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Charge transport along proton wires

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Abstract

Using density functional theory we look at the quantum mechanics of charge transport along water wires both with free ends and donor/acceptor terminated. With the intermediate geometries in the DFT iterations we can follow the charge transfer mechanism and also construct the energy landscape explicitly. It shows activation barriers when a proton is transferred from one water molecule to the next. This, together with snapshots of intermediate geometries, leads to a justification and further elucidation of the Grotthuss mechanism and the Bjerrum effect. The charge transfer times and the conductivity of the proton wire are obtained in agreement with experimental results.

Keywords: Proton wires, Charge transfer, DFT

Pacs: 82.39 Jn, 31.15 E

Background

In 1978 Nagle and Morowitz [1] suggested that linear water structures in membrane channels may act as carriers for proton transfer through the membrane wall. They also coined the term proton wires for these water whiskers. These proton wires extend through membrane channels and connect the enzyme active site with the liquid phase outside the cell with enzyme functional groups inside the cell. We list a few examples. In the transmembrane channel formed by gramicidin A proton wires are found within its helical structure [2,3]. Proton wires are also found or suspected in bacteriorhodopsin [4-7], photosynthetic centers [8], in enzymes [9] and even in viruses [10]. In most of these systems amino acid residues (His, Glu, Asp, Ser) act as proton donors and acceptors at the respective ends of the water whisker. A comprehensive review, both experimental and theoretical, was given by Cukierman [11].

As an early model of charge transfer in proton wires Nagle and Morowitz [1] adapted classical ideas by Grotthuss who, as early as 1806 suggested that in diffusion of protons in bulk water an 'excess' proton propagates through the hydrogen-bonded network by repeated cleavage and re-formation of hydrogen bonds [12]. Theoretical efforts since then have focused mainly on mixed classical/quantum methods such as a polarization model with discretized Feynman path integral-molecular dynamics

(FPI-MD) as used by Pomès and Roux [13-15], an *ab-initio* FPI Car-Parrinello MD used by Klein *et al.* [16], a Born-Oppenheimer local-spin-density MD used by Sadeghi and Cheng [17], a multiconfigurational MD with quantum transitions used by Hammes-Schiffer *et al.* [18-20], a MD with a multi-state empirical valence band (EVB) model used by Voth *et al.* [21], a quantum/molecular mechanical method used by Nemukhin *et al.* [22], a "real time" MD used by de Groot and Grubmüller [23], and an EVB model with Langevin dynamics used by Warshel *et al.* [24]. For the most part they are concerned with the stabilization of the proton wires by the walls of the membrane channel and also on simple kinetic models to describe the proton hopping process. Several groups looked at the effects of weak electrostatic fields [18,20,24,25]. Various groups have also employed fully quantum mechanical approaches such as the multiconfiguration time-dependent Hartree method used by Vendrell and Meyer [26], and density functional theory [27-30].

The existence of stable water whiskers was also postulated in the 1980's in field ion microscopy [31,32]. The evidence was as follows: exposing a field emission tip to water vapor with an electric field of the order of volts per angstroms applied and then evaporating the water film on the tip by laser pulses or higher electric field pulses resulted in mass spectra of protonated water clusters $(H_2O)_n H^+$ with up to a dozen water molecules with $n = 2 - 4$ being most abundant. The inference of water whiskers was originally made on the basis of a simple classical argument [32,33]: the water molecule has a dipole

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moment $\mu_{water} = 1.85$ *Debye*. Thus aligning a water molecule in an electric field F at an angle γ leads to an energy gain of $\mu_{water}Fcos\gamma$ which in a strong enough field will be larger than the loss due to reducing the bulk coordination of water. This problem has been re-visited recently in an extensive quantum mechanical study based on density functional theory [34] which came to the following conclusions:

(1) Neutral and protonated water whiskers form helical structures.

(2) Protonated water whiskers with more than four water molecules are only stable for fields below 0.3 V/Å.

(3) Two electronic effects of field stabilization have been identified; (i) polarization and field alignment at small fields (< 0.1 V/Å), and (ii) charge transfer and re-hybridization due to field modification of the molecular level structure at high fields (> 0.1 V/Å) that ultimately lead to field fragmentation at the point when the HOMO-LUMO gap closes and the whisker becomes conducting and field expulsion from the region of the whisker occurs. The latter effects can be understood on the basis of field-induced chemistry: applying an electric field implies that in a cluster of atoms an atom further down the field by a distance d from a reference atom changes its energy levels relative to the reference atom by eFd. This changes the character of their joint molecular orbital either weakening or strengthening its bonding character [35].

