ELECTROSTATIC CALCULATIONS FOR AN ION CHANNEL

I. ENERGY AND POTENTIAL PROFILES AND INTERACTIONS BETWEEN IONS

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ABSTRACT The electrostatic energy profile of one, two, or three ions in an aqueous channel through a lipid membrane is calculated. It is shown that the previous solution to this problem (based on the assumption that the channel is infinitely long) significantly overestimates the electrostatic energy barrier. For example, for a 3-Å radius pore, the energy is 16 kT for the infinite channel and 6.7 kT for an ion in the center of a channel 25 Å long. The energy as a function of the position of the ion is also determined. With this energy profile, the rate of crossing the membrane (using the Nernst-Planck equation) was estimated and found to be compatible with the maximum conductance observed for the gramicidin A channel. The total electrostatic energy (as a function of position) required to place two or three ions in the channel is also calculated. The electrostatic interaction is small for two ions at opposite ends of the channel and large for any positioning of the three ions. Finally, the gradient through the channel of an applied potential is calculated. The solution to these problems is based on solving an equivalent problem in which an appropriate surface charge is placed on the boundary between the lipid and aqueous regions. The magnitude of the surface charge is obtained from the numerical solution for a system of coupled integral equations.

One of the main barriers to ion transport across lipid membranes is the electrostatic energy required to move the ion from water with a dielectric constant (ϵ) of 76 to lipid with an ϵ of about 2. Parsegian (1969, 1975) has calculated the reduction of this energy barrier produced by carriers or pores. A surprising result of this calculation was that the energy barrier still was as large as 16 kT for an aqueous pore 3 Å in radius. This large energy barrier did not seem compatible with the relatively high conductances observed for model pores such as are produced by gramicidin A (Finkelstein, 1975). The calculation of Parsegian is based on the solution for an infinitely long pore and, as Parsegian states, is only valid for a pore whose radius is much less than its length. Inasmuch as the gramicidin A pore is only about 25 Å long, this assumption is not very well satisfied. In addition, the solution for the infinite pore does not provide any information about the energy profile through the pore. The purpose of this paper is to obtain a solution for the energy in a pore of finite length. This solution can be used to evaluate the error involved in the infinite pore assumption and to determine the energy

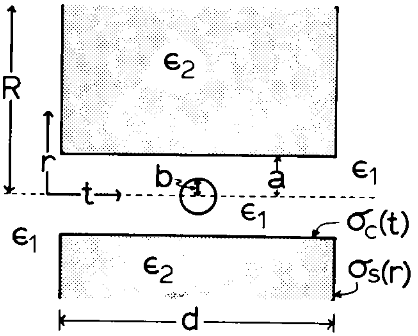

FIGURE 1 Schematic drawing of channel: a, b, pore and ion radius; d, pore length; r, t, radial and axial coordinates; R, maximum value of r used in numerical integration; ϵ_1, ϵ_2, dielectric constant in aqueous (channel) and lipid region; σ_c, σ_s, surface charge placed on channel wall and membrane side.

profiles as a function of the number and position of ions in the pore. This same procedure can also be used to determine the potential profile when an external electrical potential difference is applied to the membrane. The application of these results to an interpretation of the observed behavior of the gramicidin A channel will be presented in a second paper.

THEORY

A diagram of the pore is shown in Fig. 1. The ion is on the axis at the center of the membrane. The electrical potential (ϕ) for this system is described by the following set of differential equations:

Region 1 (water): $$\nabla^2\phi_1 = -(4\pi q/\epsilon_1)\delta(0), \tag{1}$$

region 2 (lipid): $$\nabla^2\phi_2 = 0; \tag{2}$$

boundary condition at lipid-water interface: $$\phi_1 = \phi_2 \tag{3}$$

$$\epsilon_1(\partial\phi_1/\partial n) = \epsilon_2(\partial\phi_2/\partial n). \tag{4}$$

