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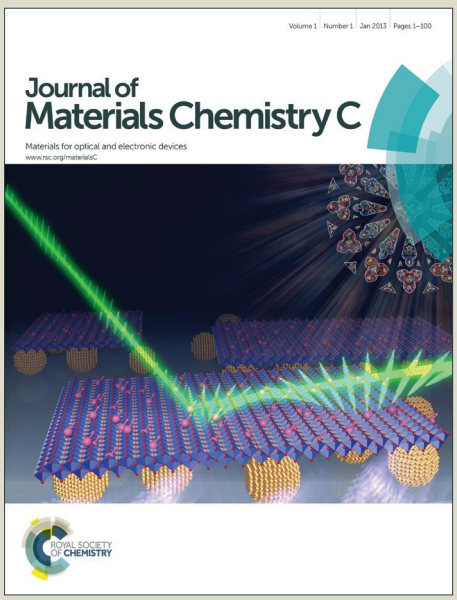

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Highlight

Taking electrons out of bioelectronics: bioprotonic memories, transistors, and enzyme logic

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The ability of bioelectronic devices to conduct protons and other ions opens up opportunities to interface with biology. In this research highlight, we report on our recent efforts to assemble bioprotonic devices. These devices monitor and modulate a current of protons with an applied voltage. Voltage-controlled proton flow mimics semiconductor devices with complementary transistors or biological behaviors such as synaptic-like memories and enzyme logic.

Introduction

Ionic species dominate biological signaling in nature, so converting biochemical ionic signals into electronic signals is an essential part of bioelectronics.[1-4] Progress in bioelectronics encompass devices that mimic biological functionality and interface with biological systems. [1] Memristors simulate synapses for neuromorphic computing.[5] Silicon nanowires record and stimulate single cell potential.[6] Gramicidin and bacteriorhodopsin are integrated with carbon nanotubes,[7] silicon nanowires,[8] and organic field effect transistors[9, 10] to develop biosensors with increased functionality. Ionic[11] and mixed conductivity in biological[12] and organic polymers [13, 14] record and stimulate physiological functions, and are assembled into logic circuits.[15] Edible batteries power these circuits.[16] Among ionic currents, proton (H^+) currents play an important role in nature.[17, 18] Examples are oxidative phosphorylation of ATP for biological energy conversion in mitochondria,[19, 20] the light activated proton pumping of bacteriorhodopsin in Archaea,[21] proton activated bioluminescence in dinoflagellates,[22] proton activated flagella in bacteria,[23] the HVCN1 voltage gated proton channel in mammals,[24] and the antibiotic Gramicidin.[25] In all of these, protons hop along proton wires[26, 27] formed by networks of hydrogen bonds between water molecules and hydrophilic residues -- Grotthuss mechanism.[28] These proton wires also support the transport of a proton vacancy, or 'proton hole', as OH^-.[29, 30] In this highlight, we summarize our recent efforts in developing devices that control the flow of H^+ and OH^- in biological and organic polymers (Fig. 1). These devices include bioprotonic complementary transistors, diodes, synaptic memories, and transducers.[31-33]

Protonic Contacts

The materials used as contacts in electronic devices (Au, Pt) are excellent electronic conductors, but very poor proton conductors and are referred to as proton blocking contacts. Contacts that conduct proton for protonic devices need to be also electrically conducting to interface with external electronics. Palladium Hydride (PdH_x) is both a proton and electron conducting and it forms by exposing Pd to a hydrogen atmosphere.[34] In our bioprotonic devices (Fig. 1), PdH_x contacts (source and drain) inject and drain protons into and from the proton-conducting channel, effectively serving as protodes[31, 34, 35]. For each proton injected into the material, an electron is collected by the leads, which complete the circuit (Fig 2). To understand H^+ injection capabilities of the PdH_x contacts we measure the proton conductivity of the well-known proton conductive organic polymer Nafion. In a Nafion device, an applied voltage (V_{DS}) causes an H^+ current (I_{DS}) to flow between the source and drain (Fig 2b). As a result of this current, hydrogen depletes from PdH_x in direct contact with Nafion. For low current densities, the diffusion flux in the PdH_x, the absorption of hydrogen from the H_2 atmosphere, and I_{DS} balance out, and the PdH_x contacts function as protodes (proton conducting electrodes).[31, 32, 34, 35] For higher current densities, as in the Nafion channel, a region of the PdH_x source contact fully depletes of hydrogen to form Pd (Fig 2a). Pd can no longer inject H^+