(4) In the classical Anway model it is assumed that the oxygen atoms lie in a straight line with the two hydrogen atoms oriented at some angle to facilitate energy gain through the field but maintain some possibility for hydrogen bonding as well. This picture is acceptable at small fields if it is modified by the fact that a lower energy state can be achieved by a staggered arrangement. Such an arrangement is also not planar but forms a helical conformer much akin to polymers. In this sense one might be tempted to call this field-induced polymerization. In addition, a simple classical dipole model does not allow for the transfer of charge down the field. In other words, a classical model does not allow field-dissociation.

(5) The presence of extra protons in the whisker has important consequences in that it destabilizes the whiskers earlier i.e. at lower field strengths, simply because the additional proton moves up the field leading also to a re-arrangement of the electrons.

(6) The most important result of this study is a stability diagram which delineates, for protonated water clusters of different sizes n, the minimum electric field needed to form linear whiskers and the maximum field at which these whiskers disintegrate.

For instance, for a protonated tetramer and hexamer the maximum fields are 0.3 V/Å and 0.2 V/Å, respectively. The presence of the proton creates a field of approximately 0.1 V/Å. Noteworthy for the present discussion is the fact that cell membrane fields are of the order of 5-50 mV/ Å[1,36] so the combination of these fields will not be sufficient to destabilize a proton water wire. This is not to say that the walls of a membrane channel do not provide a confinement potential to stabilize the linear structures even more.

In this paper we intend to elucidate the process of charge transfer along the water wire further. We will present results from density functional calculations on the stability of proton wires in weak electrostatic fields of less than 0.1 V/Å as they occur across a cell membrane. To simulate the membrane environment we terminate the water whisker with NH_3 at one end and with a cation $Zn^{++}(NH_3)_3$ as recently used by Isaev [28,29]. Employing a procedure developed in our previous paper [34] we will use the interim geometries in the iterations towards the geometry-optimized final result as snapshots to track the motion of one positive charge from the cation cluster up the water whisker to the ammonia group. By following the energy of the intermediate geometries and the position of the center of mass of the charge cloud as a function of the iteration steps we can plot the energy as a function of the center of mass position. This curve of course decreases to lower energies as the energy minimization proceeds but it also has local maxima at certain positions which are interpreted as the barriers that the charge cloud, i.e. the proton, must overcome as it moves up the wire. We take this result as the justification of the classical proton hopping model. We will also show that proton "hopping" is actually the exchange of a proton from one water molecule to the next by moving the electronic charge cloud in the opposite direction. Having the energy barriers we can get the transit times across the "membrane" and estimate the conductivity of the proton wire quantitatively. In addition, our quantum mechanical approach leads to a justification and further elucidation of the Grotthuss mechanism of charge transfer along water wires [25].

Methods

We will base our calculations on density functional theory with a large basis set as used in previous studies of water and appropriate gradient-corrected exchange-correlation functionals as implemented in the GAUSSIAN'09 software package [37]. As shown elsewhere [38-41] a reliable choice for an exchange/correlation potential and basis set for water is B3LYP/6-311++G**. It should be noted that electric field effects are quite large producing relative

changes in molecular energy levels of the order of eV. Thus more sophisticated models, such as for bulk water or van der Waals interactions, are not needed in this case because we only look at linear structures.

In the absence of a field or a confining membrane channel a water cluster will be compact with the well known coordination of three to four hydrogen bonds. However, putting this cluster into a weak external field will turn it into a quasi-linear water whisker in its converged ground state geometry. The field must be weak enough to ensure stability because for stronger fields the whisker dissociates into smaller clusters. From our previous study we know this happens e.g. for a tetramer or an hexamer in a field range of 0.01 to 0.1 V/Å i.e. in the range of typical membrane fields.

