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Proton-coupled electron transfer across benzimidazole bridges in bioinspired proton wires†

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Designing molecular platforms for controlling proton and electron movement in artificial photosynthetic systems is crucial to efficient catalysis and solar energy conversion. The transfer of both protons and electrons during a reaction is known as proton-coupled electron transfer (PCET) and is used by nature in myriad ways to provide low overpotential pathways for redox reactions and redox leveling, as well as to generate bioenergetic proton currents. Herein, we describe theoretical and electrochemical studies of a series of bioinspired benzimidazole-phenol (BIP) derivatives and a series of dibenzimidazole-phenol (Bl₂P) analogs with each series bearing the same set of terminal proton-accepting (TPA) groups. The set of TPAs spans more than 6 pK_a units. These compounds have been designed to explore the role of the bridging benzimidazole(s) in a one-electron oxidation process coupled to intramolecular proton translocation across either two (the BIP series) or three (the Bl₂P series) acid/base sites. These molecular constructs feature an electrochemically active phenol connected to the TPA group through a benzimidazole-based bridge, which together with the phenol and TPA group form a covalent framework supporting a Grotthuss-type hydrogen-bonded network. Infrared spectroelectrochemistry demonstrates that upon oxidation of the phenol, protons translocate across this well-defined hydrogen-bonded network to a TPA group. The experimental data show the benzimidazole bridges are non-innocent participants in the PCET process in that the addition of each benzimidazole unit lowers the redox potential of the phenoxyl radical/phenol couple by 60 mV, regardless of the nature of the TPA group. Using a series of hypothetical thermodynamic steps, density functional theory calculations correctly predicted the dependence of the redox potential of the phenoxyl radical/phenol couple on the nature of the final protonated species and provided insight into the thermodynamic role of dibenzimidazole units in the PCET process. This information is crucial for developing molecular “dry proton wires” with these moieties, which can transfer protons *via* a Grotthuss-type mechanism over long distances without the intervention of water molecules.

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Introduction

Energy transfer, electron transfer, and proton transfer processes are choreographed by a light-driven water-plastoquinone oxidoreductase enzyme better known as photosystem II (PSII)

in all water oxidizing photosynthetic organisms. Understanding how these processes are linked and coupled to one another is one of the key principles for designing efficient artificial photosynthetic systems.^{1–3} In PSII, photochemical events begin with either direct absorption of light by several chlorophyll *a* molecules, known collectively as P680, or the absorption of light by antenna pigments followed by energy transfer to P680. The excited singlet state of P680 (P680*) then undergoes rapid electron transfer to reduce a nearby chlorophyll (Chl), forming a charge separated pair, P680^{•+}–Chl^{•–}. In a series of electron transfer steps, the strongly reducing Chl^{•–} species reduces first a pheophytin and subsequently plastoquinone A and then B. The highly oxidizing P680^{•+} species, the other half of the charge separated pair, is reduced by electron transfer from the tyrosine Z (Tyr_Z) residue. This redox event occurs with concomitant transfer of the phenolic proton to its hydrogen-bonded partner,

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His190, in a proton-coupled electron transfer (PCET) process leading to formation of a neutral tyrosine radical (Tyr_z^\bullet).^{4–6} Subsequently, Tyr_z^\bullet advances the oxidation state of the oxygen evolving complex (OEC) by electron transfer from the $\text{Mn}_4\text{O}_5\text{Ca}$ OEC and recovers its proton, presumably from His190.

PCET reactions are also involved in the water oxidation chemistry that occurs during advancement of the OEC's oxidation state, which results in redox leveling and is central to bioenergetics.⁷ Coupled to electron transfer from the $\text{Mn}_4\text{O}_5\text{Ca}$ complex to Tyr_z^\bullet , protons are extracted from substrate water by the $\text{Mn}_4\text{O}_5\text{Ca}$ catalytic complex. These protons ultimately go to the lumen of the thylakoid membrane, most likely being transferred along Grotthuss-type proton wires.⁸ Overall the process involves transfer of four electrons and four protons to accomplish the oxidation of two water molecules. Although atomic level mechanistic details are not fully understood, there is general agreement that proton transfer along the “wires” to the lumen is coupled to the oxidation process and is part of the bioenergetic electrical system generating proton-motive force (PMF) and driving ATP synthesis.⁹

