Redox potentials along the redox-active low-barrier H-bonds in electron transfer pathways†

Keisuke Saito,‡a,b Manoj Mandal,a,b and Hiroshi Ishikita†a,b

Low-barrier H-bonds form when the pKₐ values of the H-bond donor and acceptor moieties are nearly equal. Here, we report redox potential (Eₚₐ) values along two redox-active low-barrier H-bonds in the water-oxidizing enzyme photosystem II (PSII), using a quantum mechanical/molecular mechanical approach. The low-barrier H-bond between D1-Tyr161 (TyrZ) and D1-His190 is located in the middle of the electron transfer pathway. When the proton is at D1-His190, Eₚₐ(TyrZ) is the lowest and can serve as an electron donor to the oxidized chlorophyll P₄₃�. Eₚₐ(TyrZ) and Eₚₐ(D1-His190) are equal, and the TyrZ···D1-His190 pair serves as an electron acceptor to Mn₄CaO₅ when the proton is at TyrZ. In the low-barrier H-bond between D1-His215 and plastoquinone QA, located at the terminus of the electron transfer pathway, the driving force of electron transfer and electronic coupling between QA and QB are maximized when the proton arrives at QA. It seems likely that local proton transfer along redox-active low-barrier H-bonds can alter the driving force or electronic coupling for electron transfer.

The driving force of water oxidation in photosystem II (PSII) is provided by light-induced charge separation in the reaction center. In PSII, the reaction center has a pair of chlorophylls (P₃₁/P₃₂), accessory chlorophylls (Chlₐ₁/Chlₐ₂), pheophytins (Pheo₃�/Pheo₃₂), and plastoquinones (QA/QB) in the heterodimeric D1/D2 protein subunit pairs (Fig. 1a). Electronic excitation of Chlₐ₁ leads to the formation of a charge-separated state [P₃₁P₃₂]ₚ₃�Pheo₃�Pheo₃₂. Electron transfer subsequently occurs via QA to QB. QA reduction is linked to QB protonation. After the second electron transfer, doubly protonated QA₂H₂ is released from the binding site toward the bulk water region: the quinone pool. In [P₃₁P₃₂]ₚ₃�Pheo₃�Pheo₃₂, the cationic state is more populated on P₃₁ than P₃₂ (P₃₁ₚ₃�:P₃₂ₚ₃� = 80:20 4–6). P₃₁ₚ₃� has a significantly high redox potential (Eₚₐ) for one-electron oxidation (>1100 mV 7–9), which makes P₃₁ₚ₃� abstract electrons from the substrate water molecules at the Mn₄CaO₅ cluster (700–800 mV 10) via redox-active D1-Tyr161 (TyrZ; Fig. 1b).

TyrZ must form a hydrogen bond (H-bond) with D1-His190 to serve as a redox-active cofactor. Notably, TyrZ and D1-His190 form a significantly short (2.46 Å 11) low-barrier H-bond. Low-barrier H-bonds can form only when the pKₐ values of the H-bond donor and acceptor moieties are nearly equal. 14,15 The shape of the potential energy curve of a low-barrier H-bond is symmetric, while the curve of a standard H-bond is asymmetric because pKₐ(donor) > pKₐ(acceptor) 16 (Fig. 1c and d). The pKₐ value of tyrosine (~7) is higher than that of histidine (~10) in water. In the PSII protein environment, a cluster of water molecules (whose positions are fixed by the components of the Mn₄CaO₅ cluster) donates a stable H-bond to the phenolic O site of TyrZ and decreases pKₐ(TyrZ) to the level of pKₐ(D1-His190), forming a low-barrier H-bond. 12,13

In PSII, low-barrier H-bond formation is also observed at the terminus of the electron transfer pathway (QB and the H-bond partner D1-His215) when the second electron transfer from QA₂H₂ to QAH⁺ occurs. 17 D1-His215 is the ligand of the nonheme Fe complex, and the N8 site forms an H-bond with the carbonyl O site of QA. The presence of the cationic Fe facilitates the deprotonation of D1-His215 and proton uptake by QAH⁺. Specifically, decreasing the pKₐ value of ~14 18 for deprotonation of singly protonated histidine to the level of the pKₐ value of ~11 19 for deprotonation of doubly protonated plastoquinone. It seems likely that the low-barrier H-bond between TyrZ and D1-His190 is stable enough to function repeatedly in each S-state transition, while the bond between D1-His215 and QA functions only once before QA₂H₂ is released.