Geometry optimizations in the GAUSSIAN'09 software package are implemented using the Berny algorithm using GEDIIS [42]. Because we will make extensive use of the intermediate steps in the self-consistency scheme of DFT, we recall that the optimization iterations proceed as follows: the geometry optimization begins at the molecular structure specified in the input and then steps along the potential energy surface. The energy and gradient are calculated at that point and then this determines which direction and how far to take the next step. Energy and geometry are now available. This process is repeated automatically until the convergence criteria are less than the standard cutoff values of 0.00045 Hartrees/Bohr for the maximum force component, 0.0003 Hartrees/Bohr for the root-mean square force, 0.0018 Å for the maximum step component, and 0.0012 Å for the root-mean-square step. When the convergence criteria have been satisfied, the global minimum has been reached. Further details of the optimization algorithm used can be found in the Gaussian 09 Users Reference [37].
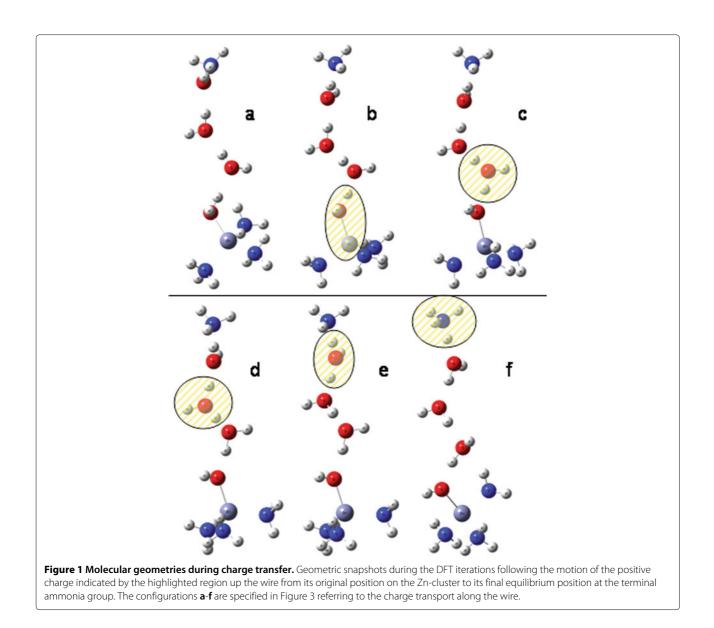
Results and discussion
Terminated tetramer
As indicated in the introduction we will take $[Zn^{++}(NH_3)_3[H_2O]_4 NH_3$ as the prototype of a short proton wire in a membrane although we have also done calculations with more water molecules which however, do not reveal new insights. This aggregate is not linear but in its lowest energy state is globular. However, if we apply a small field of 0.005 V/Å it will remain straight albeit helical. As the DFT iterations proceed a positive charge will be transferred up to the ammonia group at the other end with the lowest energy state being a linear cluster $[Zn^+(NH_3)_3][H_2O]_4[NH_3]^+$; this had been the starting configuration in Isaev's work [29]. It should be recognized that a doubly charged ion generates a field $F = 2 \times 14.4/r^2$ $[V/Å]$, i.e. about 1 $V/Å$ at the other end of the complex, compared to which the field applied in the

present work is minimal but still strong enough to ensure a linear structure.

In Figure 1 we show a series of snapshots in the DFT iterative progress with the position of the positive charge indicated by the highlighted region. The first image is the initial configuration with the terminal groups and the four water molecules clearly defined and the final image is the lowest energy state in which one of the positive charges has moved up the wire to the ammonia group. This happens as follows: in the second picture a hydrogen has already broken its bond with the lowest oxygen and is halfway in between it and the next oxygen up the wire. It moves closer creating a Zundel cation between the second and third water molecules and, at the same time one of the original hydrogens in the second water molecule detaches and moves up to the third oxygen [43]. This also results in a re-orientation of the second water molecule by an apparent clockwise rotation of about 90°. Note however, that the axis between the oxygen of the third water and one of its hydrogens does not change in its orientation. Thus the rotation of water molecules in the Grotthuss mechanism is not a rigid rotation but is simply the re-distribution of one of the hydrogen bonding orbitals. This process repeats itself one more time until a hydrogen is located close to the upper ammonia.

So far, we have deliberately talked about hydrogen moving up the wire and not protons because without further information we do not know its charge state or the energetics of the process. The latter is of course available as the total electronic energy of the system in each iteration step. This is plotted in Figure 2, lower curve. Overall the energy decreases as the system moves from an initial configuration to its absolute minimum. But, as we were anticipating, local barriers clearly show up which the hydrogen must overcome on its way from one water molecule to its neighbor up the wire. This is the quantum mechanical evidence that proton transfer is an activated process! Moreover, because the individual water molecules temporarily change their orientation we can take this, together with the re-orientation of the water molecules by bond adjustment, as a justification and elucidation of the Grotthuss mechanism of proton transfer in water.