The ion has been replaced by a point charge q (delta function) at the origin. The numerical solution is based on satisfying this set of equations by an alternative physical system in which all of space has the same dielectric constant (ϵ_1) and an appropriate surface charge (σ) is placed on the boundary between the two regions. Eq. 1 and 2 are still automatically satisfied and so is Eq. 3 because the potential is continuous across the surface charge. Because of the surface charge, there is a discontinuity in the electric field at the surface, which can be written as:

$$\left.\frac{\partial\phi}{\partial n}\right|_1 = \frac{\partial\phi'}{\partial n} - \frac{2\pi\sigma(s)}{\epsilon_1}; \quad \left.\frac{\partial\phi}{\partial n}\right|_2 = \frac{\partial\phi'}{\partial n} + \frac{2\pi\sigma(s)}{\epsilon_1}, \tag{5}$$

where ϕ' is the continuous part due to all the charges on the surface except those on the surface in the immediate neighborhood. Substituting Eq. 5 into Eq. 4 and solving for σ:

$$\sigma(s) = \frac{\epsilon_1}{2\pi}\frac{K-1}{1+K}\frac{\partial\phi'}{\partial n}; \quad K = \frac{\epsilon_1}{\epsilon_2}. \tag{6}$$

Once σ is determined from Eq. 6, the problem is solved because it is easy to determine ϕ given σ (and the point charge q), and this ϕ satisfies the boundary value problem (Eqs. 1–4). Because of the cylindrical symmetry, σ is a function of only the one variable s (either t or r, see below). The expression for ϕ' in Eq. 6 can be obtained by summing over all the other surface charges and the point source (simplified by the fact that all of space has the dielectric constant ϵ_1). One then gets an integral equation for σ that is solved numerically.

For the case where the ion is in the center of the membrane, the effect of the two halves of the membrane is symmetrical, and it is only necessary to consider the effect of one membrane side and one half of the channel. The surface charge is then divided into a charge on the membrane side ($\sigma_s(r)$) and a charge on the channel wall ($\sigma_c(t)$), where r is the radial distance from the axis of the pore and t is the distance from the side of the membrane (the ion is located at $r = 0$, $t = d/2$). For the case where the ion is not located in the center of the membrane, the surface charges in the two halves are no longer the same, and it is necessary to use three different surface functions (the two membrane sides and the channel wall) and three coupled integral equations (the ion is always on the pore axis). The details will be given below only for the case when the ion is in the center.

The following dimensionless variables are used:

$$x = (r - a)/(R - a); \quad y = 2t/d; \tag{7}$$

$$\sigma_s' = (R - a)^2\sigma_s/q; \qquad \sigma_c' = ad\sigma_c/2q, \tag{8}$$

where R is the maximum radial distance that is used in the integration. Then, using Eq. 6 for σ_s' and σ_c' one gets the following pair of coupled integral equations:

$$\sigma_s'(x) = F_1(x) + \int_0^1 A_{11}(x,\xi)\sigma_s'(\xi)\,\mathrm{d}\xi + \int_0^1 A_{12}(x,\xi)\sigma_c'(\xi)\,\mathrm{d}\xi, \tag{9a}$$

$$\sigma_c'(y) = F_2(y) + \int_0^1 A_{21}(y,\xi)\sigma_s'(\xi)\,\mathrm{d}\xi + \int_0^1 A_{22}(y,\xi)\sigma_c'(\xi)\,\mathrm{d}\xi, \tag{9b}$$

$$F_1(x) = -\frac{(R-a)^2 d}{4\pi\gamma[x^2 + d^2/4]^{3/2}}, \quad F_2(y) = \frac{da^2}{4\pi\gamma[a^2 + (y - d/2)^2]^{3/2}}, \tag{9c}$$

$$A_{11}(x,\xi) = [(R - a)/2\pi\gamma]f(x,\xi,d); \quad \gamma = (1 + K)/(K - 1), \tag{9d}$$

$$A_{12}(x,\xi) = [(R - a)^2/2\pi\gamma a][f(x,a,\xi) + f(x,a,d - \xi)], \tag{9e}$$

$$A_{21}(y,\xi) = [-da/4\pi\gamma(R - a)][g(\xi,a,y) + g(\xi,a,d - y)], \tag{9f}$$

$$A_{22}(y,\xi) = (-d/4\pi\gamma)[g(a,a,y - \xi) + g(a,a,d - y - \xi)], \tag{9g}$$