Initially, the redox-active group was identified as D1-His190 based on observations of radical formation in the Ca²⁺-depleted PSII. 20,21 Later, it was proposed that TyrZ, not D1-His190, was the origin of the radical state. 22 Since then, TyrZ has been

‡ Research Center for Advanced Science and Technology, The University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8904, Japan. E-mail: hiro@appchem.t.u-tokyo.ac.jp; Fax: +81-3-5452-5083; Tel: +81-3-5452-5056
† Department of Applied Chemistry, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8654, Japan
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These authors contributed equally to this work.
regarded as a redox-active group in the electron transfer pathway. Indeed, $E_m(TyrZ)$ is lower than $E_m(D1-His190)$, however the $E_m$ difference is not significantly large when the proton is at the TyrZ moiety.10

$E_m$ values of the H-bond donor and acceptor moieties along low-barrier H-bonds have not been reported. Here, we report $E_m$ of the two redox-active low-barrier H-bonds, considering the entire electron and proton transfer pathways quantum-chemically in the presence of the PSII protein environment.

Results
Low-barrier H-bond switching from an electron donor to an acceptor

The potential-energy profile of the H-bond shows that TyrZ and D1-His190 form a low-barrier H-bond. The difference between $pK_a(TyrZ)$ and $pK_a(D1-His190)$ is nearly zero along the low-barrier H-bond. However, the difference between $E_m(TyrZ)$ (i.e., $\text{Tyr-O}^-/\text{Tyr-O}^-$) and $E_m(D1-His190)$, (i.e., $N-\text{His-N}^-/N-\text{His-N}^+$ or $HN-\text{His-N}^-/HN-\text{His-N}^+$) depends on the H$^+$ position (Fig. 2, right panel). $E_m(TyrZ)$ decreases and $E_m(D1-His190)$ increases as the proton moves from TyrZ to D1-His190. When H$^+$ arrives at the lower $E_m$ moiety (D1-His190), $E_m(TyrZ)$ is the lowest and the driving force for electron transfer from TyrZ to oxidized chlorophyll $P_{D1}^+$ is the largest. The highest occupied molecular orbital (HOMO) is predominantly localized at the TyrZ moiety. Thus, the TyrZ moiety can serve as an electron donor to $P_{D1}^+$ most effectively when the proton is at the D1-His190 moiety. Note that the H$^+$ atom position does not affect the $E_m$ values of other cofactors in the electron transfer pathway.

In contrast, when H$^+$ is at the TyrZ moiety, $E_m(TyrZ)$ and $E_m(D1-His190)$ are equal, and the highest occupied molecular orbital (HOMO) is delocalized over the two moieties (Fig. 2b, left panel). In this case, the driving force for electron transfer from the oxygen-evolving complex (i.e., $\text{Mn}^{III/IV}_4$) to the TyrZ·D1-His190 pair is largest (Fig. 2b, right panel). Thus, the entire TyrZ·D1-His190 moiety cooperatively serves as an electron acceptor when electron transfer occurs from the oxygen-evolving complex.

Low-barrier H-bond maximizing electronic coupling and driving force

As an electron transfers to $Q_{B}H^+$, a low-barrier H-bond forms between D1-His215 and $Q_{B}H^+/Q_{B}H^-$,17 facilitating $Q_{B}H_2$ release.
from the binding site in PSII. We analyzed $E_m(N–His–N/C_15/N–His–N/C_0)$ and $E_m(QBH/C_15/QBH/C_0)$ along the low-barrier H-bond between D1-His215 and QB. Note that $E_m(QBH/C_15/QBH/C_0)$ can be analyzed based on the (fully occupied) HOMO of $Q_{BH}/C_0$, which is the same as the (singly occupied) HOMO (SOMO) of $Q_{BH}/C_15$.

