structure of the Mn_4CaO_5 cluster, and crystallography probes the structural changes of the Mn_4CaO_5 cluster and the overall protein. As the entire X-ray emission spectrum can be collected with one excitation energy, this is the method of choice, and as the same X-ray energy (7.1 keV) can be used for X-ray diffraction and excitation of Mn, both XRD and XES [61] methods can be applied simultaneously.

Figure 7 shows the design for an experimental setup for the simultaneous collection of both XRD and XES of the stable and transient intermediate states of PS II at RT using the femtosecond X-ray pulses from an XFEL.

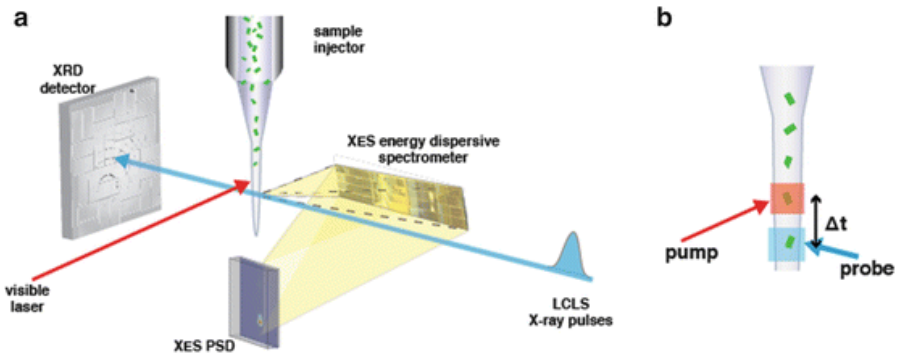

Figure 7

(**a**) XFEL setup for simultaneous collection of X-ray diffraction and emission spectra from PS II crystals in the various S state intermediates in a time-resolved manner. The crystals are injected using an electrofocusing jet to intersect the femtosecond X-ray pulses from the X-ray free electron laser. Downstream of the X-ray pulses is a multi-pixel multi-array detector for the collection of the X-ray diffraction data. Perpendicular to the direction of the X-ray beam is an energy-dispersive multi-crystal emission spectrometer, which focuses the emission spectrum onto a position sensitive detector. (**b**) Visible laser pulses advance the PS II into the various S states and the interval between the visible-laser pump and X-ray laser probe pulse gives the time dependence for the data collected.

3.1 Simultaneous X-Ray Spectroscopy and Diffraction of Photosystem II

Since the start of the first hard X-ray XFEL, the Linac Coherent Light Source (LCLS) at Stanford, the application of XFELs to important biological problems has evolved rapidly. Over the last three years, several pioneering “proof of principle” experiments both using crystallography and spectroscopy have been conducted, applying this concept to biological samples, both at LCLS and more recently at the SPring-8 Ångstrom Compact free electron LAser (SACLA), the XFEL at SPring-8 in Japan. The first application of both XES and XRD to PS II are described in this section.

3.1.1 X-Ray Emission Spectroscopy of Photosystem II at Room Temperature Using the X-Ray Free Electron Laser

In contrast to XAS, where the lowest unoccupied orbitals of the metal complexes are probed, XES probes the highest occupied orbitals of the metal complexes (Figure 8a, left) [61]. The highest occupied orbitals are of special interest as they are involved in the actual chemistry during a reaction. The excitation pulse used is at an energy higher than the binding energy of the electrons in 1s orbitals, and subsequent emission from the various levels can be examined using secondary optics. Kβ emission is from the 3p orbitals and is sensitive to the oxidation state and spin state of the metal. XES is well suited for experiments with XFELs because energy-dispersive detection schemes can be used, which allows for a full spectrum to be collected for each X-ray pulse. The scheme for such a dispersive spectrometer is shown in Figure 8a (right) [62]. It is comprised of cylindrically bent analyzer crystals arranged in a von Hamos geometry, where the X-ray emission signal is focused in the horizontal direction and dispersed in energy along the vertical direction onto a multi-pixel array detector. The signal is recorded for each individual shot and the single spectra from several shots can be added to obtain higher S/N ratios. Figure 8a (middle) illustrates the sensitivity of the XES technique to the oxidation states of Mn.

