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MINI-REVIEW

Theory of Passive Proton Conductance in Lipid Bilayers

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Abstract

The large permeability of lipid bilayers to protons compared to other small ions calls for a special proton transport mechanism. At the present time, only mechanisms involving transient hydrogen-bonded chains of water can account for the experimental result that the conductance is nearly independent of pH. Three models involving transient hydrogen-bonded chains are discussed, including an outline of the kinetic calculations that lead to predictions of current versus voltage drop and current versus pH differences. These calculations can be compared to experiment to determine which, if any, of these models pertains to lipid bilayers.

Key Words: Proton permeability; lipid bilayers; transient hydrogen-bonded chains; kinetic models.

Introduction

The passive proton leakage current through membranes is of some interest in the chemiosmotic picture (Mitchell, 1979) of bioenergetics in the sense that it is an overhead that reduces overall efficiency. From the point of view of the chemiosmotic picture, interest in this leakage current is minimal once it is amply demonstrated that it represents an acceptably small overhead. Present interest in this leakage current began with the startling results of Nichols and Deamer (1980) that the proton/hydroxide permeability near pH 7 is about five orders of magnitude larger than for other small cations and anions. Although this result was challenged (Nozaki and Tanford, 1981), it is now

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established for a number of different lipid systems (Deamer and Nichols, 1983; Gutknecht, 1984; Perkins and Cafiso, 1986). Some special mechanism is clearly implicated for passive proton/hydroxide transport through lipid bilayers and through biomembranes.

The second striking experimental result is that the conductance is nearly constant as a function of pH. This result was already anticipated in the original work of Nichols and Deamer (1980), but Gutknecht has done the most thorough study and finds, over the pH range 2–11, that the electrical conductanct $G = J/\Delta V$, where J is the electrical current and ΔV is the potential across the membrane, increases by at most a factor of 10 for bacterial phosphatidylethanolamine black lipid membranes (Gutknecht, 1984), as shown in curve A of Fig. 1, and by somewhat less for diphytanoyl phosphatidylcholine membranes (Gutknecht, preprint). In this paper we will refer to this simply as a constant conductivity as a function of pH.

The reason that the constant conductivity result is so surprising is seen by recalling the simple transport formula from electrodiffusion theory (Goldman, 1944)

$$G \equiv J/\Delta V = \sum c_i P_i/kT \tag{1}$$

where c_i is the concentration of the ith species of ion being transported and P_i is its permeability. In this standard theory the permeability through the membrane is mostly a property of single ions in the membrane and should not depend strongly upon the pH of the external solutions. However, as pH is varied from 2 to 11 the concentrations of the hydronium and hydroxide ions vary by factors of 10^9. The conductance G as a function of pH that one would expect from electrodiffusion theory is shown in curve B in Fig. 1 and is strikingly different from the experimental curve A. [See also Nichols and Deamer (1980), Fig. 3] There are other theories of ionic conduction across membranes that involve hopping along barriers of various shapes and that yield different voltage dependences than Eq. (1) (Johnson *et al.*, 1954; Lauger, 1973; Hall *et al.*, 1973). However, these theories also involve the concentration as a simple factor just as in Eq. (1) and therefore have the same difficulty as the electrodiffusion theory in accommodating the experimental result of a constant proton/hydroxide conductance as a function of pH.

It has been amply demonstrated (LeBlanc, 1971; McLaughlin and Dilger, 1980) that weak acids uncouple the proton gradient in mitochondrial membranes by acting as carriers of protons. This mechanism leads to quite different formulas than Eq. (1); both theory and experiment were carried out most elegantly by LeBlanc (1971) and his results are also shown as curve C in Fig. 1. Again, the conductance varies far too strongly with pH for weak acid contamination to be the sole contributor to the large H/OH permeability at pH 7. Clearly, the experimental results of a nearly constant conductance