The thermodynamics of these processes are crucial to the control of proton activity in catalysis and the generation of proton currents involved in bioenergetics. The relatively high redox potential required for water splitting is delivered by Tyr_z^\bullet , which seems to require participation in a local hydrogen-bond network. Model studies indicate that losing the phenolic hydrogen-bonded proton in the Tyr_z –His190 pair to the surroundings would result in a redox couple ($\text{Tyr}_z^\bullet/\text{Tyr}_z^-$ instead of $\text{Tyr}_z^\bullet/\text{Tyr}_z$) with a midpoint potential ($E_{1/2}$) that is insufficient to oxidize water (and would likely render the redox process irreversible).^{10,11} At the other limit, if the phenolic proton remains on the Tyr_z residue and is not transferred to its

hydrogen-bonded partner His190, the oxidation of Tyr_z and formation of $\text{Tyr}_z^{\bullet+}$ by P680^{++} would be thermodynamically uphill.^{10,11} To keep the redox potential of Tyr_z in the appropriate range, nature employs the reaction pathway alluded to above, involving hydrogen-bonded assemblies where both electrons and protons are transferred in a PCET process.^{9,12–15}

The PCET concept has been extensively studied in connection with chemical and biochemical catalysis, bioenergetics, and Grotthuss-type proton wires and has inspired many researchers to build artificial constructs to mimic the Tyr_z –His190 function.^{16–21} Among them, a benzimidazole-phenol (BIP, containing an unsubstituted benzimidazole group, see structure in Scheme 1, ESI Page S5†), where the phenol moiety mimics Tyr_z and the benzimidazole mimics His190, provides a minimalist structure demonstrating PCET.^{11,22–25}

In our previous work, the amino-substituted BIP (**4**, see Fig. 1) featured a concerted one-electron, two-proton transfer (E2PT) process upon electrochemical oxidation of the phenol (see Fig. 2).²² The PCET process in this genre of compounds is concerted in that no thermodynamically stable intermediate was found. This designation is further supported by the agreement between the calculated redox potential for the E2PT process and the experimentally measured redox potential. However, PCET in these systems may be asynchronous on the femtosecond timescale, although such asynchronicity does not impact the electrochemical measurements. As a consequence of transferring the proton to the terminal proton-accepting (TPA) group in **4**, the potential of the phenoxyl radical/phenol redox couple is ~ 300 mV lower than that measured in experiments using BIP. This drop in the $E_{1/2}$ would restrict its use as a redox mediator in a water splitting process at near neutral pH. Theoretical calculations predicted that BIPs bearing



Fig. 1 Molecular structures of BIP (**1–4**) and BI₂P (**1'–4'**) constructs bearing different terminal proton-accepting groups (color-coded as in Fig. 4–6). The numbering system is shown in **1**, and the incorporation of a second benzimidazole to form dibenzimidazole based bridges between the phenol moiety and the terminal proton-accepting group are shown in dark grey in **1'–4'**.



substituents on the 7-position of the benzimidazole with lower pK_a 's than the amino group would have $E_{1/2}$ values closer to the ~ 0.95 V vs. SCE associated with the one-electron one-proton transfer (E1PT) process characteristic of the BIP phenoxyl radical/phenol redox couple.²² Indeed, BIP compounds substituted with *N*-phenylimines as a TPA group did have midpoint potentials near 1.00 V vs. SCE.²⁶ Moreover, the ratio of E2PT to E1PT products following oxidation of the phenol could be modulated by the nature of the substituents at the *para*-position of the *N*-phenylimine moiety. Density functional theory (DFT) calculations and infrared spectroelectrochemistry (IRSEC) results showed that with stronger electron-donating substituents the proton of the benzimidazole is transferred to the imine group upon phenol oxidation, leading to a net proton movement of ~ 6.4 Å along the hydrogen-bond network.²⁶

To extend the proton translocation, new constructs bearing an additional benzimidazole moiety, which generates a dibenzimidazole bridge and increases the spatial separation between the oxidation center (the phenol moiety) and the TPA group, have been synthesized (see Fig. 1). These molecules were designed to investigate the control of phenol redox potentials in amino and imine-substituted BIP systems,^{22,26} and to further explore the thermodynamics of proton transfer across a dibenzimidazole bridge unit (see Fig. 2). Fig. 1 shows compounds **1**, **2**, **3** and **4**, which are BIPs substituted at the 7-position with *para*-cyano-*N*-phenylimine, *para*-methoxy-*N*-phenylimine, *N*-cyclohexylimine, and an exocyclic diethylamino group, respectively. By including a second benzimidazole, the analogous compounds, BI₂Ps **1'**–**4'** bearing the same TPA groups as in **1**–**4**, were synthesized.