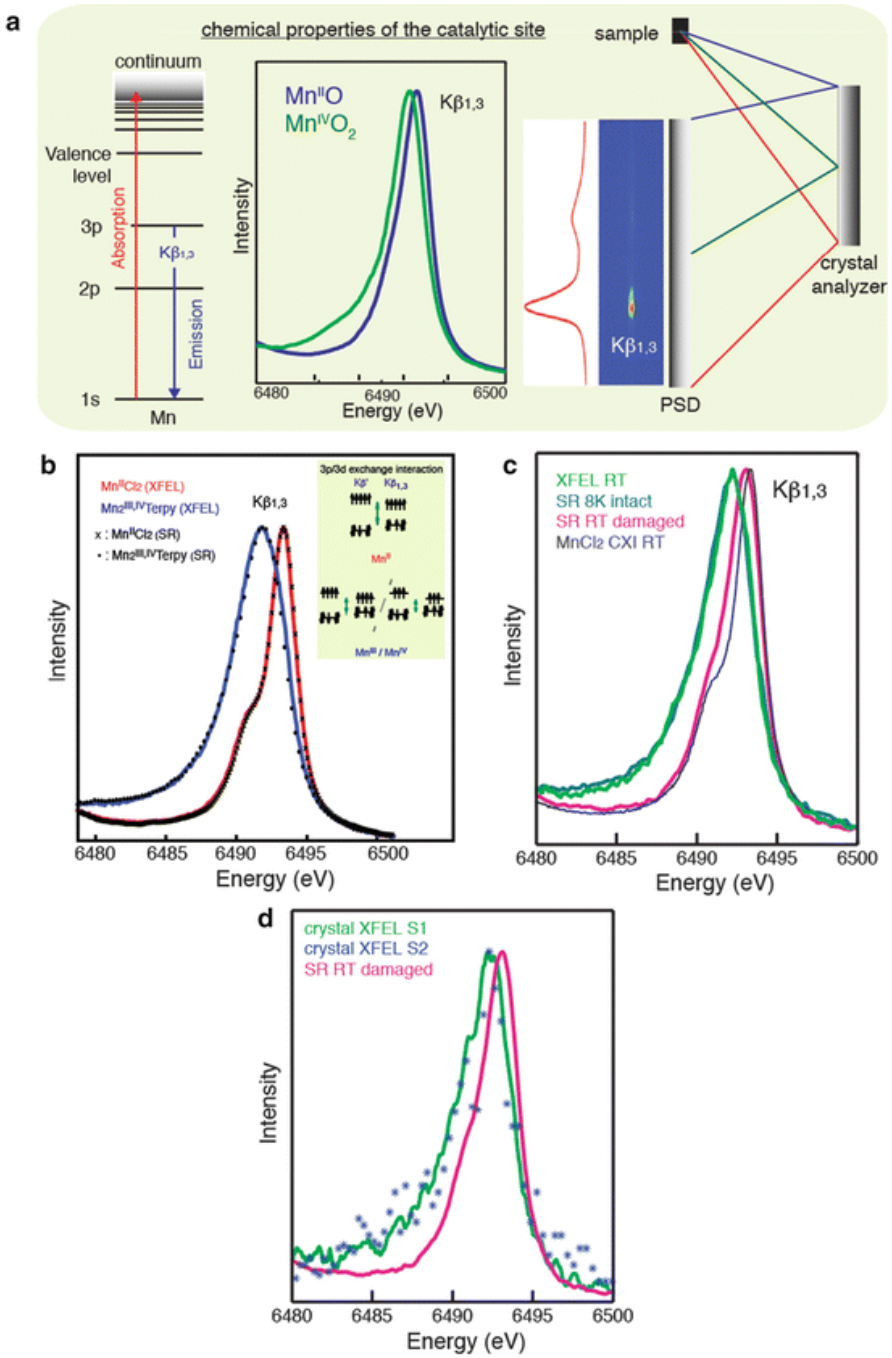

Figure 8

(**a**) The $K\beta_{1,3}$ emission spectra from Mn(II) and Mn(IV) are shown in the middle. $K\beta_{1,3}$ spectra are sensitive to the oxidation state of Mn. The energy level diagram is shown on the left for the $K\beta_{1,3}$ process and the cross-section of the energy dispersive emission spectrometer and the spectrum on the position sensitive detector, with the integrated emission spectrum at the right. (**b**) The $K\beta_{1,3}$ spectra from a $Mn(II)Cl_2$ solution and the $Mn_2(III,IV)$(Terpy) complex are given. The data collected using the XFEL at room temperature is shown in red and blue lines, and the data collected using synchrotron radiation at 10 K are shown as crosses and dots. The spectra at RT using the XFEL and SR at 10 K are identical. The inset shows

the exchange coupling showing the sensitivity of the Kβ emission process to the number of unpaired electron in the 3d orbitals of Mn. (**c**) X-ray emission spectra of PS II solutions in the dark state collected using the XFEL at RT (green) or collected using SR under cryogenic conditions with low dose ("8 K intact", light blue) and using SR at RT under photo-reducing conditions ("RT damaged", pink). The spectrum from $Mn(II)Cl_2$ in aqueous solution collected at RT at the XFEL is shown (grey) for comparison. (**d**) The $K\beta_{1,3}$ XES data collected from PS II crystals using the XFEL in the S_2 state are shown in blue (✶). The XFEL spectrum of microcrystals of PS II in the S_1 state is shown as a green line. For comparison an X-ray emission spectrum of completely photo-reduced ("damaged") PS II collected at RT at a synchrotron is shown in pink (adapted from [63]).

There have been concerns that the X-ray emission spectrum could be sensitive to changes in the electronic structure induced by the intense X-ray pulse, either because of the potential Coulomb explosion or inner-shell ionizations. XES data from solutions of $Mn(II)Cl_2$ and Mn_2(III,IV)Terpy are shown in Figure 8b and the spectra of both the complexes are in good agreement with the data collected at SR sources under cryogenic conditions [63]. This was especially relevant for the Mn(III,IV) complex, as this compound is highly redox sensitive and can only be measured in frozen solutions at 10 K using synchrotron X-rays. The absence of any deviation from cryogenic SR data indicated that undisturbed Kβ XES can be measured from aqueous solutions of transition metal compounds at the LCLS. More importantly, no change in the electronic structure of the Mn was observed, indicating that under the conditions normally used for hard X-ray protein crystallography at the LCLS, the "probe before destroy" approach is also feasible for spectroscopy of radiation-sensitive transition metals.

Figure 8c shows the Mn Kβ emission spectra of the S_1 state of PS II at RT using an XFEL. The RT XFEL spectrum is identical to that collected with SR at 8 K, and clearly different from the data from $Mn(II)Cl_2$ or that of PS II collected at RT at SR sources. The spectra of damaged PS II are similar to that obtained for $Mn(II)Cl_2$. The XFEL XES data are very encouraging as they clearly demonstrate that it is indeed possible to collect spectra from undamaged PS II using the very intense XFEL pulses even at RT. Moreover, these spectra from PS II can be collected simultaneously with the collection of the XRD data (see below), which shows that the crystallographic data originate from an intact PS II, and that XES can be used to determine the integrity of the PS II samples and to confirm the intermediate state of PS II (see below).