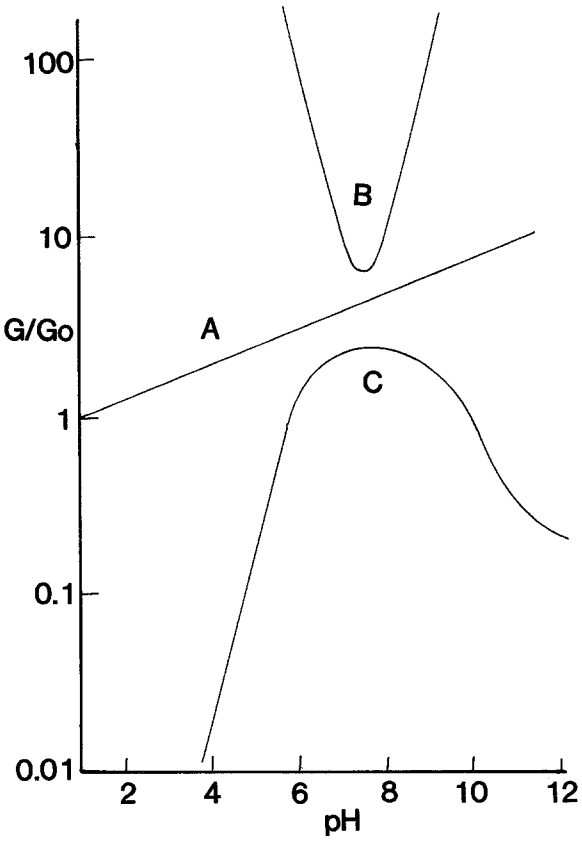


Fig. 1. Logarithmic plot of the pH dependence of the relative conductance G/G_0. (A) the nearly constant conductance measured by Gutknecht (1984); (B) the expected dependence for simple electrodiffusion or Eyring-type hopping theories; (C) the result of theory and experiment for weak acid carriers (LeBlanc, 1971). G_0 is chosen to normalize the curves to nearly the same value at pH 7. Three transient HBC models predict a constant conductance as a function of pH.

as a function of pH is effective in rejecting possible models for the transport mechanism. (It may be noted that Gutknecht, who has been the main proponent for the weak acid carrier model, has agreed (this volume) that the weak acid carrier model cannot account for the measured conductance at low pH, which he discounts as a "background" conductance while arguing that weak acid contamination may still account for the majority, say 90% of the conductance at higher pH. Whether or not this is correct, the "background" conductance yields a permeability for protons at neutral pH that is still some four orders of magnitude larger than for sodium. Explaining this "background" conductance appears to be the more fundamental problem than

discussing the possibility that weak acid contaminants may increase the effective permeability by one additional order of magnitude.)

Hydrogen-Bonded Chains of Water

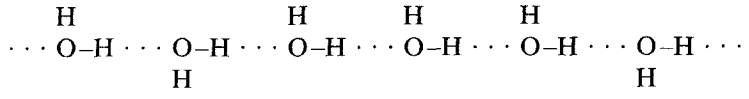
In the discussion of their original paper Nichols and Deamer (1980) proposed that chains of water molecules in the bilayer might provide the special transport pathway for protons. Some, but not necessarily all, of the detailed kinetic mechanisms for this transport would be presumed to be analogous to those that occur in ice and that were invoked by Nagle and Morowitz (1978) for active transport through hydrogen-bonded chains in membrane proteins, which have been called proton wires.

While there are many similarities between the proposal of Nichols and Deamer (1980) and that of Nagle and Morowitz (1978), it is important to recognize the differences and the fact that the experimental verification/falsification of either one does not bear upon the other one. The proton wires that would occur in proteins involve the side chains of the amino acids, as well as perhaps some bound water. They would be supposed to be specific to the amino acid sequence and the conformation of the protein. Consistent with the term proton wire, they would be long-lived, though with some disruption and reformation as the protein goes through its inevitable fluctuations and/or conformational changes.

In contrast to semipermanent proton wires in proteins, it is most likely that any assembly of waters in the fluid hydrocarbon part of the membrane would have transient lifetimes due to thermal fluctuations. Although they would continually reform, they would do so in different positions laterally in the lipid bilayer. Accordingly, the structural proposal of Nichols and Deamer (1980) for the enhanced permeability of protons versus other ions will be called a transient hydrogen-bonded chain (abbreviated tHBC). Unfortunately, the transience means that there is no permanent structure that can be imaged. Rather, the structure is more closely related to the question of correlation functions in fluid mixtures.