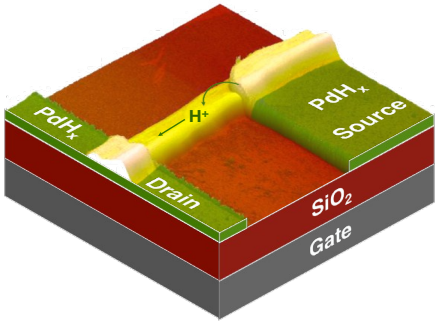


Figure 1. Schematic of a protonic device, in this case a protonic field effect transistor (H^+-FET). A PdH_x source and drain inject and drain H^+ into and from a biopolymer or organic polymer. A potential applied to a back gate, which is insulated from the polymer with a SiO_2 layer modules the source drain current in transistors. AFM image of maleic chitosan thin film (false coloured) overlaid onto a back-gated FET structure. Reproduced from ref. 31.

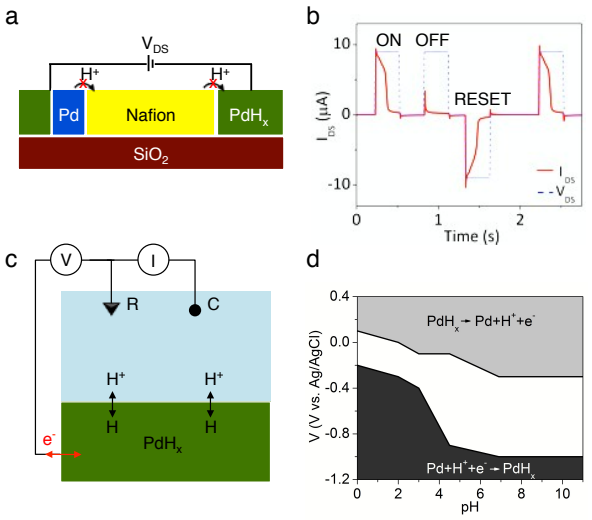


Figure 2. PdH_x interface. (a) Schematic of a PdH_x-Nafion two terminal device. The PdH_x source and drain inject or sink protons according to the reversible reaction $PdH_x \rightarrow Pd + H^+ + e^-$. External electronics measure the resulting electron current and complete the circuit. Applying a voltage (V_{DS}) to the PdH_x contacts causes a proton current (I_{DS}) to flow through the Nafion. This H^+ current depletes the PdH_x source of hydrogen to form Pd (not proton conducting) and the protonic device is OFF. (b) ON and OFF switching in a PdH_x-Nafion device with ±1.25V, 0.25s pulses. (c) Schematic of a PdH_x electrochemical cell. Electrons and protons travel into the Pd/PdH_x during formation and out of it during depletion due to the electrochemical potential. Ag/AgCl is the reference electrode, Pt is the counter electrode and PdH_x is the working electrode (d) Formation of PdH_x and depletion to Pd depend on the solution pH and V. Reproduced from ref. 33 and ref. 36.

in the Nafion and I_{DS} decays as a function of time with the device in the OFF state (Fig. 2b). Reversing the polarity of V_{DS} injects H^+ back into the source to reform PdH_x and resets the device to the ON state (Fig. 2b). This behavior is similar to short-term depression (STD) in a chemical synapse in the brain. To further characterize the dynamics of the PdH_x proton-conducting interface, we measure the electrochemical behavior of a Pd/PdH_x reversible electrode in solution (Fig 2c). This reversible reaction depends on the protochemical potential (μ^{H+}) difference between solution and PdH electrode. [36] As solution pH increases, the threshold values of formation voltage and depletion voltage decrease, as expected due to the influence of pH on the proton chemical potential in solution (Fig. 2d).[36] In the range of pH and V (white area) that the solution and the PdH_x are in equilibrium, no H^+ exchange across the interface occurs.

A phenomenological description of proton transport and acid and base doping

A proton wire supports H^+ conduction via the exchange of a covalent bond on a hydronium ion with the hydrogen bond of a neighbouring water molecule or hydrophilic residue (Fig. 3a). Successive events in the same direction result in the transfer of a H^+ and associated positive charge along the chain. The same mechanism also supports the transport of OH^- as a proton hole (Fig. 3b). The exact dynamics and the kinetics of H^+ and OH^- are more complex[37] than the simplified description used here. However, this description provides enough insights to further elaborate on the conductivity of proton wires.