This work provides insights regarding structure–function relationships governing the influence of hydrogen-bond networks involving phenols, bridging benzimidazoles and TPAs on the $E_{1/2}$ of the phenol redox process, which initiates the fully reversible PCET reaction. This is a requirement for the

design of efficient artificial proton wires able to conduct protons over distances of ~ 30 Å, necessary for the construction of functional artificial biological membranes.

Results and discussion

Synthesis and structural characterization

Model compounds **1**–**3** were obtained by reaction of a derivative of BIP containing a formyl group at the 7-position (BIP–CHO) with the corresponding aromatic or aliphatic primary amino derivatives in the presence of a catalytic amount of pyrrolidine.^{26,27} Compound **4** was obtained by reduction of the tertiary amide group in the 7-position of BIP (BIP–CONEt₂) following a procedure previously described.²² The second benzimidazole moiety of the BI₂P family was introduced by condensation of BIP–CHO with methyl 2,3-diaminobenzoate followed by conversion of the ester group to the aldehyde (BI₂P–CHO), the precursor of compounds **1'**–**4'**. The complete synthetic route, conditions, and structural characterization are described in the ESI (Pages S4–S16†).

The spatial arrangement of the proton donor–acceptor systems and the strength of the hydrogen bonds connecting them are important design parameters for the success of intramolecular PCET reactions.^{28–30} In this regard, the crystal structures of both **4** and **2'** indicate the presence of the intramolecular hydrogen bonds in these molecules (see Fig. 3, CCDC deposition no. 1968269 and 1968270, respectively). In the case of **4**, the O₁–N₁ distance between the phenolic O and the proximal N of the benzimidazole is 2.59 Å, and the N₂–N₃



Fig. 2 Generic structure of BIP derivatives **1**–**4** (top), and BI₂P analogs **1'**–**4'** (bottom) showing the electrochemical oxidation of the phenol coupled with two (E2PT) or three (E3PT) proton transfers. Red arrows indicate proton movement for the forward and reverse processes.



Fig. 3 Crystal structures of (a) **4** and (b) **2'**. Carbon atoms are shown in gray, oxygens in red, nitrogens in light violet, and hydrogens in white. The heteroatoms involved in hydrogen bonds are labeled. Thermal ellipsoids are drawn at the 50% probability level. A molecule of DCM was found in the crystal unit cell (see ESI†) of **2'** and has been omitted for clarity.



In solution strong hydrogen bonds in **4** have been previously demonstrated²² and, in the case of **2'**, evidence for strong hydrogen bonds is clear from the relatively downfield phenolic proton resonances observed in the 400 MHz ¹H NMR spectra (see Table 1 and structural characterization in the ESI). In CDCl₃ solution, the chemical shift of the phenolic proton appears at 13.40 ppm, and the chemical shifts of both benzimidazole NH groups are clearly resolved. The signal corresponding to the distal NH proton (second benzimidazole) forming the hydrogen bond with the imine N (N₄H··N₅ in Fig. 3b) is assigned to the

The existence of isomers resulting from 1,3-tautomerism is seen in some benzimidazole-containing compounds.³⁴ Indeed, depending on both the hydrogen-bond ability of the solvent and the strength of the hydrogen bond between the phenol and the imidazole N, compounds **1–4** may have additional isomers resulting from 1,3-tautomerism and rotation around the bond linking the benzimidazole and the phenolic moiety.^{22,26} In the case of **1–4**, only one isomer has the internal hydrogen-bond network necessary to achieve two intramolecular proton transfers upon phenol oxidation. Because compounds **1'–4'** have an additional benzimidazole unit, the number of possible isomers in solution increases relative to **1–4**. For **1'** and its precursors (BI₂P–COOCH₃, BI₂P–CH₂OH and BI₂P–CHO, see synthesis and NMR characterization in the ESI[†]), the presence of at least two isomers in CDCl₃ was detected, and one of them lacks the hydrogen-bond network necessary for the two-proton intramolecular translocations. On the contrary, the ¹H NMR spectra of compounds **2'–4'** clearly show the existence of essentially one isomer in non-polar solvents such as CDCl₃, suggesting that a more basic group (*N*-phenylimine *p*-substituted with a strong electron donating group such as –OCH₃, cyclohexylimine, or tertiary amine) strengthens the terminal hydrogen bond and thereby favors the conformation where the hydrogen-bond chain is unbroken across the molecule.²⁷