3.1.2 X-Ray Diffraction Studies of Photosystem II at Room Temperature Using the X-Ray Free Electron Laser

Single-crystal XRD experiments, when performed with conventional SR, generally use one or a few crystals that are rotated through a set of angles to collect a complete data set for deriving the electron density of the macromolecule. The XFEL destroys the sample with a single X-ray pulse, requiring the full data set to be assembled from a series of still diffraction shots of individual microcrystals [64, 65]. This technique is now becoming known as serial femtosecond crystallography (SFX). The ~40 femtosecond-duration XFEL pulse can deliver diffraction/spectroscopy information on time scales that outrun

radiation damage, allowing PS II reaction dynamics to be studied under functional physiological conditions, while the small beam focus size permits the investigation of extremely small and weakly diffracting PS II microcrystals.

In the case of XRD measurements, using femtosecond pulses from XFELs it has been postulated that there is a self-gating mechanism where the signal contains contributions only from the initial undamaged sample. It is thought that the later part of the X-ray pulse will interact with a strongly distorted or a disrupted crystal lattice, contributing only to diffuse background scattering rather than the Bragg scattering. Hence, the signal that is collected would only reflect the mostly undamaged sample as it is seen during the initial part of the pulse. Thus, XRD data from XFELs is free of data resulting from damaged sites expected at the intensities that are common with XFELs. The initial XRD experiments of PS II at LCLS have largely confirmed these observations. Moreover, the simultaneous XES data obtained from the crystals has shown that under these conditions, the Mn_4CaO_5 cluster is also undamaged [66, 67].

The structure of PS II obtained using the XFEL is isomorphous to that from SR structures, showing that there are no specific large-scale differences either due to radiation damage or due to temperature differences (cryo-cooled crystals at SR and RT with XFEL) (Figure 9a). The maximum of the electron density map (Figure 9b) was found in the region of the Mn_4CaO_5 cluster. The lack of influence of model bias was confirmed by computing the various omit maps; omitting the Mn_4CaO_5 cluster, or the non-heme iron (located at the stromal side of the PS II complex), or the four central Chls from the phasing model. In each case, positive difference electron density for the omitted cofactors was visible in the omit map at the expected location and is an unbiased indication of the presence of these groups in the PS II microcrystals. The mF_o-DF_c difference peak in the Mn_4CaO_5 omit map is shown in Figure 9c.

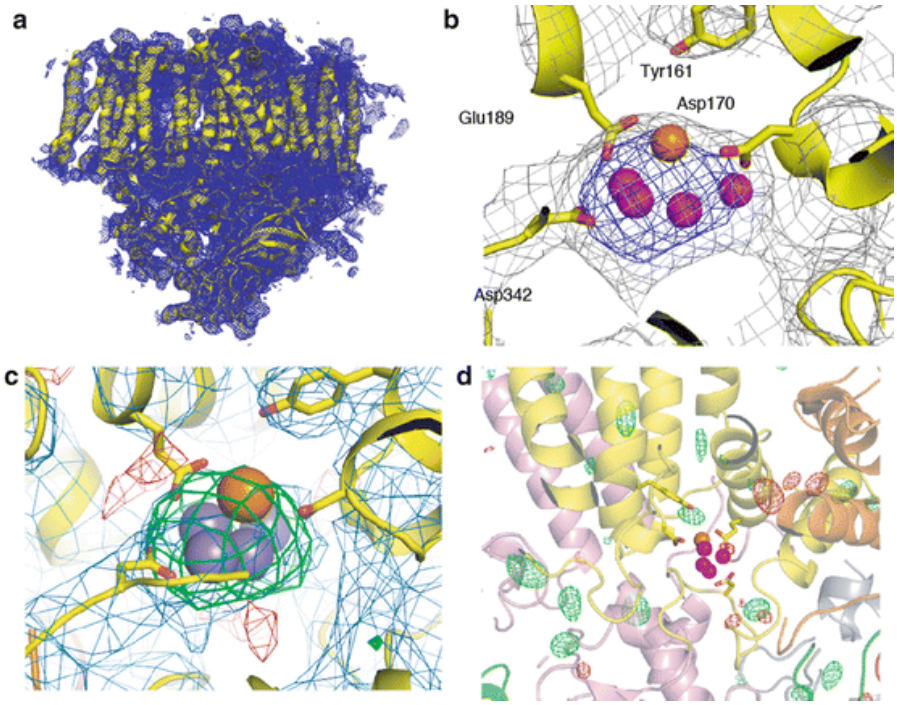

Figure 9

Electron density of PS II obtained from femtosecond XRD measured at the CXI instrument of LCLS. (**a**) Electron density of one monomer of the dimer is shown in blue with the protein shown in yellow, view is along the membrane plane with the lumenal side on bottom and the cytoplasmic side on top. The density is contoured at 1.2 σ. (**b**) Electron density in the vicinity of the OEC, Mn (magenta) and Ca (orange) ions are shown as spheres, the protein backbone in yellow and the electron density as grey (1.0 σ) and blue (4.0 σ) mesh. (**c**) Omit map obtained by excluding the Mn_4Ca cluster from the phasing model. Electron density is shown as in (c), view direction and coloring of Mn and Ca is similar to panel (b). (**d**) Isomorphous difference map between the XFEL-illuminated (S_2 state) and the XFEL-dark (S_1 state) XRD dataset in the region of the Mn_4CaO_5 cluster, with F_o-F_o difference contours shown at +3 σ (green) and −3 σ (red). The map indicates that there are no major changes between the S_1 and S_2 states at this resolution. Metal ions of the Mn_4CaO_5 cluster are shown for orientation as violet (Mn) and orange (Ca) spheres, subunits are indicated in yellow (D1), orange (D2), pink (CP43), and green (PsbO) (adapted from [66, 67]).