Eigen and de Maeyer describe H^+ and OH^- transport along proton wires with an analogy with electronic semiconductors (Fig 3c-3f).[38]

Neutral proton wires do not conduct current without an H^+-OH^- pair.[39] The energy required to create such an H^+-OH^- pair is the effective band gap (Fig. 3c and d). This band gap is calculated from the dissociation constant of water as E_{gap} = 0.83 eV, which is remarkably close to the band gap of Ge = 0.76 eV and Si = 1.1 eV. Acidic functionalities (Fig. 3e) donate an H^+ to the proton wire "conduction band" in the same way a group V (P, As) impurity donates an electron to the Si conduction

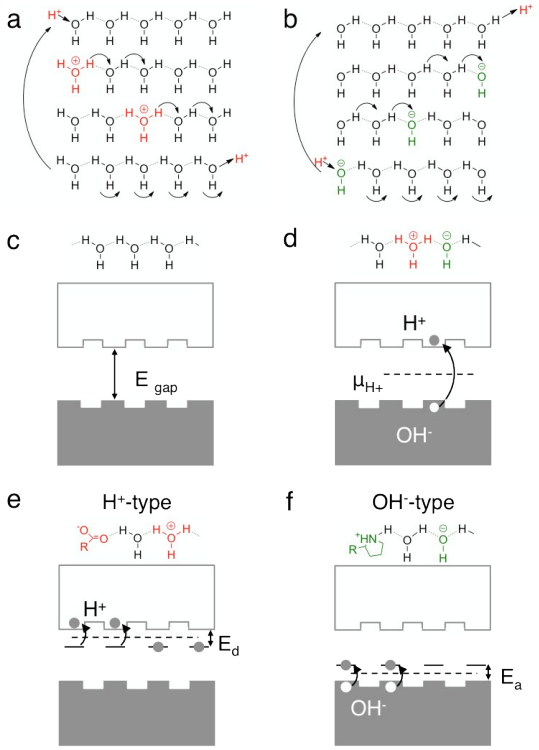


Figure 3. (a) Hop and turn Grotthuss mechanism for conductivity of H^+ as hydronium ion along a proton wire. b) Equivalent mechanism for OH- conductivity as proton hole along proton wire. (c) A wire with no H^+ or OH^- defect does not conduct. The band gap is defined as the energy required to create a H^+ OH^- pair (proton-proton hole) and is derived from the $E_{gap} = \Delta G^0 = -k_B T \ ln \ K_w$ = 0.83 eV (Gibbs-Helmholtz equation).(d) For an intrinsic proton wire, the protochemical potential u_{H+} is in the middle of the band-gap. The H^+ is not completely delocalized along the conduction quasi band. Protons must overcome hopping barriers of hydrogen bond dissociation energy for conduction to occur. (e) An acid donates a H^+ into the conduction band of a proton wire to yield a H^+-type protonic conductor. $E_d = \Delta G_a = -KT \ ln \ K_a$, K_a is the acid dissociation constant. (f) A base accepts a H^+ to create a OH^- (proton hole) in the valence band of a proton wire to yield a OH^- -type protonic conductor. For both H^+ type and OH^- type the protochemical potential is $\mu_C^{H+} = \mu_0 + KT \ ln \ a_{H+}$ where a_{H+} is the activity of H^+. Reproduced from ref. 32.

band, while basic functionalities (Fig. 4f) accept H^+ to create OH^- proton holes in the proton "valence band".