Fig. 4 shows cyclic voltammograms (CVs) recorded using BI₂Ps 1'-4' and their analogous BIPs 1-4. For compounds 1-4, data

Compound	δ_{OH} (ppm)	δ_{NH} (ppm) ^a	δ_{NH} (ppm) ^b
1	13.19 ^c	—	11.48 ^e
2	13.30 ^c	—	11.84 ^c
3	13.30 ^d	—	11.87 ^d
4	13.45 ^e	—	11.17 ^e
1'	13.36	12.07	11.54
2'	13.40	12.12	11.83
3'	13.42 ^d	12.15 ^d	11.90 ^d
4'	13.43	12.20	~12.20 ^f

^a NH involved in the internal hydrogen bond between benzimidazoles ($\text{N}_2\text{H}\cdots\text{N}_3$ in Fig. 3b). ^b NH involved in the internal hydrogen bond between the benzimidazole and the terminal proton-accepting group (either imine, such as $\text{N}_4\text{H}\cdots\text{N}_5$ in Fig. 3b, or exocyclic amine, such as $\text{N}_2\text{H}\cdots\text{N}_3$ in Fig. 3a). ^c Data from ref. 26. ^d Data from ref. 27. ^e Data from ref. 22. ^f Broad signal presumably overlapped with the NH signal assigned to the internal hydrogen bond between benzimidazoles ($\text{N}_2\text{H}\cdots\text{N}_3$ in Fig. 3b).



Fig. 4 (a–d) Cyclic voltammograms of BI₂Ps 1'–4' (dashed lines). The cyclic voltammograms of analogous BIPs 1–4 (solid lines) are included for comparison. Concentration: 1 mM of the indicated compound, 0.5 M TBAPF₆ supporting electrolyte in dry acetonitrile. WE: glassy carbon. Pseudo RE: Ag wire (ferrocene as internal reference). CE: Pt wire. Scan rate, 100 mV s^{−1}. Compound 3' has low solubility in acetonitrile.

relevant to the chemical and electrochemical reversibility of the phenoxyl radical/phenol redox couples are included in Table 2. In 0.5 M tetrabutylammonium hexafluorophosphate (TBAPF₆) acetonitrile solutions containing 1–4, the cathodic to anodic peak intensity ratios (i_c/i_a), a measure of chemical reversibility, are ≥ 0.65 at a scan rate of 100 mV s^{−1} (see ESI†), and the peak-to-peak separations (ΔE_p), a measure of electrochemical reversibility, are 0.07 V for 1–3 and 0.10 V for 4. In the BI₂P series, the ΔE_p is 0.11 for 1', 2' and 4', and 0.10 for 3'.

Experimental and calculated $E_{1/2}$ values for the phenoxyl radical/phenol couple, as well as ΔE_p 's, are summarized in Table 2. Each $E_{1/2}$ was calculated assuming that all possible intramolecular proton transfer events occur, i.e., two protons transfer in 1–4, and three protons transfer in 1'–4'.

For BIPs 1–4, $E_{1/2}$ values of the phenoxyl radical/phenol redox couples were taken as the average of the anodic and cathodic peak potentials, yielding values of 0.99, 0.93, 0.77 and 0.61 V vs. SCE, respectively.^{22,26} In the case of the BI₂P family, the same trend in the $E_{1/2}$ to lower values with increasing basicity of the TPAs was observed. The reduction of the $E_{1/2}$ across the BI₂P series follows the same trend as the hydrogen-bond strength caused by the nature of the TPA group. Compound 1' has the weakest hydrogen-bond network in the BI₂P series, consistent with the chemical-shift values of the protons attached to the heteroatoms (NHs and OH, Table 1), and the phenol is relatively more difficult to oxidize (highest $E_{1/2}$). The opposite effect is observed in the case of 4', which exhibits the strongest hydrogen-bond network in the BI₂Ps series, and the phenol is easier to oxidize. In our previous work, we observed a clear relationship between the electronic effect of the imine substituents (–CN and –OCH₃ groups in compounds 1 and 2, respectively) and the $E_{1/2}$ of the phenol at ~ 12 Å distance from the substituent.²⁶ In the case of 1' and 2', the effect of the substituent on the $E_{1/2}$ is still present, even though the distance between the phenol group and the substituent is even larger (~ 16 Å).