The minimal tHBC would be composed of approximately 20 water molecules, each of which would be hydrogen bonded to two other waters in a donor–acceptor hydrogen bonding arrangement that is conveniently portrayed as

Scheme I



The donor–acceptor configuration of the protons is energetically favored over configurations in which some waters are either double donors or double acceptors of hydrogen bonds (Del Bene and Pople, 1970; Hankins *et al.*, 1970; Yoon *et al.*, 1985). The tHBC would stretch preferentially along the normal to the bilayer. In two of the specific models to be discussed below it would span the bilayer, and in the third model it would span half the bilayer. Of course, the average structure need not be just the minimal wire, and one would expect to have some waters hydrogen-bonded to more than two waters and then the single tHBC portrayed in Scheme I would become a multiply stranded and multiply connected array. However, the thickness parallel to the bilayer of the assembly in this model would not be so large as to constitute a fluid water pore. (Fluid pores would have diffusion constants, and therefore permeabilities, of other small ions, such as sodium, that would be only about an order of magnitude smaller than for protons.)

Conrad and Strauss (1985) recently determined that the spectrum of water molecules in bulk alkane solvents can be accounted for by monomeric waters that are not hydrogen bonded to others in aggregates. At first glance this would appear to eliminate the possibility of HBCs in lipid bilayers. However, there are three considerations that prevent drawing this conclusion. First, it would be expected that the vast majority of waters would be in monomeric form which would dominate the spectroscopic signal. (Incidentally, we would also expect the water permeability to be mostly due to the diffusion of water monomers. However, most monomers would be uncharged due to the high Born energy barrier for small ions in the hydrocarbon portion of the bilayer, including hydronium and hydroxide ions. By comparison, tHBCs would partially hydrate the hydronium and hydroxide ions, thereby reducing the Born energy barrier as well as providing a special transport pathway.) Second, the concentration of water in bulk alkanes is probably lower than in the hydrocarbon interior of lipid bilayers. Even a modest increase in concentration of total water in lipid bilayers compared to bulk hydrocarbons might be expected to be leveraged into a considerably enhanced concentration of aggregates, in much the same way as the increase in concentration of lipid or surfactant molecules in water results in enhanced concentration of aggregates when one is near or above the critical micelle concentration. Third, as conclusively demonstrated by resonance studies (Seelig, 1977; McConnell, 1976), the hydrocarbon interior of a lipid bilayer is an anisotropic medium, with the hydrocarbon chains proceeding preferentially in the direction of the bilayer normal. This would favor the formation of tHBC running in the same direction. In contrast, the bulk *n*-decane used in the study of Conrad and Strauss is a fully isotropic fluid. For these reasons, the result of their study, though not supportive of tHBCs in lipid bilayers, falls short of eliminating the possibility. This discussion also

may pertain to possible differences in permeability for different bilayer preparations. All other variables being equal, such as temperature and lipid type, it might be expected that large vesicles might have higher permeabilities than small unilamellar vesicles (SUV) and bilayer lipid membranes (BLM) because the SUV is under curvature strain which lowers their order parameters and the BLM usually has at least a small amount of hydrocarbon solvent that makes the hydrocarbon interior more isotropic.

The detailed mechanism for transport of protons/hydroxides along such HBCs are, from studies in ice and water, thought to involve the sequential transport of a hopping defect followed by the sequential transport of a turning defect. It will be useful for further discussion to portray the sequence of transport steps schematically for a very short tHBC consisting of only three water molecules. For convenience, the nonbonded protons are not shown.

Scheme II

(a) H → OH · · · OH · · · OH

(b) HOH · · · OH · · · OH

(c) HO · · · HOH · · · OH

(d) HO · · · HO · · · HOH

(e) HO · · · HO · · · HO → H

(f) HO · · · HO OH

(g) HO OH · · · OH

(h) OH · · · OH · · · OH

In step (a) above a proton (hydronium) from the left-hand solution enters the chain, in steps (b)–(d) it hops along (with much backtracking that is not shown), and in step (e) it reenters the solution on the right-hand side of the membrane. In order for the chain to transport another proton in the same direction, transport of a turning defect is required, as shown in (f)–(h). It is also assumed that the probability of two protons or turning defects on the chain simultaneously is small because of the Born energy associated with having charges in the membrane. The reader is referred to a review (Nagle and Tristram-Nagle, 1983) for further details regarding these steps.