The dose deposited on the PS II crystals by the XFEL for each individual shot was ~10^8 Grays (Gy or J kg^{-1}). This dose is an order of magnitude higher than the Henderson/Garman limit of 2–3 × 10^7 Gy [68, 69], generally considered to be the limit for loss of diffractivity in cryogenic SR-based XRD, and about 100 times higher than the dose used for SR XRD data collection of PS II at 100 K (~1 × 10^6 Gy for the 1.9 Å crystal structure). With PS II microcrystals, cryogenic SR measurements are not possible due to the extent of X-ray exposure and loss of diffraction; however, the same PS II microcrystals exhibit diffraction spots with the XFEL technique at RT. Despite applying this high dose at RT, there appears to be no loss of diffractivity or visible differences between the RT XFEL and cryogenic SR structures. This fact demonstrates that the femtosecond XFEL pulses (~45 fs) are short enough to outrun the damage processes present in conventional SR XRD [70].

It should be noted that, for several protein structures, there were recent reports on differences between structures obtained at RT and cryogenic temperatures [69]. PS II shows several large loop regions that are extrinsic to the membrane and are potentially flexible. In addition, only a small number of amino acid residues are involved in providing crystal contacts, raising the possibility that these loop regions could adopt different conformations depending on the crystal conditions. Interestingly, no deviations in position for these loop regions are found when comparing the SR cryogenic and the XFEL RT structures, indicating that there are no large-scale effects on the structure of PS II due to the freezing necessary for cryogenic XRD.

3.2 Intermediate S State Transitions and Mechanism of Dioxygen Evolution

A real advantage of XFEL-based XRD or spectroscopy is not only to study biological systems at RT under physiological conditions, but to also study the enzymatic reactions in real time so that one can understand the electronic and structural processes in play. In

pursuit of this goal with PS II, and to advance PS II into the higher S states, an *in situ* illumination setup has been integrated into the sample delivery system (Figure 7). The illumination setup consists of three lasers directly coupled via fiber-optic cables to the silica capillary for sample delivery and a fourth laser intersecting the jet at the X-ray interaction point. The idea is to be able to advance PS II through the S state cycle and study the last light-induced S_3 to S_0 advance via the transient and other possible intermediate states in a time-resolved manner to understand the O-O bond formation step. In preparation for these studies, the very first illuminated state, the S_2 state, has been generated *in situ* and studies using both XRD and XES (see below).

3.2.1 X-Ray Free Electron Laser-Based X-Ray Diffraction and X-Ray Emission Spectroscopy of Photosystem II in the S_1 and S_2 States

Recently, XES and XRD data from PS II microcrystals highly enriched in the S_2 state have been successfully collected and analyzed. The XES data did not exhibit a significant difference from the S_1 data (Figure 9d), showing that there was no damage to the electronic structure of the Mn cluster in either state by the visible-laser pump/X-ray-probe method. Due to the limited sample amount, the quality of the S_2 data was poorer and the small shift expected between the S_1 and S_2 state could not be resolved within the signal/noise ratio of the spectra.

XRD data for PS II enriched in the S_2 state was collected using the XFEL with the setup described in Figure 7. As the S_2 state data are isomorphous to the S_1 state data, isomorphous difference map between the S_1 and S_2 states was calculated (Figure 9d). A detailed analysis of this map revealed no statistically relevant difference peaks. This indicates that within the limits of the currently available resolution there are no larger scale structural changes associated with the oxidation of the Mn_4CaO_5 cluster from the dark stable S_1 to the first illuminated S_2 state. These results represent the first step in determining the electronic and geometric structure changes during the water oxidation reaction in PS II in a time-resolved manner.

4 Membrane Inlet Mass Spectrometry and Photosystem II

Monitoring the isotopic composition of the product, O_2, by time-resolved isotope-ratio membrane-inlet mass spectrometry (TR-IR-MIMS) is a powerful method for kinetic and functional analyses in PS II research in particular, in combination and for the study of the mechanism of photosynthetic water-oxidation to O_2.

Schematic views of a TR-MIMS set-up employing an isotope ratio mass spectrometer are shown in Figure 10. This type of mass spectrometer is normally equipped with an electron-impact ion source, magnetic sector field analyser, and individual detectors (Faraday cups) that provide simultaneous detection of several masses (ions) with high sensitivity and signal stability. For its ability to monitor and to selectively analyze all *isotopologues* (molecules that differ only in their isotopic composition) of gaseous

products with one instrument, the TR-MIMS approach in combination with isotope enrichments became an indispensable tool for kinetic and functional analyses of photosynthetic enzymes [71, 72, 73]. The key part of the TR-MIMS instrument is a gas inlet system that is integrated within a MIMS cell. The design of MIMS cells may vary depending on the measuring purposes [71, 72], but all of them contain a gas-permeable membrane functioning as analyte inlet system into the vacuum of the mass spectrometer. The coupling of such a cell to various light sources (e.g., Xenon lamps or lasers) allows carrying out the measurements of light-induced O_2 evolution in photosynthetic samples or light-driven O_2-evolving artificial catalysts. Before entering the ion source of the mass spectrometer the analytes pass through a cryogenic trap, which freezes out water vapor that inadvertently pervaporate through the membrane in trace amounts. Enrichment of the aqueous sample suspension with oxygen's heavy isotope (^{18}O) for isotope ratio measurements of O_2 (and/or CO_2) isotopologues is a useful and commonly used tool in studies of water-splitting chemistry and/or related reactions. Therefore, most of the experiments are carried out in H_2 ^{18}O-labelled sample suspensions/solutions.