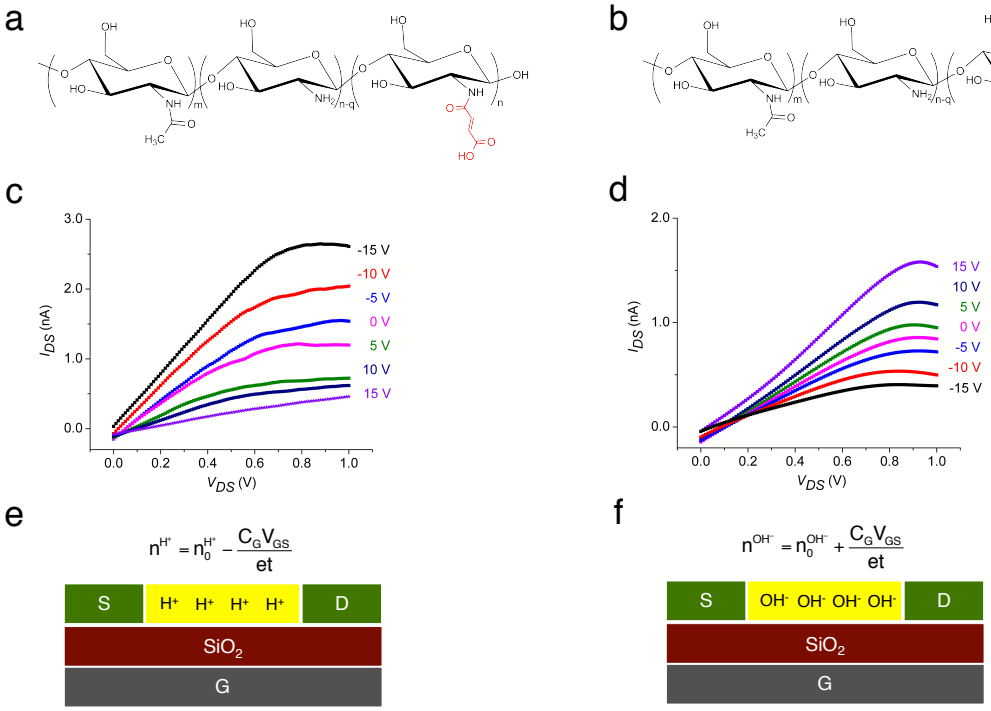


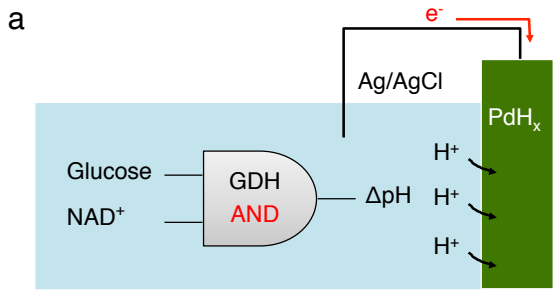
Figure. 4. H^+-FET and OH^--FET. (a) H^+-type proton conductor maleic-chitosan (poly (b- (1,4)-N-Maleoyl-D-glucosamine)) and (b) OH^--type proton conductor proline-chitosan (poly (b- (1,4)-N-Proline-D-glucosamine)). (c) (d) I_{DS} as a function of V_{GS} and V_{DS} (RH 75%) for a maleic chitosan H^+-FET and a proline chitosan OH^--FET with PdHx contacts. Device dimensions: length 8.6 µm, width 3.5 µm, height 82 nm for (c) and 9.6 µm, width 28 µm, height 200 nm for (d). The small deviation of I_{DS} from zero at $V_{DS} = 0$ is likely due to hysteresis as previously observed for these types of devices, (e) (f) Schematics of H^+-FET and OH^--FET capacitive charge carrier n^{H+} and n^{OH-} modulation C_G = gate capacitance per unit area, t = device thickness, e = proton charge. Reproduced from ref. 32.

Complementary protonic transistors

To verify the analogy of H^+-type and OH^--type protonic semiconductors with electronic semiconductors, we fabricate bioprotonic field effect transistors (protonic-FET) with maleic-chitosan (H^+-type) (Fig. 4a) and proline-chitosan (OH^--type) channels (Fig. 4b). In a protonic-FET, the potential of the gate electrode (V_{GS}) modulates source-drain current, I_{DS}, which flows as a result of a drain-source bias V_{DS}. For the H^+-type FET, the dependence of I_{DS} on V_{GS} is consistent with an FET with positive charge carriers (H^+) (Fig. 4c, e). In contrast, the proline-chitosan FET shows the opposite V_{GS} dependence indicating negative charge carriers[40] (Fig. 4d, f). The I_{DS} dependence on V_{GS} follows the canonical gradual channel relationship for I_{DS}[41] in an FET when modified to take into account acid and base doping.[32] Field effect modulation of H^+ channel current was also demonstrate in Nafion-based field-effect devices.[42] More recently, the first protein-based H^+-FETs were demonstrated using reflectin from squid skin.[43] Protein based H^+-FETs are particularly attractive because genetic engineering affords to dial in specific functionalities in the channel materials such as acid base doping.[44]

Enzyme logic bioprotonic transducer

As a proof of concept for bioprotonic device integration with biological function, we demonstrate an enzyme logic with Pd/PdH_x as the transducer between the enzymatic function and the electronic output signal.[36] In this logic system, two input signals activate glucose dehydrogenase (GDH); input A is oxidized nicotinamide adenine dinucleotide (NAD^+) and input B is glucose (Fig. 5a). GDH requires the presence of both NAD^+ and glucose to function, effectively serving as an



b

Input A		Input B		Output		
Logic	NAD^+	Logic	Glucose	ΔpH	I_{max}	Logic
0	0 mM	0	0 mM	-0.03	4 µA	0
0	0 mM	1	30 mM	-0.05	24 µA	0
1	1 mM	0	0 mM	-0.07	7 µA	0
1	1 mM	1	30 mM	-1.71	167 µA	1