As illustrated in Fig. 5, the $E_{1/2}$ of each compound in the BI₂P series (1'–4') is 60 mV lower than in each analogous compound in the BIP series (1–4). In other words, this 60 mV shift is a consequence of the added benzimidazole and is independent of the TPA group. A similar 60 mV shift following each successive addition of a bridging benzimidazole was previously reported for a series of BIPs having the same TPA group but containing either one, two, or three bridging benzimidazole groups making up the Grothuss-type proton wire.²⁷ Thus, in that case the $E_{1/2}$ is 120 mV lower for the BIP featuring three benzimidazole groups than the $E_{1/2}$ of the BIP featuring one benzimidazole group.²⁷

In Fig. 5 we show that the $\Delta E_{1/2}$ shift of 60 mV does not depend on the TPA group. Therefore, it must be a property of the electronic structure of the linked benzimidazole groups and their partial conjugation with the phenol. Fig. 5 also shows the changes in redox potential of the phenoxyl radical/phenol couple within the 1–4 or 1'–4' series (see E_{drop} and E'_{drop}

Table 2 Electrochemical data of BIP and BI₂P analogs in acetonitrile

Compound	Calculated ^a $E_{1/2}$ (V vs. SCE)	Experimental ^b $E_{1/2}$ (V vs. SCE)	ΔE_p (V)	i_c/i_a
1	1.00	0.99 ^c	0.07 ^c	0.76 ^c
2	0.93 ^d	0.93 ^c	0.07 ^c	0.65 ^c
3	0.77	0.77	0.07	0.83
4	0.61	0.61	0.10	0.67
1'	0.91	0.93	0.11	0.88
2'	0.77	0.87	0.11	0.98
3'	0.72	0.71	0.10	1.00
4'	0.55	0.55	0.11	0.98

^a Each computed redox potential assumes the maximum number of intramolecular proton transfers. The redox potentials corresponding to the intermediates that would arise from only some of these proton transfers are shown in Table S25. ^b The potential of the pseudoreference electrode was determined using the ferrocenium/ferrocene redox couple as an internal standard and adjusting to the saturated calomel electrode (SCE) scale (with $E_{1/2}$ taken to be 0.40 V vs. SCE in acetonitrile).³⁵ ^c Values from ref. 26. ^d Reference potential for all compounds in this table; agrees by construction.





Fig. 6 (a and c): IRSEC spectra of 2' and 4', respectively, (19 mM solutions) polarized in 50 mV or 100 mV steps in the 1700–1400 cm⁻¹ region. (b and d): IRSEC spectra of 2' and 4', respectively, under the same conditions in the 3500–3100 cm⁻¹ region. Solvent: DCM, 0.1 M TBAPF₆. Some of the characteristic bands showing changes upon electro-oxidation are indicated with upward and downward arrows.

whereas the band at 1530 cm⁻¹ is not apparent and a new band appears at ~1542 cm⁻¹, suggesting that both benzimidazole NHs have been transferred to their nearest basic sites (the second benzimidazole moiety and exocyclic amine) forming the E3PT product. As previously discussed for the imine 2', the absence of the characteristic NH in-plane bending band (~1556 cm⁻¹) of the benzimidazolium ion confirms non-detectable levels of E1PT and E2PT products following electrochemical oxidation of 4'. This conclusion is also supported by the absence of the characteristically strong NH stretching mode of the benzimidazolium ion (at ~3320 cm⁻¹).^{22,26} Upon phenol oxidation, the intensity of the ν_{NH} increases and a shift from 3366 cm⁻¹ to 3392 cm⁻¹ is observed (Fig. 6d), suggesting that the hydrogen-bond network weakens in the oxidized form of 4'. This weakening is ascribed to a disruption of the hydrogen bond due to protonation of the tertiary amine.²² Moreover, all assignments and changes observed for both molecules (2' and 4') are supported by DFT calculations (see ESI, Fig. S19 and Table S26†).