It is clear that HBCs are especially suited to transport of protons. Hydroxide transport involves taking the rightmost proton off the chain in (a) above followed by hopping of the protons along the bonds as shown in (d)–(b). Rather than explicitly considering hydroxide transport in the subsequent discussion, we will, without loss of generality, restrict the discussion

to the pH range in which proton hopping transport as shown in Scheme II (a)–(e) dominates. While these structures would also be more favorable for transporting sodium than a pure hydrocarbon bilayer simply because the tHBC could partially solvate the ion, the kinetics of transport would be far slower than for protons because of the necessity for the sodium ion to get around each water in the chain or to push the whole chain through, in contrast to proton transport which requires no movement of any atom heavier than a proton.

Three tHBC Models

Three models have been identified that employ transient hydrogen-bonded chains of water molecules, but which are sufficiently different in their detailed mechanisms and in their current response characteristics that it is pertinent to treat them separately. The common result for all three models is that they easily yield a constant conductance as a function of pH.

A. Model With Turning Defect Rate Limiting

This model assumes that each tHBC is sufficiently long-lived to transport several protons on average. In order to obtain a constant conductance as a function of pH, it is necessary that steps (a) and (e) in Scheme II are not the rate-limiting step and that the rate-limiting step be independent of pH. Now, from studies in ice, the turning defect is thought to be about an order of magnitude slower than the hopping defect (Nagle and Tristram-Nagle, 1983). Furthermore, the rate of entry of the turning defect onto the HBC is due to the rate of breaking hydrogen bonds between neutral waters. This is essentially independent of the pH in solution until such low pH that more than 1% of the waters become hydroniums. Therefore, this model rather easily yields a constant conductance as a function of pH.

B. Very Transient HBC Model

The transport of the turning defect in model A requires the breaking of a hydrogen bond. If the chain is a minimal chain with only one strand of water, this means that the tHBC is temporarily broken, as is seen in (f) and (g) of Scheme II. Such breaking is not especially destructive for ice which has a three-dimensional structure, or for HBCs in proteins in which the amino acid side chains would be held in place by the protein backbone. However, for a tHBC in a fluid hydrocarbon environment, such a breaking might very well cause the chain to fall apart, never to come together again. This leads to the concept of a "very transient HBC" which can transport at most one

proton before disintegrating. In terms of Scheme II, the transport of the turning defect involves the dissolution of the chain followed by creation of another chain elsewhere in the membrane. If the rate-limiting step is formation of the tHBCs and not the rate of transport of protons across them, then this model also predicts a constant conductance versus pH.

C. Half tHBC Model

This model has been suggested by Deamer and Nichols (1985). It supposes that, instead of each tHBC going all the way across the membrane, most of the time each tHBC only goes across one monolayer. Half chains that are connected to a solution with low pH will have a higher probability of containing an excess proton and chains that are connected to a solution with a higher pH will have a relatively higher probability of having a deficit proton. A schematic drawing of these two situations is shown below:

Scheme III

low pH solution $HO\cdots HO\cdots HO\cdots HOH$ | | $O\cdots HO\cdots HO\cdots HO$ high pH solution

These half chains diffuse about laterally in the membrane. When they meet, it is favorable for the excess proton and the deficit proton to combine. When the neutralized half chains diffuse apart they can again pick up excess/deficit protons, so the recombination step involves the net transfer of one full proton/hydroxide from one side of the membrane to the other. If recombination is the rate-limiting step, then the probability of an excess proton on the left half chain is proportional to $[H_3O^+]_{left}$ and the probability of a deficit proton on the right half chain is proportional to $[OH^-]_{right}$. The forward current (to the right) is then proportional to the product $[H_3O^+]_{left}\,[OH^-]_{right}$, which is independent of ambient pH and only depends upon the pH difference between right and left. Therefore, this model also is consistent with a constant conductance with pH.

One concern about model C is that it will be most probable that a half chain will have neither an excess nor a deficit proton. When two chains meet, it will be less probable that they will both have the requisite opposite charges than that only one of them will be charged. Therefore, there is a different competing mechanism of proton transfer which is the transfer of an excess/deficit proton from one half chain to a neutral chain. However, as a function of pH this mechanism yields a conductance that behaves similarly to the electrodiffusion conductance shown in Fig. 1 rather than a constant conductance. In order for the recombination mechanism that characterizes

model C to dominate, the probability of recombination must be correspondingly larger than the probability of transfer of a proton between a neutral chain and one that has an excess/deficit proton.