(i) Driving force. $E_m(Q_{BH}/C_15/Q_{BH}/C_0)$ increases and $E_m(D1-His215)$ decreases as $H^+$ moves from D1-His215 to $Q_{BH}/C_15/Q_{BH}/C_0$ along the low-barrier H-bond (Fig. 3b, right panel). $E_m(Q_{BH}/C_15/Q_{BH}/C_0)$ increases and the difference between $E_m(Q_{A}/C_15/C_0)$ and $E_m(Q_{BH}/C_15/Q_{BH}/C_0)$ (the driving force for electron transfer) also increases when $H^+$ moves to the lower $E_m$ moiety ($Q_{BH}/C_15$).

(ii) Electronic coupling. The HOMO is predominantly localized at the $Q_{BH}/Q_{BH}$ moiety when $H^+$ is at the D1-His215 moiety ($O_{TyrZ}–H = 1.38 \text{ Å}$) with the HOMO population of TyrZ: D1-His190 = 96.1:0.4 and (b) at the TyrZ moiety (1.02 Å) with the HOMO population of TyrZ: D1-His190 = 51.4:44.7. Red arrows indicate electron transfer from TyrZ to $P_{D1}$. Blue arrows indicate electron transfer (ET) from Mn4 to the TyrZ/D1-His190 pair. Cyan arrows indicate movement of the proton between the D1-His190 and TyrZ moiety. The gray dotted vertical line indicates the $H^+$ position where $E_m(tyrZ)$ and $E_m([His190]$ are nearly equal and the TyrZ/His190 pair serves as an electron acceptor, finalizing the electron transfer process.
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quantum-chemically considered, which is consistent with the absence of the redox change of the Fe complex in electron transfer from QA to QB. This suggests that the entire [D1-His215/C1/C1/H+]/C15/QBH/C15 moiety serves as an electron acceptor for QA/C15/C0 and decreases the substantial donor–acceptor distance from QA/C15/C0/QBH/C15 (12.7 Å) to QA/C15/C0/D1-His215 (8.3 Å), increasing electronic coupling (Fig. 3b, left panel).

**Discussion**

The redox-active low-barrier H-bond between TyrZ and D1-His190 plays a dual role in electron transfer by serving as both an electron donor and an electron acceptor. The movement of the proton by only 0.35 Å from the D1-His190 moiety along the low-barrier H-bond alters $E_m$ by ~120 mV and switches its role from an electron donor to acceptor (Fig. 2). As the proton moves back to the TyrZ moiety in the low-barrier H-bond, $E_m$(TyrZ) and $E_m$(D1-His190) become equal within the barrier-less potential (O$_{TyrZ}$·H = 1.02 Å; Fig. 2b, right panel). Thus, TyrZ·D1-His190 can serve as both an electron donor and acceptor in the middle of the electron transfer pathway during the S-cycle without being destabilized by proton movement.

Until now, it has been thought that D1-His190 is not redox-active, but that TyrZ is$^{22}$ (however see ref. 20 and 21). However, this result suggests that both TyrZ and D1-His190 are redox-active components in the electron transfer pathway, in particular when abstracting an electron from the oxygen-evolving complex (Fig. 2b).

On the other hand, movement of the proton by only 0.35 Å along the low-barrier H-bond between D1-His215 and QB/C1/C1/H+ increases $E_m$(QA/H+)+$E_m$(QB/H+) to the level of $E_m$(D1-His215), leading to delocalization of the HOMO over the D1-His215 and QB moiety. The involvement of D1-His215 in the electron acceptor decreases the donor-to-acceptor distance from QA···QB to QA···D1-His215 (8.3 Å), increasing electronic coupling between the donor QA and the acceptor QB/C1/C1/H+, because the electronic coupling increases as the electron donor-to-acceptor distance decreases.$^{23,24}$ The role of the redox-active low-barrier H-bond in increasing electronic coupling is observed specifically for D1-His215···QB/H+QB/C1/C1/H+, since the axis of the low-barrier H-bond is consistent with the
axis of the electron transfer pathway and delocalization of the HOMO over D1-His215 and Qb decreases the substantial donor–acceptor distance (Fig. 3, left panel).