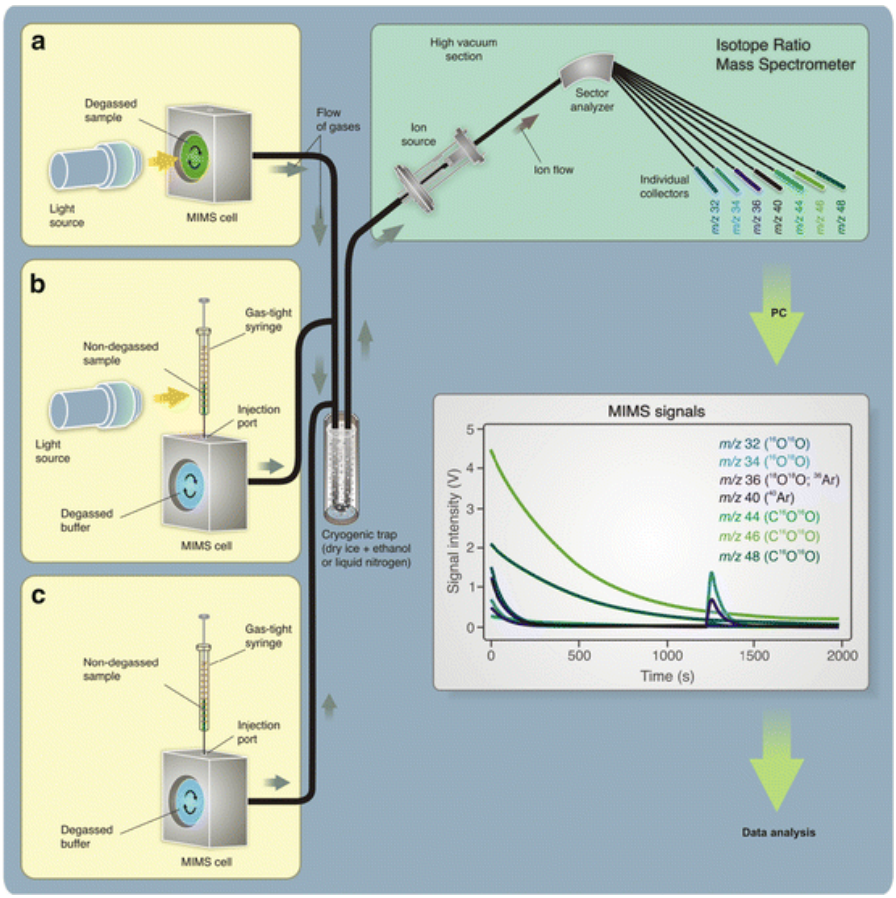

Figure 10

Simplified scheme of a MIMS set up, in which the production of gaseous analyte is initiated by (**a**) illumination of degassed photo-active samples, (**b**) illumination of non-degassed samples that were subsequently injected into a degassed buffer, and (**c**) the reaction of non-degassed chemicals injected into the degassed sample. The gaseous reaction products penetrate through the gas-permeable membrane and reach the high vacuum section where they are ionized by electron impact. The generated ions are

separated by a magnetic field according to their mass-to-charge ratios and detected by Faraday cups. The resulting signals of the different isotopes are amplified and recorded online simultaneously.

4.1 Membrane Inlet Mass Spectrometry and S State Turnover in X-Ray Free Electron Laser Studies

In the simultaneous XRD and XES experiments using the XFEL, although XES provides an *in situ* check for the quality of the sample and the advancement of the S states in the Kok cycle, it is advantageous to have another independent method to confirm the turnover status of the PS II samples. MIMS has been the method of choice for these studies.

In order to achieve a high population of the illuminated states, the illumination parameters had to be optimized. For this purpose, MIMS has been critical. Using this method the conditions required for the best turnover under the conditions of the XFEL experiments have been optimized. These include the flow rate of PS II, the power and frequency of the laser illumination, and the delay conditions. The MIMS experiment has been used to achieve about 73 % of the sample in the first illuminated state (S_2, see Figure 11). Such independent assessments and optimizations of the turnover are critical for a success of the XFEL experiment.

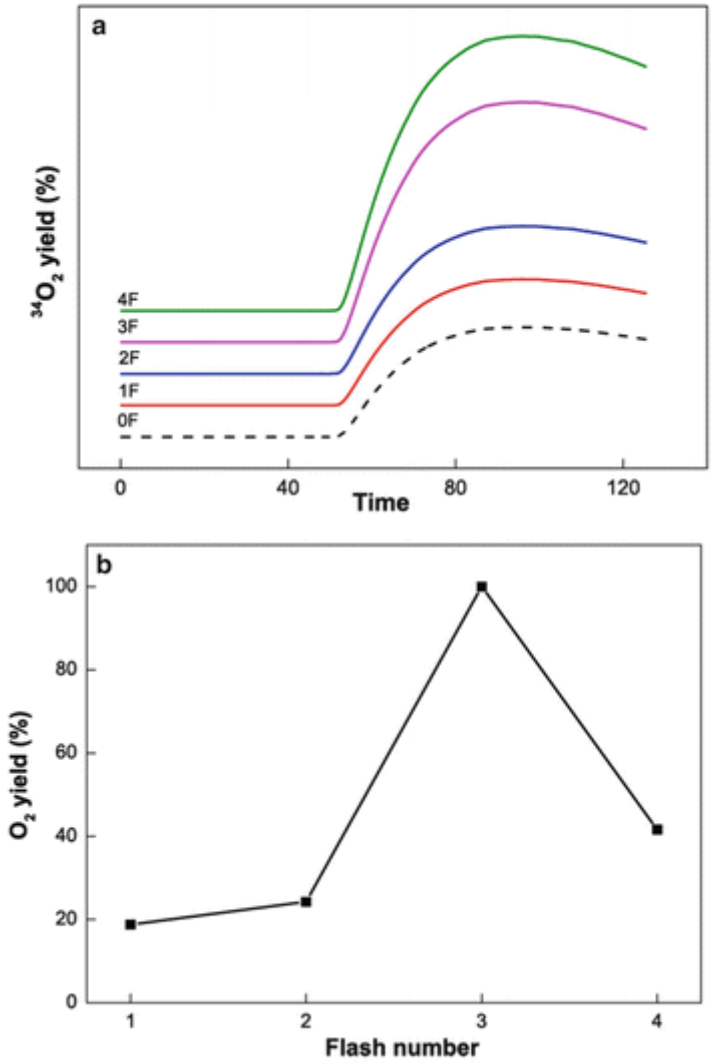

Figure 11

On-line MIMS measurements of light-induced O_2 yield detected as mixed labeled $^{16}O^{18}O$ species after illumination of photosystem II from *Thermosynechococcus elongatus* with 0, 1, 2, 3, and 4 flashes at pH 6.5 and 20 °C (yield *versus* time in seconds) (panel **a**). Panel (**b**) displays the flash pattern derived from (**a**) by subtracting the signal of x flashes from that obtained with x + 1 flashes (panel **b** adapted from [67]).