However, at this stage caution is advised because the iterations themselves are purely numerical in nature (similar to the steps in Monte Carlo simulations). We need to extract additional information. In our previous work [34] we suggested following a characteristic length scale as a function of the iterations and then eliminating the iteration steps to obtain the energy versus this length scale. For a proton wire this is the electronic charge cloud $\rho(\mathbf{r})$ around the cluster. To get a single coordinate we take the
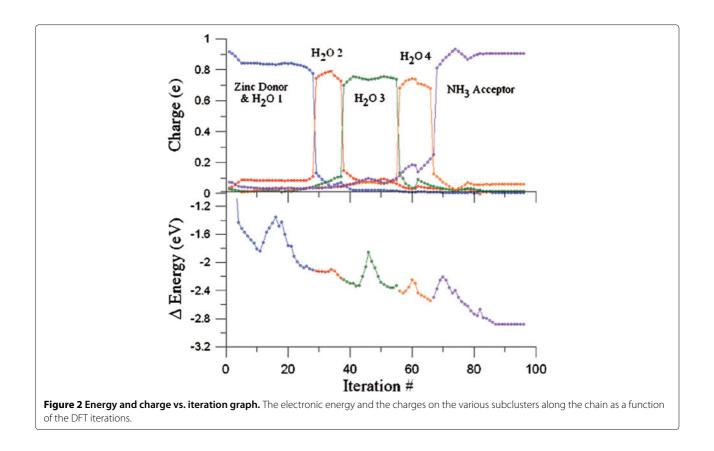
Figure 1 Molecular geometries during charge transfer. Geometric snapshots during the DFT iterations following the motion of the positive charge indicated by the highlighted region up the wire from its original position on the Zn-cluster to its final equilibrium position at the terminal ammonia group. The configurations **a**-**f** are specified in Figure 3 referring to the charge transport along the wire.

center of this charge cloud in the nth iteration

$$r_{cm}^{(n)} = \int \rho^{(n)}(\mathbf{r})\mathbf{r}d\mathbf{r} \tag{1}$$

A convenient way to evaluate this average efficiently is to use the Mulliken charges $q_i^{(n)}$ on atom i in the cluster as this is a standard output of the Gaussian software. We would then get

$$r_{cm}^{(n)} = \sum_i \mathbf{r}_i^{(n)} q_i^{(n)} \tag{2}$$

The diffficulty with implementing such an idea is the fact the local atomic charges within an assembly of atoms such as molecules are NOT quantum mechanical observables, i.e cannot be defined or calculated rigorously. This point is amply demonstrated in the present case by the fact

that we cannot assign a proton that is halfway between two oxygen atoms to either one. Having this ambiguity we simply put forward as a criterion that we assign a proton to a given water molecule if it is within half the distance to the next oxygen i.e. a distance of about 1.2 Å. In the upper curve of Figure 2 we show the local charges on the Zn-cluster (including the lowest water molecule, the remaining three water molecules and the ammonia group at the other end) as a function of the iterations. Anticipating that one charge remains on the Zn cluster we have only plotted the one charge that is moving up. As the proton moves across the halfway distance between two oxygen atoms the charge drops abruptly on one water molecule and is picked up on the next one up the ladder. Noteworthy is the fact that there is never a charge of 1.0e on one of the subclusters but approximately 0.8e because the other

Figure 2 Energy and charge vs. iteration graph. The electronic energy and the charges on the various subclusters along the chain as a function of the DFT iterations.