$$f(x,y,z) = \frac{-4yz}{[(x + y)^2 + z^2]^{1/2}[(x - y)^2 + z^2]} E(2\beta);$$

$$\beta = \left[\frac{xy}{(x + y)^2 + z^2}\right]^{1/2}; \tag{9h}$$

$$g(x,y,z) = \frac{2x(x^2 - y^2 + z^2)}{y[(x - y)^2 + z^2][(x + y)^2 + z^2]^{1/2}} E(2/\beta) - \frac{2x}{y[(x + y)^2 + z^2]^{1/2}} K(2\beta). \tag{9i}$$

The functions K and E in Eqs. 9*h* and 9*i* are the complete elliptic integrals of the first and second kind, respectively. Eq. 9 is just Eq. 6 with ϕ' written out explicitly in terms of all the charges in the system. In Eq. 9*a*, $F_1(x)$ is the contribution from the ion to the normal component of the gradient of ϕ' at the radial position x on the membrane side; $A_{11}(x,\xi)\sigma_s'(\xi)$ is the contribution from a ring of charge at a radial position ξ on the opposite side of the membrane; and $A_{12}(x,\xi)\sigma_c'(\xi)$ is the contribution from a ring of charge at an axial position ξ on the channel wall. The integrals are over all the surface charges. Eq. 9*b* is the corresponding expression for the channel wall. The function $f(x,y,z)$ (or g) is proportional to the contribution to the normal component of the electric field at the membrane side (or channel wall) at the radial position x due to a ring of charge with a radius y, separated by a perpendicular distance z.

These integral equations are then solved for σ_c' and σ_s' by the method of "averaging functional corrections" (Lucka, 1965).[1] The functions are evaluated at $N(= 50)$ points by an iteration procedure in which, at the first step, σ' is approximated by F plus a functional correction, and a new σ' is determined from the integral equations. The procedure is then repeated until the result converges to a limit. For the integration along the pore wall the 50 points were equally spaced along the axis, whereas for the integration over the membrane side the 10 points next to the pore were spaced at 0.5-Å radial intervals, and the last 40 points were divided equally over the remaining outer portion of the radius. The solution was relatively insensitive to the value of R if it was greater than 100 Å, and an R of 200 Å was used for most of the results.

The electrostatic energy of an ion in an infinite homogeneous medium is given by the Born charging energy:

$$E = \int_0^q \phi_b(e)\,\mathrm{d}e = q^2/2\epsilon b, \tag{10}$$

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[1] This approach for solving the electrostatic problem was suggested by Dr. John P. Moran, Department of Aerospace Engineering and Mechanics, University of Minnesota.

where ϕ_b is the potential at the surface of the ion (and b is the ion radius). This energy is identical to the energy stored in the electric field external to the ion. This derivation requires only that the ion's charge distribution be spherically symmetric. For the case of an ion in the pore, the potential at the ion surface consists of two components: (*a*) the potential due to the charge of the ion itself, and (*b*) the potential due to the surface charges. The contribution of the first term will be identical to the energy of the ion in the homogenous medium and thus the contribution due to the surface charges represents the extra work (E) necessary to move the ion from the bulk water to the center of the pore. The average potential at the ion's surface due to the surface charges will be approximated by the potential at the center of the ion (ϕ_0). This potential is given by:

$$\phi_0(q) = 4\pi q/\epsilon_1 \phi_0', \tag{11}$$

$$\phi_0' = (R - a)^{-2} \int_a^R \sigma_s'(r)[(d/2)^2 + r^2]^{-1/2} r\,\mathrm{d}r + 2d^{-1} \int_0^{d/2} \sigma_c'(t)[a^2 + (t - d/2)^2]^{-1/2}\,\mathrm{d}t.$$

The work of transferring the ion from the bulk water to the center of the channel is:

$$E = \int_0^q \phi_0(e) de = 2\pi \phi_0' q^2/\epsilon_1. \tag{12}$$

For the case where there is more than one ion in the channel, the direct electrostatic interaction (E_d) should also be included in E:

$$E_d = q^2/\epsilon_1 \,|\, t_1 - t_2 \,|\,. \tag{13}$$

The inclusion of this term makes the assumption that the direct interaction in the bulk solution is negligible (due to the screening by counter-ions).