4.2 Time-Resolved Membrane Inlet Mass Spectrometry and Insights into Oxygen Evolution

The most significant contribution of the TR-MIMS in understanding of the water-oxidation mechanism has been its application for studying substrate H_2O binding in the different S states of the OEC. In these experiments the binding of water to the OEC was probed by the rapid injection of H_2 ^{18}O into the PS II samples which were preset into the desired S state by pre-illumination with 0, 1, 2, or 3 flashes as illustrated in Figure 12. After the desired incubation time, O_2 evolution is induced by a sequence of additional

flashes. The exchange rates of the two water molecules are calculated from the dependence of the $^{16}O^{18}O$ and $^{18}O^{18}O$ yields as a function of incubation time (Table 1). A short mixing time of the H_2 ^{18}O with PS II samples after injection and a very low level of dissolved O_2 in the H_2 ^{18}O are highly important for these experiments since they determine the time resolution of the TR-MIMS measurements. In the first H_2 $^{16}O/H_2$ ^{18}O-exchange TR-MIMS experiments the water exchange kinetics could not be resolved [74, 75]. The development of the MIMS cell by Messinger, Badger, and Wydrzynski [76], which allowed for fast mixing of H_2 ^{18}O with the sample and also implemented O_2 removal from the labeled water by the glucose – glucose oxidase – catalase method, greatly improved the time resolution down to the milliseconds scale and allowed measurements of substrate water exchange in all S states [76, 77, 78].

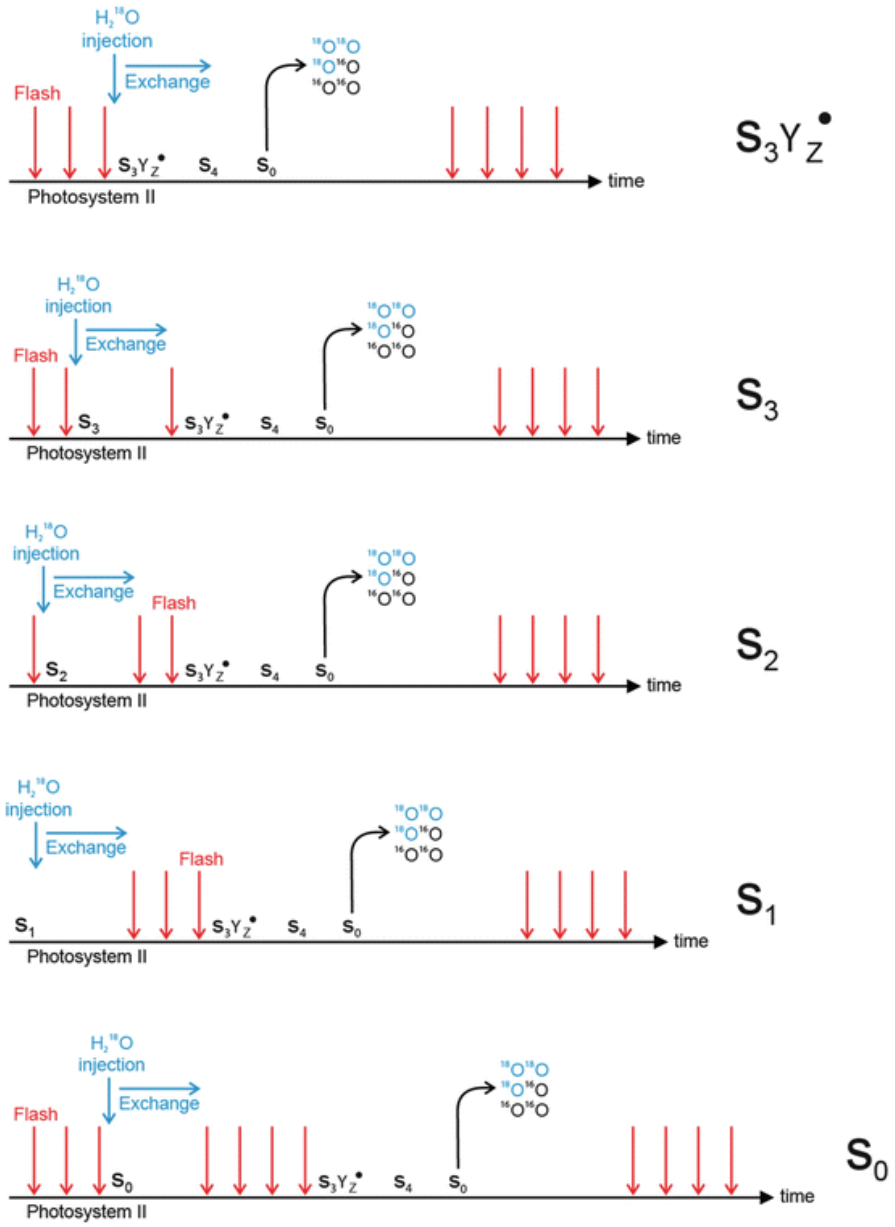

Figure 12

The protocol for the TR-MIMS measurements of substrate water exchange in the S states.

Table 1

S state dependence of substrate water exchange rates measured by TR-MIMS in spinach thylakoids at 10 °C, pH 6.8.[a]

S_i state	k_s, s^{-1}	k_f, s^{-1}
S_0	~10	–
S_1	~0.02	>120
S_2	~2.0	~120
S_3	~2.0	~40

[a]Table adapted from [80].