subclusters continue to carry some charge. In other words, the total charge cloud $\rho^{(n)}(\mathbf{r})$ is rather diffuse. Yet the picture that a "charge" or proton moves up the wire is quite convincing.
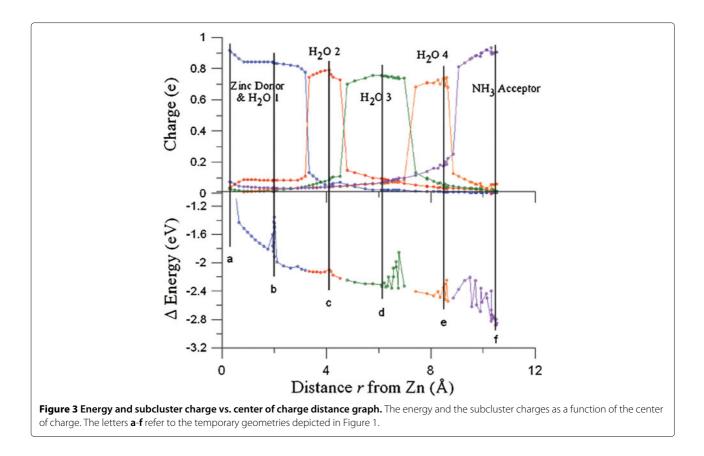
To get a length scale we pick a number of points in the charge vs. iteration graph, e.g. the local maxima and measure the distance of this maximum from the Zn atom using the geometries shown in Figure 1. At this stage we can eliminate the iteration number and plot the energy as a function of the distance the charge cloud has traveled. This gives us the anticipated physical information about the energy landscape seen during charge transfer along the wire! This results in Figure 3: as the charge moves up the wire the electronic energy of the whole system is lowered except when the center of charge moves from one water molecule to the next, there is an energy barrier to be overcome. The picture of activated proton hopping is complete! To check the uniqueness of our results we started from several, quite different initial structures and produced identical results.

For clarification: the jaggedness within the activation barriers is a reflection that the hopping proton will make several attempts to get to the next water molecule, i.e. it is a reflection of local fluctuations. This can be taken as evidence of the Bjerrum effect [4] as recently discussed again by Pavlenko [25].

Looking at the geometries along this energy curve we can now identify what causes the barriers. To this end we have plotted in Figure 4 five geometries, namely at the beginning, at the height and at the end of the green barrier, and at the beginning and at the height of the orange barrier.

At the height of the green barrier the hydrogen bonds to the second oxygen are stretched which costs energy, i.e. results in a barrier for further migration. One of the two bonds is re-formed at the end of the green barrier re-gaining this energy and at the beginning of the orange barrier the second hydrogen bond is re-formed.

Protonated hexamer

A number of papers on the role of proton wires in biology simplify the model to one without terminal donor and acceptor groups [13,14,16-20,25,26]. Such a cluster of water molecules, either protonated or neutral, will assume a globular structure unless a small electric field is added to keep it in a linear configuration. Although we have reported a systematic study of such structures [34] we want to briefly show some results for a protonated hexamer as it shows some surprising differences to the terminated whiskers (in a field). We follow the procedure used for the latter starting this time from a neutral whisker in a field. Adding a proton we follow the motion of the

Figure 3 Energy and subcluster charge vs. center of charge distance graph. The energy and the subcluster charges as a function of the center of charge. The letters **a**-**f** refer to the temporary geometries depicted in Figure 1.
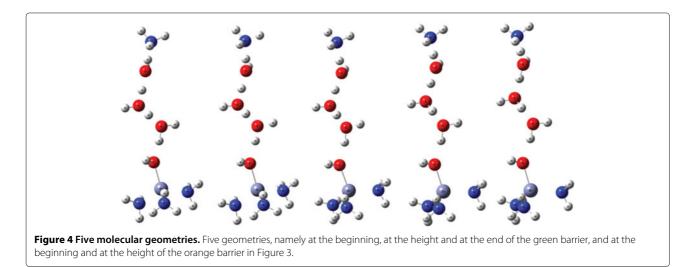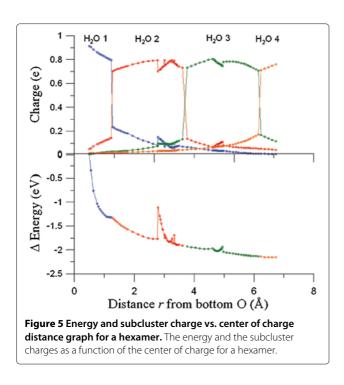
charge cloud up the wire, see Figure 5. The fifth and sixth water molecules remain neutral and thus are not shown.

The most remarkable feature of this graph is the large reduction in the barriers to 0.001 (0.029), 0.66 (15.19), and 0.09 (1.98) eV (kcal/mol), (apart for the one really high barrier around 3 Å) as compared to the terminated whisker. The main reason for this is the fact that a whisker without heavy donor and acceptor groups at the ends has greater rotational freedom i.e the two water molecules

involved in a particular transfer event can more easily rotate at lower energy cost. This is obvious when one examines a series of snapshots like those in Figure 1. The exceptionally high barrier is associated with an attempt by the chain to twist as a whole.