RESULTS

The numerical solution was first tested by comparing it with the analytical expressions derived by Parsegian (1975) for two special cases:

$$E_\infty = (q^2/\epsilon_1 a) f(K); \quad E_S = -(q^2 K/\epsilon_1 d) \ln [2K/(1 + K)], \tag{14}$$

where E_∞ is the energy required to place an ion in an infinitely long pore (the function $f(K)$ is given in tabulated form; $f = 6.8$ for $K = 40$), and E_S is the energy of interaction between the membrane surface charge and an ion in the center of a pure lipid membrane without a pore. The numerical solutions agreed with the analytical results to better than 1% for both cases. Because the first case (E_∞) involves placing surface charges on the pore wall whereas the second case (E_S) involves placing charges on the membrane side, the agreement between the numerical and exact solutions suggests that

TABLE I

ENERGY (kT) OF ONE ION AT MEMBRANE CENTER ($\epsilon_1/\epsilon_2 = 40$)

Pore length	Pore radius		
	2	3	5
		Å	
Infinite	24.0	16.0	9.62
50	17.2	10.2	4.59
35	15.6	8.48	3.50
25	13.3	6.72	2.59
15	9.3	4.34	1.54

the numerical solution is also valid for the general case when there are charges on both the pore wall and membrane side.

The numerical solution for the electrostatic energy required to move the ion from water to the center of a finite length pore as a function of pore length and radius is shown in Table I. It can be seen that E for a pore of the length postulated for gramicidin A (25 Å) is significantly less than the infinitely long pore result of Parsegian. All the results in Table I are for a value of $K = 40$, corresponding to a dielectric constant of 80 for the water and 2 for the hydrocarbon.

A rough estimate of the energy for the finite pore length can be obtained simply by adding E_∞ and E_S (Eq. 14).[2] This assumes that there is no interaction between the charges on the membrane surface and the pore wall. For the case of $a = 3$ Å, $d = 25$ Å ($K = 40$), this approximate energy is 8.48 kT, about 26% larger than the numerical result (6.72 kT). The percentage error is about the same for most of the other values in Table I. This approximation breaks down for values of d and a that make the sum negative. However, for most cases this sum provides a useful qualitative estimate for the energy in a pore of finite length.

In calculating the energy profiles for a pore that has a structure similar to that postulated for gramicidin A, it is necessary to include the effects of both the high dielectric region of the water in the pore and of the polypeptide channel wall. A rough estimate of the dielectric constant of the gramicidin wall is provided by measurements of the dielectric constant of dry synthetic polyalanylglycine (Tredgold and Hole, 1976), in a β-sheet structure (Fraser et al., 1965) similar to that postulated for gramicidin A. In addition, the side groups of alanine and glycine are nonpolar as in gramicidin. The inner 2 Å of the gramicidin channel wall is formed by the polypeptide backbone with the nonpolar side groups on the outside. If one assumes that the major contribution to the dielectric constant of 5 found for polyalanylglycine is due to the polypeptide backbone that occupies about half the crystalline volume, one can estimate that the inner 2 Å of the gramicidin channel wall should have an ϵ of about 10 and the rest of the wall should be similar to hydrocarbon ($\epsilon = 2$). To estimate the electrostatic energy

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[2] This approximation was suggested by Dr. V. Adrian Parsegian.