The previously published IRSEC of 3' indicated the formation of the E3PT product unequivocally,²⁷ while the IRSEC of 1' shows the formation of the E3PT product, although in low yield (see ESI, Fig. S13†). In this case, the formation of the E2PT product is slightly favored theoretically, but the experimental IRSEC data is inconclusive concerning the formation of such a product.

Kinetic isotopic effect

Deuterium kinetic isotope effect values have been determined electrochemically and are shown in Table S22.† The KIE values for 1, 2 and 4 have been previously reported,^{22,26} and the values obtained for 2'–4' are similar (within experimental error) to those of their analogous BIPs with only one benzimidazole bridge. The experimental values obtained for 4 and other related BIPs agree with the values obtained theoretically, assuming a concerted mechanism.^{22,26} However, the experimental error and the uncertainty inherent in the calculated values precluded the extraction of mechanistic information. The KIE values obtained for 1–4 are relatively small (*i.e.*, 0.9–1.5) but are in agreement with previously reported values for related systems.^{28,29,31,33} These small values have been explained theoretically in terms of dominant contributions from excited vibronic states with significant overlap integrals between the reactant and product proton vibrational wave functions.²² Similarly, small KIE values were obtained for the more extended 2'–4' systems.

Conclusions

Using both experimental and theoretical techniques, we have characterized a PCET process in which the translocation of



protons across a benzimidazole or a dibenzimidazole proton wire to a TPA is initiated by the electrochemical oxidation of the phenol. In contrast to our previous report, in which different length proton wires using the same TPA were studied, herein several different TPAs were used with the same benzimidazole and dibenzimidazole wires.

From the experimental observations summarized in Fig. 5, it is clear that the E_{drop} values do not depend on the addition of a second benzimidazole to the bridge but rather are governed by the basicity of the TPA, and that the $\Delta E_{1/2}$ shift does not depend on the structure or basicity of the TPA. Therefore, we associate the 60 mV $\Delta E_{1/2}$ shift with the expansion of the partially conjugated system due to the addition of the second benzimidazole to the bridge.

Within the DFT error of ~ 100 mV, our theoretical model reliably predicts the increasingly negative Gibbs free energy change indicated by the decreasing $E_{1/2}$ for oxidation of the phenol with increasing basicity of the TPA and addition of a second benzimidazole. However, theoretically it is difficult to parse the origin of the changes in $E_{1/2}$ into separate contributions from changing the intrinsic nature of the TPA and extending the π -electronic structure upon addition of the second benzimidazole.

The structural framework supporting the hydrogen-bond network may play several roles in these systems. By extending the framework, the benzimidazole/dibenzimidazole bridge plays a key role in supporting the hydrogen-bond network and thereby providing a reversible pathway for the protons, resulting in essentially electrochemically and chemically reversible redox behavior.²⁷ The observation that the equilibrium electrochemical oxidation of the phenol decreases by up to 440 mV (4' vs. 1) as a function of the TPA and changes in the extended π system suggests that the coupling provided by PCET during the electron and proton transfer processes occurs over ~ 11 Å. Moreover, in our previous report this coupling extended over a hydrogen-bond network that spanned ~ 16 Å.²⁷

Looking to the future, PCET in a construct that would include the generation of biomimetic proton currents, in conjunction with chemical reversibility, must provide a low overpotential pathway for redox processes driving proton currents. A low overpotential, chemically reversible pathway coupling redox processes to proton activities is characteristic of myriad biochemical processes. For example, these processes include the efficient generation and maintenance of PMF and its dissipation in the performance of biochemical work, and proton management at catalytic sites such as those involved in water oxidation as well as CO_2 and O_2 reduction. Our combination of theoretical and experimental approaches to understanding and expanding PCET will enable the design of efficient artificial proton wires conducting proton currents over considerably longer molecular distances. This basic knowledge is necessary to develop a new generation of artificial photosynthetic systems and to re-engineer natural photosynthesis to improve its efficiency.

Conflicts of interest

There are no conflicts to declare.

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