Figure 13 illustrates the characteristic water exchange kinetics in the S_3 state. The yields of the singly-labeled ($^{16}O^{18}O$) and doubly-labeled ($^{18}O^{18}O$) isotopologues of O_2 are plotted as a function of H_2 ^{18}O incubation time in the S_3 state. Figure 13 (top) shows the result when only one of the two possible ^{18}O-water substrates is exchanged, while Figure 13 (bottom) is for the case when both ^{18}O-waters are exchanged. The biphasic behavior of the $^{16}O^{18}O$ rise (detected at $m/z = 34$) is known to represent the exchange rates of two independent *slowly* (W_s, see below) and *fast* exchanging substrate water molecules (W_f, see below) bound at separate sites within the OEC. In contrast, the $^{18}O^{18}O$ product (monitored at $m/z = 36$) exhibits a mono-exponential rise with a rate equal to that of the slow phase kinetics of the $^{16}O^{18}O$ data, thus-reflecting the exchange of the same 'slowly' exchanging substrate water as observed at $m/z = 34$. This finding clearly confirms that the two phases of the $^{16}O^{18}O$ data are an intrinsic feature of the OEC and do not originate from PS II heterogeneity [73, 76, 77].

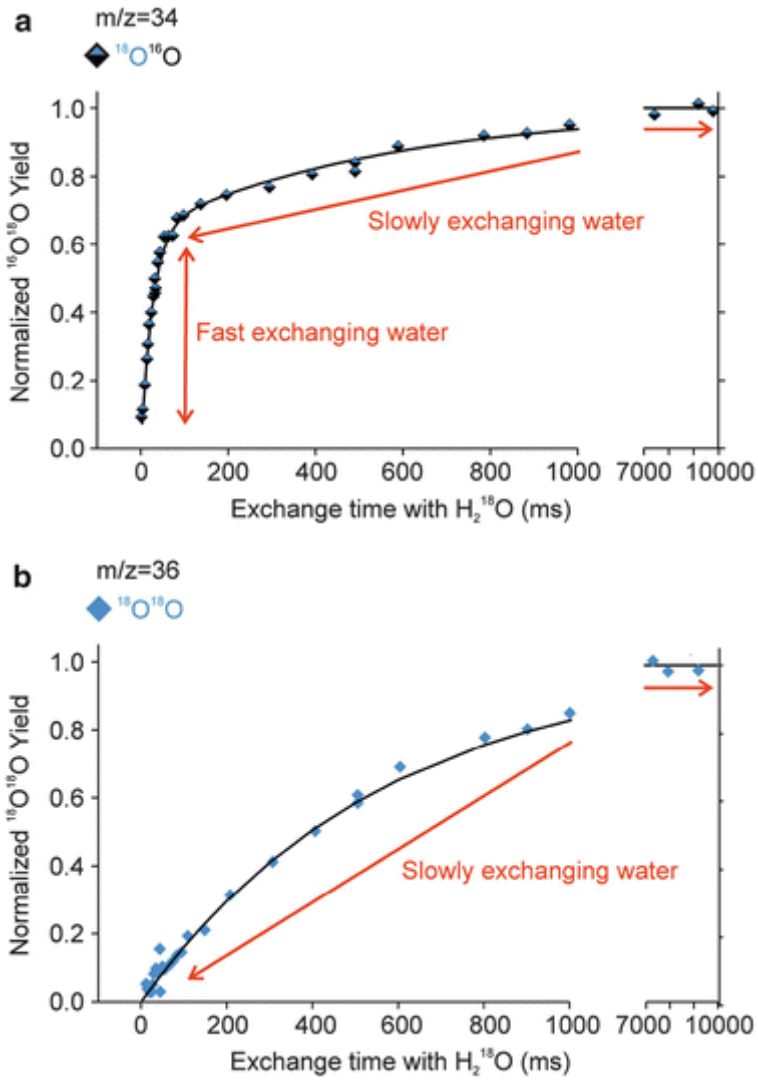

Figure 13

The characteristic water exchange kinetics in the S_3 state as measured in spinach thylakoids with the time resolution of 8 ms. The yields of the singly-labeled ($^{16}O^{18}O$) and doubly-labeled ($^{18}O^{18}O$) isotopologues of molecular oxygen are plotted as a function of $H_2{}^{18}O$ incubation time in the S_3 state. While the former plot reflects the result when only one of the two possible ^{18}O-water substrates is exchanged, the latter one is for the case when both ^{18}O-waters are exchanged. The biphasic behavior of the $^{16}O^{18}O$ rise (detected at $m/z = 34$) is known to represent the exchange rates of two independent *slowly* (W_s) and *fast* exchanging substrate water molecules (W_f) bound at separate sites within the OEC (see Table 1). The data in panel (**b**) are kinetically limited by the exchange of W_s and thus show a single slow phase identical to that in panel (**a**).

Further TR-MIMS experiments also revealed that the 'slowly' exchanging water is bound to the OEC in all the S states, while the 'fast' exchanging water was detected only in the S_2 and S_3 states [77, 78, 79, 80]. Thus, the TR-MIMS technique provides not only the most direct evidence for independent substrate water binding within the OEC, but also allows

to monitor the change in their binding affinities throughout the reaction cycle. For a complete overview of the TR-MIMS findings in this field, we refer the readers to recent reviews [72, 81, 82].

The most likely mechanisms presently being considered are presented in Figure 14 below. The water-exchange results do not support the nucleophile attack mechanisms in which Ca-bound water attacks a terminal oxo or a μ-oxo bridge. Similarly, mechanisms involving two μ-oxo bridges, or two terminal waters seem unlikely. Two likely options are that O5 is W_s, where W_f is either W_2, the terminal hydroxo ligand to Mn_{A4}, or a water not seen in the crystal structure (see above, Figure 1, inset) [35, 82, 83, 84].