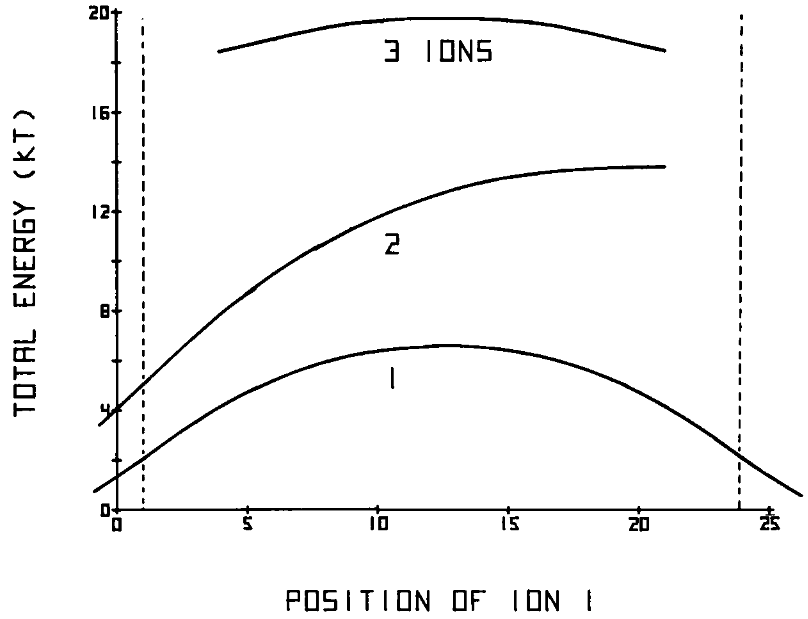

FIGURE 2 Total electrostatic energy required to move one, two, or three ions from the bulk solution into the channel as a function of the distance of ion 1 from left end. Dashed lines indicate assumed position of energy wells (1 Å from each end). When there are two ions in the channel, ion 2 is always in the right well. When there are three ions in the channel, ions 2 and 3 are always in the two wells.

for the gramicidin channel it has been assumed here that the 2 Å inner wall can be approximated by a 1 Å wall with an ϵ equal to that of water (76). Thus, the gramicidin channel, which is thought to have a channel radius of 2 Å, has an effective radius of 3 Å for calculations of the electrostatic energy. This approximation could be avoided by placing another cylindrical charged surface at $r = 4$ Å, corresponding to the change in dielectric constant between the polypeptide backbone ($\epsilon \cong 10$) and the hydrocarbon. This would add an additional coupled integral equation.

Fig. 2 shows the total energy required to move one, two, or three ions from the bulk solution to a channel that is 25 Å long and 3 Å in radius ($K = 40$) as a function of the position of ion 1. For the case where there are two ions in the channel, ion 2 is always at a position 1 Å from the right end ($x = 24$ Å), whereas the position of ion 1 is varied. It can be seen that there is very little interaction when the ions are at opposite ends of the channel. That is, the energy required to put two ions in the channel at a position 1 Å from each end (5.02 kT) is only 1 kT greater than twice the energy required to put one ion in the channel at the same position (2.03 kT). For the case where there are three ions in the channel, ion 2 and ion 3 are 1 Å from each end and the position of ion 1 is varied. The energy required to put three ions in the channel is about 12 kT greater than that required to put three "independent" ions in the channel. This is such a large value for the interaction energy that it seems unlikely that a channel of this size could hold more than two cations (unless the effect of anions is included). This is considered in more detail in the second paper (Levitt, 1978).

Profile of an Applied Potential

This same theoretical approach can be used to estimate the profile through the channel of an applied potential difference. The potential is applied by two plates with a fixed uniform surface charge. The point charge source term in Eq. 9 is replaced by the plate surface charges. A slight modification is necessary to compensate for the fact that the induced surface charges do not go to zero at large distances from the pore (see Appendix for details). This calculation is only a rough approximation because it assumes that the aqueous regions are nonconducting. This assumption is valid for a channel that does not contain an ion but it is poor for the bulk aqueous regions. However, as will be shown, the potential differences in the bulk regions are so small for a 3-Å radius pore that this error can be neglected.

Fig. 3 shows the potential profile along the pore axis as a function of the pore radius for a pore 25 Å long ($K = 40$). Also shown in the figure is the potential profile that would be expected if there were no pore and the membrane were pure lipid. It can be seen for the 3 Å pore that the potential profile is not significantly different from what would be found in the absence of a pore. Although the profile for the 50 Å pore is markedly different, this result is not very useful because the nonconducting assumption is clearly invalid for this case.