The extra proton moves close to the lowest water molecule forming a H_3O^+ which in turn rotates and loosens its bond to the hydrogen in the direction of the field. This proton in turn moves closer to the next

Figure 4 Five molecular geometries. Five geometries, namely at the beginning, at the height and at the end of the green barrier, and at the beginning and at the height of the orange barrier in Figure 3.

Figure 5 Energy and subcluster charge vs. center of charge distance graph for a hexamer. The energy and the subcluster charges as a function of the center of charge for a hexamer.

water molecule leaving a "neutral" H_2O behind and forming a new H_3O^+ which again rotates to accommodate the extra charge which is by now located beyond the second water molecule. This process - motion of the extra proton up the wire, rotation of the two closest water molecules and eventual attachment to the new host molecule repeats itself until the proton has reached the fourth water molecule in the chain.

Conclusions

Charge transfer along a water wire is an atomic exchange mechanism in which a proton moves the short distance of less than the $O - O$ distance leaving behind a quasi-neutral water molecule and forming a temporary diffuse hydronium ion H_3O^+.

What is then the overall picture of charge or proton transfer through a membrane channel? We start from the equilibrium configuration $[Zn^+(NH_3)_3][H_2O]_4[NH_3]^+$. At some point in time a proton or hydronium ion, getting close to the Zn cluster will accept an electron getting neutralized and turning the Zn^+ into Zn^{2+}. If in a time interval before this charge transfer is reversed by another fluctuation, an electron is transferred from a water molecule on the other side of the membrane to the ammonia molecule a charge transfer has occurred across the membrane with the proton now on the other side. This results in the configuration $[Zn^{++}(NH_3)_3][H_2O]_4[NH_3]$ which will trigger the next round of charge transfer.

We stress again that a protonated water whisker without acceptor and donor groups has negligible activation barriers i.e. typically of the order of thermal energy at room temperature. This obviously casts doubt on the validity of classical Ising-type chain models in which one postulates well-defined and permanent minima along the chain for the extra proton which then hops over a barrier in the same way as an adsorbed particle hops from one adsorption site to the next in lattice gas models for surface diffusion. What emerges from our quantum mechanical calculations is a picture in which the transfer of a charge cloud from one water molecule to the next creates a local minimum and a barrier that disappears as soon as the charge has moved on.

Having dynamic information about the proton transfer mechanism we can estimate the transfer time and also the conductance of the proton wire. For the transfer time τ we note that it is limited by the sum of the inverse of the hopping rates over the barriers

$$\tau = \sum r_i^{-1}$$

Because the transfer time is much longer than any thermalization we can write

$$r_i = \frac{k_B T}{h} \exp[-Q_i/k_B T]$$

where the barrier heights can be read off from left to right in Figure 2 to be 0.45 (10.39), 0.04 (0.89), 0.48 (11.07), 0.22 (5.02), and 0.33 (7.71) eV (kcal/mol) in agreement with the measured values for carbonic anhydrase of 0.043-0.11 eV (1.0-2.5 kcal/mol) for proton transfer and an overall energy barrier of 0.42-0.47 eV (9.8-11.0 kcal/mol) [45-47]. Because the transit time from one barrier to the next one a distance of a few angstroms away is less than a picosecond the proton arrives with some kinetic energy that has not been completely thermalized leading to a small reduction in the barrier heights. Taking this into account we get overall transit times of the order of microseconds, and possibly nanoseconds.

For the total current we get

$$I = \frac{e}{\tau} = GV$$

Here V is the membrane potential. For the two estimated transit times we get conductances of nS down to pS. We could not find measured values for isolated proton wires but note that for proton channels in Gramicidin A one finds 1.5 nS [36]. One should note that in a Gramicidin A channel the transit time is on the order of nanoseconds in the range of our estimates.

Our final comments concern the relation of this work with previous studies.

In his quantum mechanical studies of proton wires Isaev [28,29], using the same cluster and the same DFT framework apart from a somewhat smaller basis set rightly observes that without a field an extra proton will settle in the middle of the wire, i.e. at equal distances from the acceptor and donor which are both charged. He examines

extensively the variation in hydrogen bond lengths along the cluster which he finds are within a few hundredth of an angstrom. This is also what we find but do not put any emphasis on it as such a small variation is easily within the thermal fluctuations of the hydrogen bond at room temperature.