Figure 5. Enzyme logic. (a) Schematic of the proton-electron transducer. A PdH electrode is controlled by enzyme logic proton modulation. Logical proton modulation occurs by using glucose dehydrogenase (GDH) as an AND logic. The GDH enzyme reacts with NAD^+ and glucose to produce NADH and gluconic acid, lowering the electrolyte solution pH. The pH change acts as an "on-off" switch that controls the PdH formation. (b) Truth table for pH and current output when varying inputs, as: (InputA: NAD^+, InputB: Glucose). An output of 1 indicates significant pH and current change; an output of 0 indicates no change and current. Reproduced from ref. 36.

enzymatic AND logic. [45-50] The absence of glucose or NAD^+ is defined as a logic "0", while their presence is defined as logic "1". The formation of PdH_x at V_D= -0.85 V and the resulting I_D measured (V_D= 0 V) use as the logic output. The higher I_D corresponds to a logic "1", while the lower I_D corresponds to a logic 0. In the absence of either substrate (logic input "0,0", "0,1", or "1,0"), GDH is not active and the solution pH remains the same. At pH 6, PdH_x does not form at V_F = -0.85 V and the resulting I_D correspond to logic 0. The presence of the both NAD^+ and glucose (logic "1,1") activates the biocatalytic reaction of GDH (Fig. 5b), which produces gluconic acid and lowers the solution pH from 6.0 to 4.0. At pH 4.0, PdH_x forms at V_F= -0.85 V and the resulting I_D = 0.164 mA at V_D= 0 V corresponds to a logic output 1. These results demonstrate that the Pd/PdH_x system transduces proton signals from biochemical inputs into readable electronic currents.

Future outlook

We have developed bioprotonic devices that can control and record H^+ and OH^- currents, including memories, complementary transistors, and transducers. These devices are analogous to semiconductor-based devices for electrons and holes. One of the goals for developing these devices was to provide an interface with proton-driven biological phenomena and we have demonstrated a H^+ driven enzyme logic. Whether these devices will find further applications in bioelectronics and translational applications remains to be seen due to limitations in performance compared to traditional semiconductor devices, such as low on-off ratio for the transistors. However, in developing these devices we have rediscovered PdH_x as proton-injecting contacts that can enable the DC measurement of proton currents in soft materials such as reflectin based proteins and melanin.[43, 44, 51]

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Notes and references

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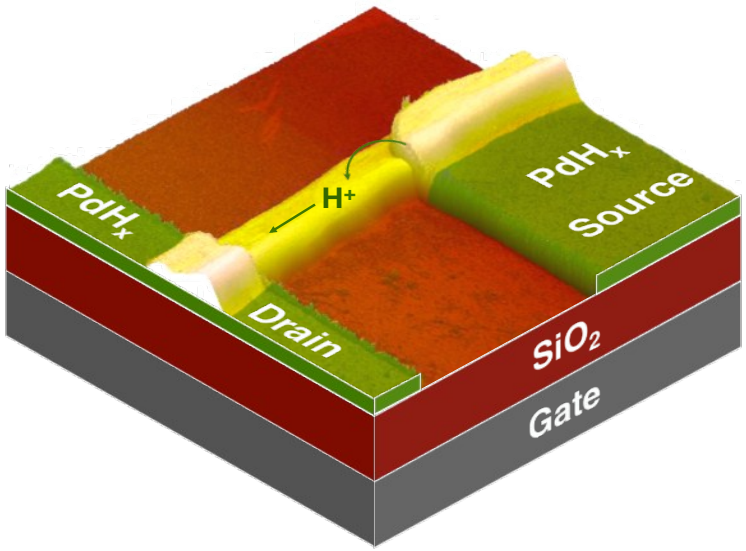

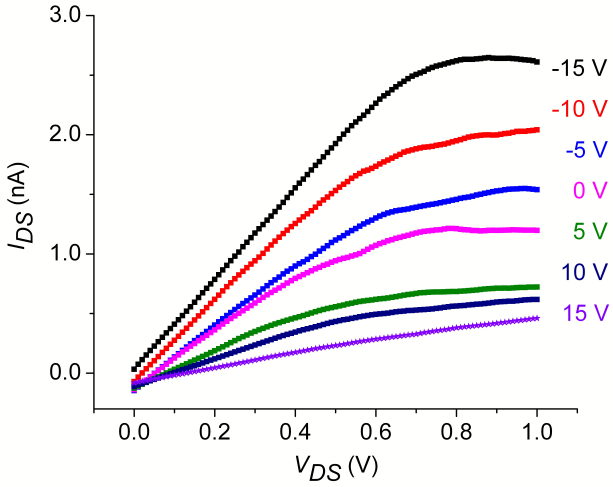

We highlight our recent efforts in developing devices that control the flow of H^+ and OH^- in biological polymers.