Distinguishing Features of the Three Models

Fortunately, it should be possible to discriminate between models A, B, and C experimentally by investigating the H/OH current under potential differences across the membrane, ΔV, and chemical potential differences across the membrane, ΔpH, and comparing them with the theoretical prediction of detailed kinetic analysis. Before the theoretical formulas are given, it is useful to emphasize some facts about transport with driving potentials ΔV in excess of $kT/e \sim 25\,\text{mV}$ at room temperature.

It has been known for some time that, for any kind of ion, the current J versus ΔV need not be and often is not linear as a function of ΔV when ΔV exceeds kT/e. This is not a violation of linear transport theory, which only holds for $e\Delta V/kT \ll 1$ (Onsager, 1967). It may happen, as in a simple electrodiffusion model, that J versus ΔV is linear over a much wider range. However, various hopping models (Johnson *et al.*, 1954; Lauger, 1973; Hall *et al.*, 1973) have distinctly nonlinear J versus ΔV responses. The degree of nonlinearity depends upon the detailed free energy as a function of the distance along the normal to the membrane. If this function has a sufficiently sharp maximum inside the membrane, such as for the trapezoidal potentials (Hall *et al.*, 1974), then the J versus ΔV curve is substantially superlinear, similar to curve A in Fig. 2.

Discussion of linearity of J versus ΔpH is more complicated. For both the simple electrodiffusion model and for the hopping models, Fick's law holds, $J = P(c_1 - c_2)$. However, this familiar formula for transport involves concentrations, not chemical potential differences which, for small concentrations, is given by $\delta = kT \ln(c_1/c_2)$. A number of possible ways of reexpressing Fick's law in terms of the driving potential δ are exhibited below, where $\beta = 1/kT$:

$$\begin{aligned} J &= Pc_1(1 - e^{-\beta\delta}) = Pc_2(e^{\beta\delta} - 1) \\ &= P(c_1c_2)^{1/2}2\sinh(\beta\delta/2) \\ &= P(c_1 + c_2)\tanh(\beta\delta/2) \\ &= Pc_0\beta\delta, \end{aligned} \tag{2}$$

where

$$c_0 = c_2(e^{\beta\delta} - 1)/\beta\delta$$

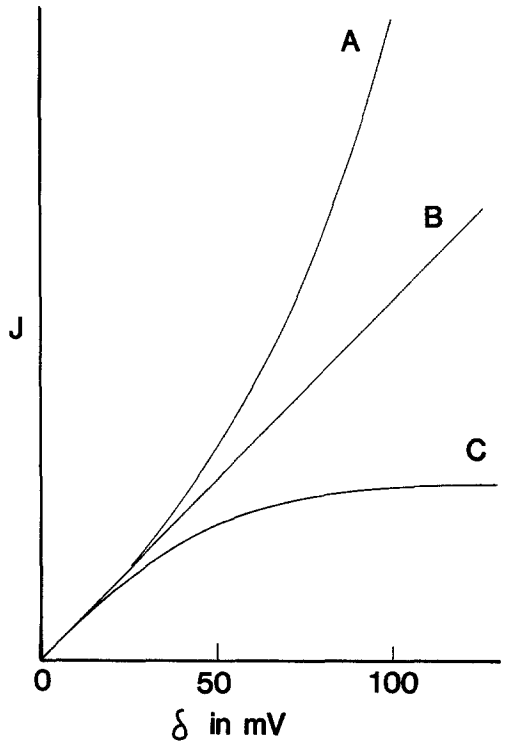


Fig. 2. Different current responses to driving potentials δ in millivolts for $1/\beta = 25\,\text{mV}$: (A) $J = 2\sinh(\beta\delta/2)$ (superlinear); (B) $J = \beta\delta$ (linear); (C) $J = 2\tanh(\beta\delta/2)$ (sublinear and saturating).