In contrast to the TyrZ · D1-His190 H-bond, the difference between $E_m$(D1-His215) and $E_m$(Qb) is small but not zero within the barrier-less potential as the proton moves to the Qb moiety ($H_{D1-His215-H}$ = 1.43 Å; Fig. 3b, right panel). Indeed, the HOMO is still predominantly localized at Qb (Fig. 5, red). Only after the proton exceeds the barrier-less potential by 0.1 Å is the HOMO evenly delocalized over D1-His215 and Qb and the difference between $E_m$(D1-His215) and $E_m$(Qb) reaches zero ($H_{D1-His215-H}$ = 1.53 Å, Fig. 3b, right panel). In reality, the low-barrier H-bond is unlikely to exist when $H_{D1-His215-H}$ = 1.53 Å because the potential energy profile was obtained assuming the presence of the H-bond (see Methods). Consistently, the donor–acceptor N···O distance ($N_{D1-His215}···O_{Qb}$) is 2.47 Å when the proton is located at the D1-His215 moiety ($N_{D1-His215-H}···O_{Qb}$) and it is lengthened to 2.55 Å when the proton arrives at the Qb moiety ($N_{D1-His215-H}···O_{Qb}$). Thus, QbH2 is released from the binding site (D1-His215) when $H^+$ leaves the barrier-less potential (after cleavage of the low-barrier H-bond). The irreversibility of the reaction is characteristic of, and required for, Qb serving as the terminal electron acceptor in the electron transfer pathway. Intriguingly, the corresponding change in the donor–acceptor distance in response to the $H^+$ movement is absent in the TyrZ · D1-His190 1H-bond ($O_{TyrZ-H}···N_{D1-His190}$ = 2.52 Å and $O_{TyrZ-H}···N_{D1-His190}$ = 2.50 Å). This is consistent with the role of the TyrZ · D1-His190 pair in the middle of the electron transfer pathway, which involves reversibly donating and accepting an electron during the entire S-cycle. As reported, environmental fluctuations may affect the potential energy profile,25 particularly for standard H-bonds. Proton transfer is energetically uphill in the standard H-bond (Fig. 1c). To overcome this energy barrier, fluctuation/rearrangement of the protein environment is a prerequisite for unstable protonation of the acceptor moiety. In contrast, proton transfer is barrier-less in the low-barrier H-bond, which does not require the corresponding fluctuation/rearrangement of the protein environment (Fig. 1d). Consistently, the $B$-factors of TyrZ and D1-His190 are specifically low11 because the H-bond network is fixed by the PSII protein electrostatic environment, namely the Mn4CaO5 cluster and the ionized ligand residues.12

For the redox-active low-barrier H-bonds to serve as a redox-active cofactor in the electron transfer pathway, the presence of the protein electrostatic environment is a prerequisite. First, TyrZ and D1-His190 cannot form a low-barrier H-bond in the absence of the PSII protein environment12 because of the difference in $pK_a$ ($~3$) between tyrosine and histidine. Second, the protein electrostatic environment is required for the formation of the downhill electron transfer pathway that proceeds from the Mn4CaO5 cluster via TyrZ, as it increases $E_n$(PDI) by ~400 mV with respect to $E_n$(Chla).6,26 Thus, the environment, in which the $pK_a$ values of the proton donor and acceptor moieties are equal and the $E_m$ values of the electron donor and acceptor moieties are in the tunable range by proton transfer, is ultimately provided by the common protein electrostatic environment.

In summary, the $pK_a$ values of the two moieties are equal, but the $E_m$ values depend on the $H^+$ position in redox-active low-barrier H-bonds. The results also suggest that redox-active low-barrier H-bonds can differ in their characteristics, whether they serve as a redox-active cofactor in the middle of the electron transfer pathway (TyrZ · D1-His190) or in the terminus of the electron acceptor pathway (D1-His215 · Qb). These findings provide a key to understanding how nature optimizes electron and proton transfer in biological systems using abundantly available protons.

**Methods**

The atomic coordinates of PSII were obtained from the PSII crystal structure (PDB code, 3ARC).11 The atomic charges of the other cofactors in the MM region were taken from a previous study.27