In the classical Ising-type model of proton hopping Pavlenko [25] assumes that the hydrogen has four well-defined adsorption sites between any two oxygens along the chain. Such an assignment assumes that there are energy barriers on either side of these sites. We see some evidence for that, see Figure 3.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
HJK conceived of the study, analysed the data, and drafted the manuscript. MLK performed the calculations, analysed the data, and helped draft the manuscript. Both authors read and approved the final manuscript.

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References

1. Nagle JF, Morowitz HJ (1978) Molecular mechanism for proton transport in membranes. Proc Natl Acad Sci USA 75: 298–302
2. Akeson M, Deamer DW (1991) Proton conductance by the gramicidin water wire. Biophys J 60: 101
3. Sagnella DE, Laasonen K, Klein ML (1996) Ab initio molecular dynamics study of proton transfer in a polyglycine analog of the ion channel gramicidin. A. Biophys, J 71: 1172
4. Wikström M (1998) Proton translocation by bacteriorhodopsin and heme-copper oxidases. Curr Opin, Struct Biol 8: 480
5. Bondar AN, Baudry J, Suhai S, Fischer S, Smith JC (2008) Key role of active-site water molecules in bacteriorhodopsin proton-transfer reactions. J Phys Chem, B 112: 14729
6. Hofacker I, Schultn K (1998) Oxygen and proton pathways in cytochrome C oxidase. Proteins: Struct Funct Genet 30: 100
7. Namslauer A, Lepp H, Baenden M, Jasaitis A, Verkhovsky MI, Brzezinski P (2007) Plasticity of proton pathway structure and water coordination in cytochrome c oxidase. J Biol Chem 282: 15148
8. Kozlova MA, Juhnke HD, Cherepanov DA, Lancaster CRD, Mulkidhanian AY (2008) Proton transfer in the photosynthetic reaction center of blastochloris viridis. FEBS Lett 582: 238
9. Frank RAW, Titman CM, Pratap JV, Luisi BF, Perham RN (2004) A molecular switch and proton wire synchronize the active sites in thiamine enzymes. Science 306: 872
10. Schweighofer KJ, Pohorille A (2000) Computer simulation of ion channel gating: the M2 channel of influenza A virus in a lipid bilayer. Biophys, J 78: 150
11. Cukierman S (2003) The transfer of protons in water wires inside proteins. Front Biosci 8: 1118–1139
12. de Grotthuss CJT (1806) Theory of decomposition of liquids by electrical currents "Sur la décomposition de l'eau et des corps qu'elle tient en dissolution à l'aide de l'électricité galvanique". Ann Chim 58: 54–73
13. Pomès R, Roux B (1995) Quantum effects on the structure and energy of a protonated linear chain of hydrogen-bonded water molecules. Chem Phys Let 234: 416–424
14. Pomès R, Roux B (1996) Theoretical study of H^+ translocation along a model proton wire. J Phys Chem 100: 2519–2527
15. Pomès R, Roux B (1996) Structure and dynamics of a proton wire: A theoretical study of H^+ translocation along the single-file water chain in the gramicidin A channel. Biophys, J 71: 19–39
16. Mei HS, Tuckerman ME, Sagnella DE, Klein ML (1998) Quantum nuclear ab initio molecular dynamics study of water wires. J Phys Chem B 102: 10446–10458
17. Sadeghi RR, Cheng HP (1999) The dynamics of proton transfer in a water chain. J Chem Phys 111: 2086–20894
18. Drukker K, de Leeuw SW, Hammes-Schiffer S (1998) Proton transport along water chains in an electric field. J Chem Phys 108: 6799–6807
19. Decornez H, Drukker K, Hammes-Schiffer S (1999) Solvation and hydrogen-bonding effects on proton wires. J Chem Phys, A 103: 2891–2898
20. Decornez H, Hammes-Schiffer S (1999) Effects of model protein environments on the dynamics of proton wires. Israel J Chem 39: 397–407
21. Brewer ML, Schmitt UW, Voth GA (2001) The formation and dynamics of proton wires in channel environments. Biophys, J 80: 1691–1702
22. Nemukhin AV, Grigorenko BL, Topol IA, Burt SK (2003) Quantum chemical simulations of the proton transfer in water wires attached to molecular walls. J Phys Chem B 107: 2958–2965
23. de Groot BL, Grubmüller H (2001) Water permeation across biological membranes. Science 294: 2353
24. Braun-Sand S, Burykin A, Chu Z, Warshel A (2005) Realistic simulations of proton transport along the gramicidin channel: Demonstrating the importance of solvation effects. J Phys Chem B 109: 583–592
25. Pavlenko N (2003) Proton wires in an electric field: the impact of the Grotthuss mechanism on charge translocation. J Phys: Condens Matter 15: 291–307
26. Vendrell O, Meyer HD, J Chem Phys, 122 (2005) Proton conduction along a chain of water molecules. Development of a linear model and quantum dynamical investigations using the multiconfiguration time-dependent Hartree method. 104505–1 104505–12
27. Cui Q, Karplus M (2003) Is a "proton wire" concerted or stepwise? A model study of proton transfer in carbonic anhydrase. J Phys Chem, B 107: 1071–1078
28. Isaev A, Kar T, Scheiner S. (2007) Periodicity in proton conduction along a H-bonded chain. Application to Biomolecules. Int J Quantum Chem 108: 607–616
29. Isaev AN (2010) Quantum-chemical calculations of a long proton wire. Application of a harmonic model to analysis of the structure an an ionic defect in a water chain with an excess proton. J Phys Chem, A 114: 2201–2212
30. Viswanathan U, Basak D, Venkataraman D, Ferman JT, Auerbach SM (2011) Modeling energy landscapes of proton motion in nonaqueous, tethered proton wires. J Phys Chem, A 115: 5423–5434
31. Jaenicke S, Ciszewski A, Drachsel W, Weigmann U, Tsong TT, Pitts JR, Block JH, Menzel D (1986) Field-assisted photodesorption of ions from metal and semiconductor surfaces. J de Physique (Paris) 47-C7: 343–347
32. Jaenicke S, Ciszewski A, Dösselmann J, Drachsel W, Block JH, Menzel D (1988) Field-induced structural changes in adsorbed layers of polar molecules studied by photon-stimulated desorption. J de Physique (Paris) 49-C6: 191–196
33. Anway AR (1969) Field-ionization of water. J Chem Phys 50: 2012–2021
34. Karahka M, Kreuzer HJ (2011) Water Whiskers in High Electric Fields. Phys Chem, Chem Phys 13: 11027–11033
35. Kreuzer HJ (2004) Physics and chemistry in high electric fields. Surface Interface Anal 36: 372–379
36. Cukierman S, Quigley EP, Crumrine DS (1997) Proton conduction in gramicidin A and in its Dioxolane-linked dimer in different lipid bilayers. Biophys, J 73: 2489–2502
37. Gaussian 09, Revision A. 1, Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, *et al* (2009). Gaussian Inc., Wallingford CT
38. Wang RLC, Kreuzer HJ, Grunze M, Phys Chem Chem Phys (2000) The interaction of oligo(ethylene oxide) with water: a quantum mechanical study 2: 3613