The equivalent expressions in Eq. (2) differ in the choice of the ambient concentration. If the larger solution concentration is chosen, as in the first expression, then the current as a function of δ is sublinear and saturating. But if the smaller solution concentration is chosen, as in the second expression, then the current is superlinear. If the geometric mean is chosen, as in the third expression, then the J/δ curve remains superlinear, but if the arithmetic mean is chosen, as in the fourth expression, then it becomes sublinear and saturating again, as is shown in curve C in Fig. 2. It has also been proposed (Kedem and Katchalsky, 1963; Essig and Caplan, 1981) that the ambient concentration be chosen such that J/δ is constant, as in the fifth expression. This trick of linearizing the current with respect to δ by cleverly choosing the ambient concentration can be extended to the situation when the driving force δ is a combination of electrical potential and chemical (concentration) potential. However, as has recently been discussed (Nagle, 1986), the resulting formula for c_0 is different for the simple electrodiffusion model than for the

simple hopping models. Since the appropriate model is not known in advance, it therefore seems inappropriate to manipulate data to make J versus δ linear. Rather, one of the simpler conventions, such as use of the geometric or arithmetic means for the ambient concentration, seems preferable. The formulas in Eq. (3) then show that one should expect nonlinearities in J versus chemical potential even for models that obey Fick's law.

Before returning to the special case of proton conductance, the final point to be emphasized in this review of ordinary ionic conduction is that the magnitude of the current J is not required to be the same when the driving potential is electrical, $\delta = e\Delta V$, as when it is chemical, even though the magnitude of the driving force δ is the same when expressed in common units. Only when the system is in the linear transport regime ($\delta \ll kT \sim 25\,\text{meV}$) is it true that the current must be the same (Onsager, 1967; Nagle, 1986).

From the preceding review of ionic conductance in general it is clear that one should expect different J vs. ΔV and J vs. ΔpH curves for different models of proton transport. We now give the results for models A, B, and C. Some details of the derivations are given in the Appendix. The symbol δ for the driving potential will be used for both electrical potential ($\delta = e\Delta V$) and pH differences ($\delta = 2.303\,kT\Delta\text{pH}$). It will also be convenient to define f to be the fraction of the elementary protonic charge that is carried by the hopping (ionic) defect. In ice the value of f is about 0.62 (Scheiner and Nagle, 1983).

For model A

$$J = J_0 \tanh(\beta\delta/2) \qquad \text{for } \Delta\text{pH} \tag{3}$$

and

$$J = J_0 g(\delta) \sinh(\beta\delta/2)/\cosh(\beta\delta f/2) \qquad \text{for } \Delta V$$

where the function $g(\delta)$ depends upon the details of the free energy F as a function of distance x along the normal to the bilayer of the membrane. When $F(x)$ has a trapezoidal shape, J is a strongly superlinear function of δ, qualitatively similar to curve A in Fig. 2. When $F(x)$ has a rounded maximum corresponding to image charges, J is weakly superlinear and lies between curves A and B in Fig. 2. When $F(x)$ is constant as a function of x inside the membrane, J is slightly sublinear, falling below curve B in Fig. 2, but not saturating to a finite value as δ grows large as occurs for curve C. In strong contrast J versus δ for pH gradients is strongly sublinear and saturating as shown in curve C in Fig. 2.

For model B

$$J = J_0 \tanh(\beta\delta/2)/2 \qquad \text{for pH gradients} \tag{4}$$

and

$$J = J_0 (e^{\beta\delta} - 1)/[(e^{\beta\delta f} + 1)(e^{\beta\delta(1-f)} + 1) \qquad \text{for } \Delta V$$

J versus ΔpH, plotted as curve C in Fig. 2, is the same as in model A which in turn is the same as Fick's law when the arithmetic mean is chosen for the ambient concentration. The function J versus ΔV is also sublinear and saturating. However, for any value of δ and for $f \neq 0$ or 1, J is larger for ΔV than for the equivalent ΔpH, and the saturation level is higher for ΔV.

For model C with pH in the range 1–13

$$J = J_0 \sinh[\beta\delta] \qquad \text{for pH gradients} \tag{5}$$

and

$$J = J_0 h(\delta) \sinh[\beta\delta]/(\cosh[\beta\delta(1 - f)/4])^2 \qquad \text{for } \Delta V$$

For both ΔpH and ΔV, J is strongly superlinear in δ with the ΔpH result being even more superlinear than curve A in Fig. 2. Incidentally, this is the first model, in this author's experience, in which J may [depending upon the free energy barrier profile which determines $h(\delta)$] be larger when δ is due to ΔpH than when δ is due to an $e\Delta V$ of the same magnitude.