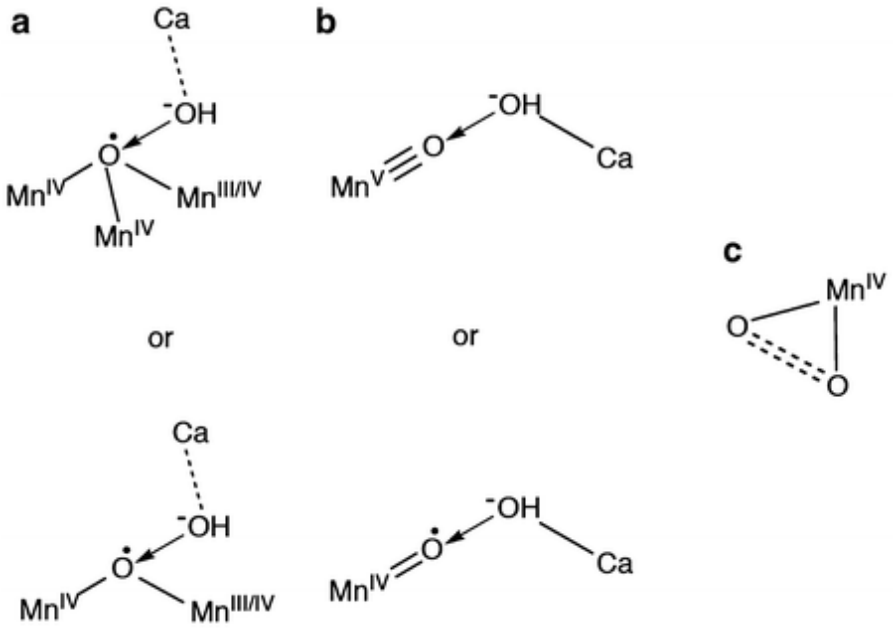

Figure 14

Schematic presentation of three mechanisms proposed for O-O bond formation during the S_3 - [S_4] - S_0 transition. (**a**) involves a bridging O ligand and a radical and/or a delocalized charge on the Mn cluster. (**b**) involves the electrophilic mechanism with a high valent Mn(V) and terminal O ligation, and (**c**) involves an end-on peroxo ligand to a single Mn center. These schematics do not represent all the possible variations that have been proposed within the categories of radical-based and nucleophilic attack mechanisms.

5 Concluding Remarks and Future Directions

Ultimately, understanding the water splitting mechanism requires the characterization of the last step (S_3-S_4-S_0), where the O-O bond is formed and O_2 is evolved. Unlike other intermediate S states (S_0 through S_3), the kinetically unstable S_4 state cannot be cryo-trapped by freeze-quenching techniques, and therefore requires time-resolved studies at ambient conditions [55]. The S_3-S_4-S_0 transition includes five sequential events: (a)

extraction of one electron, (b) release of two protons, (c) release of molecular oxygen, (d) binding of one or two substrate water molecules to the Mn_4CaO_5 cluster, and (e) four-electron-reduction of the Mn_4CaO_5 cluster.

Several O-O bond formation mechanisms have been proposed [83], and three representative ones are shown in Figure 14. Mechanism (a) invokes an O-O bond formation by a radical-type mechanism, mechanism (b) involves an electrophilic high-valent Mn(V), and mechanism (c) has an end-on peroxo ligand to a single Mn center. Fundamental differences in the chemistry of O-O bond formation and O_2 evolution exists between the three types of mechanisms. In the first case there is delocalization of the charge to the ligands, while in the second case the charge is mainly centered on the Mn. Not much is known about the electronic structure of the third case, although such intermediates have been observed for Cu and Fe metalloenzymes and Mn model compounds. Mn(V) has also been proposed as a transient intermediate in the catalytic cycle of epoxidation reactions, and the water-oxidation in PS II might involve a similar intermediate. The high reactivity of the S_4 state intermediates is not in line with the stability of synthetic Mn(V) compounds, which are all in a low-spin configuration. We would therefore rather expect a high-spin, reactive Mn(V) to be involved. However, so far there is no direct spectroscopic evidence for the existence of such a Mn(V) species in PS II. It is known that up to the S_3 state all four Mn centers are in a high-spin configuration, hence it is likely that if Mn(V) is involved it would also be in a high-spin configuration, and therefore reactive. The presence of Mn(V) or lack thereof and its spin state is particularly important for developing artificial inorganic water splitting catalysts, a central issue in solar fuel generation. These questions, along with the need to characterize the proposed transient S_4 state and other kinetic intermediates that may be present, offer challenges for the future and they need to be addressed before we can fully understand where and how plants oxidize water to dioxygen.

Notes

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Abbreviations and Definitions

Chl

chlorophyll

CXI

coherent X-ray imaging

Dbm

dibenzoylmethane

DFT

density functional theory

ENDOR

electron nuclear double resonance

EPR

electron paramagnetic resonance

EXAFS

extended X-ray absorption fine structure

fs

femtosecond

FTIR

Fourier transform infrared spectroscopy

Htphpn

N,N,N’,N’-tetra(2-methylpyridyl)-2-hydroxypropanediamine

IR

infrared spectroscopy

LCLS

Linac coherent light source

MIMS

membrane inlet mass spectrometry

OAc

acetate

OEC

oxygen-evolving complex

PS II

photosystem II

PSD

position sensitive detector

RIXS

resonant inelastic X-ray scattering

RT

room temperature

SACLA

Spring-8 Ångstrom compact free electron laser

SFX

serial femtosecond crystallography

SR

synchrotron radiation

Terpy

2,2':6',2"-terpyridine

TR-MIMS

time-resolved membrane inlet mass spectrometry

XANES

X-ray absorption near edge spectroscopy

XAS

X-ray absorption spectroscopy

XES

X-ray emission spectroscopy

XFEL

X-ray free electron laser

XRD

X-ray diffraction

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