$E_m$ calculations for the electron transfer pathway via TyrZ · D1-His190

The HOMO energy level is largely correlated with $E_m$ for one-electron oxidation (e.g., ref. 28 and 29). For the Mn4CaO5 cluster, the HOMO in $S_a$ corresponds to the molecular orbital, which predominantly contributes to the release of an electron in the $S_a$ to $S_{1h}$ transition. We included all redox-active cofactors (Mn4CaO5 cluster, TyrZ, PDI, and P O2) simultaneously in the QM region (see below), identified HOMOs of Mn4CaO5, TyrZ, PDI, and P O2 in $S_1$ on the basis of the Mulliken population analysis32 (results provided in a previous study), and obtained the $E_m$ values (note, $E_m$(S1/S0) for the Mn4CaO5 cluster). The $E_m$ values of the redox sites are calculated using eqn (1):

$$E_m = -0.15499E_{HOMO} + 1205.65,$$

where $E_{HOMO}$ is the HOMO energy level (meV).10

**QM/MM calculations**

The unrestricted density functional theory method was employed with the B3LYP functional using the QSite program. B3LYP is a widely used functional to calculate redox potentials and HOMO and LUMO energy levels (e.g., ref. 34 and 35). Using B3LYP can also make a comparison with our previous studies for Mn4CaO5,10,36 TyrZ,12,13 PDI,6,37 and Qb18 in PSII. In the QM region, all the atomic coordinates were fully relaxed. In the MM region, the positions of the H atoms were optimized using the OPLS2005 force field, while the positions of the heavy atoms were fixed.

To investigate the H-bond between TyrZ and D1-His190, the LACVP* basis set was employed. The Mn4CaO5 cluster was considered to be in S1 with antiferromagnetically coupled Mn ions; the resulting Mn oxidation states (Mn1, Mn2, Mn3, Mn4) and the total spin $S$ were $S = 8/2$ (↑ ↑ ↑ ↑) in S1. Note that the difference in $S$ (for example, $S = 0$ in $S_{1h}$39) did not affect the calculated $E_m$ values ($\leq 3$ mV).10 O1–O5 was considered to be unprotonated (O3–). The four water ligand molecules, W1–W4, were considered to be water molecules (H2O). The Mn4CaO5 geometry was obtained from our previous studies.40,41 The initial-guess
wavefunctions were obtained using the ligand field theory\(^1\)\(^2\) implemented in the QSite program. The QM region was defined as the Mn\(_4\)CaO\(_2\) cluster (including the ligand side-chains of D1-Asp170, D1-Glu189, D1-His332, D1-Glu333, D1-Asp342, and CP43-Glu354, and backbone of D1-Ala344), ligand water molecules of W1–W4, O4–water chain (W539, W538, and W393), CI-1 binding site (Cl-1, W442, W446, and side-chains of D1-Asn181 and D2-Lys317), second-sphere ligands (side-chains of D1-Asp61 and CP43-Arg357), the H-bond network of TyrZ (side-chains of D1-Tyr161, D1-His190, and D1-Asn298), diamond-shaped cluster of water molecules\(^3\) (W5, W6, and W7), and P\(_{D1}/P\_D2\). The MM region was defined as the entire PSII protein, as in a previous study.\(^1\) D1-His337 was considered to be protonated,\(^4\) whereas all other titratable groups were in the standard protonation states. See ref. 17 for the QM/MM-optimized atomic coordinates.

To investigate the H-bond between D1-His215 and Q B, the LACVP++ basis set was employed. The QM region was defined as [Q\(_B\), D1-His252, D1-Ser264, bicatearinate, Fe, D1-His215, D1-His272, D2-His214, and D2-His268]. We assumed a high-spin state (\(S = 2\)) of Fe\(^{2+}\) and set the spin multiplicity of the system to \(S = 2\) in the calculations for Q\(_B\)\(^-\) and Q\(_B\)\(^2-\). The MM region was defined as the D1 and D2 protein subunits, as in a previous study.\(^1\) D1-His252 was considered to be protonated before Q\(_B\)\(^2-\) formation,\(^4\) whereas all other titratable groups were in the standard protonation states. See ref. 17 for the QM/MM-optimized atomic coordinates.

To obtain the potential energy profiles of the O···H···N H-bond, the QM/MM optimized geometry was used as the initial geometry. The H atom under investigation was moved constraining the O–H and H–N distances, and the energy was calculated. This procedure was repeated until the H atom reached the O and N atoms. This approach, which is based on the single QM/MM-optimized geometry, provides the unique minimum-energy pathway, in particular for the H-bond between TyrZ and D1-His190, as demonstrated by analyzed proton-transfer pathways in the different protein conformations.\(^1\)\(^2\)

Conflicts of interest

There are no conflicts to declare.

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