39. Wang RLC, Kreuzer HJ, Grunze M (1997) Molecular conformation and solvation of oligo(ethylene glycol)-terminated self-assembled monolayers and their resistance to protein adsorption. J Phys Chem B 101: 9767–9773
40. Wang RLC, Grunze M, Kreuzer HJ (2006) Theoretical modeling and interpretation of X-ray absorption spectra of liquid water. Phys Chem, Chem Phys 8: 4744–4751
41. Kreuzer HJ, Wang RLC, Grunze M (2003) Hydroxide ion adsorption on self assembled monolayers. J Am Chem, Soc 125: 8384–8389
42. Li X, Frisch MJ (2006) Energy-represented DIIS within a hybrid geometry optimization method. J Chem Theory, Comput 2: 835–839
43. Zundel G, Metzger H (1968) Energiebänder der tunnelnden Überschuß-Protonen in flüssigen Säuren. Eine IR-spektroskopische Untersuchung der Natur der Gruppierungen H_5O_2, $^+$. Z Phys Chem 58: 225–245
44. Bjerrum N (1951) Structure and properties of ice. Danske Vidensk Selks Skr 27:1
45. Silverman DN, Tu C, Chen X, Tanhauser SM, Kresge AJ, Laipis PJ (1993) Rate-equilibria relationships in intramolecular proton transfer in human carbonic anhydrase III. Biochemistry 32: 10757–10762
46. Ren X, Tu C, Laipis PJ, Silverman DN (1995) Proton transfer by Histidine 67 in site-directed mutants of human carbonic anhydrase III. Biochemistry 34: 8492–8498
47. Silverman DN (2000) Marcus rate theory applied to enzymatic proton transfer. Biochimica et biophysica acta 1458: 88–103