Conclusion

The two most important experimental results of H/OH transport would appear to be the high permeability compared to other small ions and the nearly constant conductance as a function of pH. Thus far, only special transport models involving transient hydrogen-bonded chains of waters are compatible with these results. Three such models have been distinguished. The current as a function of ΔpH and as a function of ΔV has been derived for these three models. Since these current functions are different for the three models, this suggests experiments that may determine which, if any, of the three models is the appropriate one for the H/OH transport observed in lipid bilayer systems.

Appendix: Some Details of the Kinetic Calculations

For model A the calculations follow the analysis of Section VB in Nagle *et al.* (1980) except that the assumption there that the free energies are constant across the barrier is not made here. The full result is

$$J = \frac{b'b_1 \exp[\beta(F_1' - F_n')] - b'b_2 \exp[\beta(F_n - F_1)]}{S'(b_1 + b_2 \exp[\beta(F_n - F_1) + S(b' + b' \exp[\beta(F_1' - F_n')])} \tag{6}$$

where the primed quantities refer to the turning defects and the unprimed quantities refer to the hopping defects, the b refer to hopping rates of the

defects onto the HBC, with subscripts for the hopping defects to account for the two different solutions with $\log b_2/b_1 = \Delta\text{pH}$, the F_i refer to the barrier heights for defects at the ith water on the HBC, and

$$S = \sum_i \exp[\beta(F_i - F_1) \quad \text{and} \quad S' = \sum_i \exp[\beta(F_i' - F_n') \tag{7}$$

When the turning defect is rate limiting, the first term in the denominator dominates. For the cases of purely electrical potentials or for purely ΔpH, straightforward algebraic manipulations reduce Eq. (6) to Eq. (3) in the text, where the S' term varies with ΔV but not with ΔpH.

In model B the probability of forming an OH · · · OH · · · OH · · · chain will be denoted $p_{OH}(0)$ and the probability that the chain remains in the OH · · · OH · · · OH state after equilibrating with the protons from the solutions will be denoted $p_{OH}(\infty)$. The current is then given by $J = J_0[p_{OH}(0) - p_{HO}(\infty)]$. When the driving potential is ΔpH, $p_{OH}(0) = 1/2$ since both the OH · · · OH · · · OH and the HO · · · HO · · · HO states have the same energy by symmetry, but $p_{OH}(\infty) = [1 + \exp(-\beta\delta)]^{-1}$ because there are more protons in the left solution with lower pH that drive the OH · · · OH · · · OH chain to become an HO · · · HO · · · HO chain than there are in the right solution driving the reverse process. When $\delta = e\Delta V$, $p_{OH}(0) = [1 + \exp(-\beta\delta(1 - f)]^{-1}$ because OH · · · OH · · · OH has its dipole moment aligned along the electrical field, and $p_{OH}(\infty) = [1 + \exp(\beta\delta f)]^{-1}$ because energy can be lost by transport of a proton from left to right. Insertion of these probabilities into the formula for J yields the results in Eq. (4).

For model C the net current is given by the forward current that occurs when a half chain from solution 1 carrying a proton (+) meets a half chain from solution 2 carrying a hydroxide (−) minus the reverse current when the proton and hydroxide are on the opposite chains. This is expressed as

$$J = J_0[p_1(+)p_2(-) - p_1(-)p_2(+)] \tag{8}$$

When $\Delta V = 0$, the probabilities p in Eq. (8) are simply related to the pH differences, giving Eq. (5a). (Technically, this ignores some normalization factors, but these play only a negligible role for pH in the range under consideration.) The electrical case is a bit more involved. The relative probability of forming an OH · · · OH · · · OH half tHBC is $\exp[bd(1 - f)/4]/2\cosh[bd(1 - f)/4]$ and it is $\exp[-\beta\delta(1 - f)/4]/2\cosh[\beta\delta(1 - f)/4]$ for HO · · · HO · · · HO half chains. The probability that one of these chains has a charge then requires an additional factor of $\exp[\pm\beta\delta f/4]$. Finally, achieving a complete cycle with the same initial and final tHBC chain states requires passage of turning defects along both half chains and this gives a factor of $h(\delta)\exp[\pm\beta\delta(1 - f)/2]$. Putting these together with Eq. (8) yields Eq. (5b).

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