These calculations are for an ion located on the axis of the pore. However, the varia-

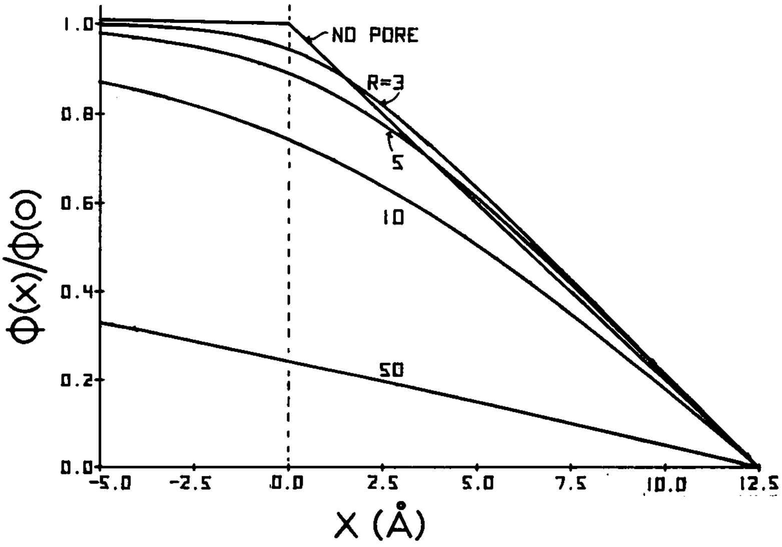

FIGURE 3 Potential profile on the axis of the channel produced by infinite planar surfaces on opposite sides of and parallel to the membrane with a uniform fixed charge of opposite sign. The channel is 25 Å long and has a radius of 0 (no pore) 3, 5, 10, and 50 Å.

tion in energy with the radial position of the ion should be small because of the long range of the electrostatic potential. For example, the K$^+$ ion (1.4 Å in radius) could only move about 0.6 Å off the axis in the gramicidin channel (2 Å in radius), whereas most of the electrostatic energy is due to charges at a distance of many angstroms. Furthermore, by symmetry, the ion must be at a potential minimum, and there is a parabolic increase in energy from the minimum.

DISCUSSION

These results indicate that for a pore of the size postulated for gramicidin A (25 Å long and an "effective" radius of 3 Å), the infinite pore solution overestimates the energy barrier height by a factor of about 2.4 (Table I). Because this energy enters the conductance equation as an exponential, this is an important difference. One can estimate the conductance that would be found for the case where this barrier is the rate-determining step. Writing the electrochemical potential in the form:

$$\mu(x) = RT \ln c(x) + F\Psi(x) + F\Phi(x) + \mu_0, \tag{15}$$

where the first term is the concentration dependence, the second is the contribution of the applied potential, the third is the contribution of the image potential, and the last term is the standard chemical potential in the pore and includes the local interactions between the ion and the wall. This last term determines the overall partition of the ion between the pore and the solutions. For this calculation, it will be assumed that μ_0 is a constant within the channel (the local variation in μ_0 enters into the diffusion coefficient). The ion flux is then given by:

$$\begin{aligned} J &= -D[\mathrm{d}c/\mathrm{d}x + c(\mathrm{d}/\mathrm{d}x)(\psi + \phi)], \\ &= -D(\mathrm{d}/\mathrm{d}x)[c e^{(\psi+\phi)}]/e^{(\psi+\phi)}, \\ \psi &= F\Psi/RT, \qquad \phi = F\Phi/RT. \end{aligned} \tag{16}$$

If the transport across the central barrier is rate limiting, then the rate of movement between the bulk solutions and the pore ends must be relatively fast, and it will be assumed that there is rapid equilibration between the bulk solution and a position 1 Å into the pore. The further the ion equilibrates into the channel, the smaller the barrier that the ion sees. This assumption of 1 Å is probably a minimum distance, and, therefore, this calculation should underestimate the actual conductance through the channel. Integrating Eq. 16 from 1 Å (position 1) to 24 Å (position 2):

$$\begin{aligned} J &= -D[c_2 e^{(\psi_2+\phi_2)} - c_1 e^{(\psi_1+\phi_1)}] \Big/ \int_1^{24} e^{(\psi+\phi)}\,\mathrm{d}x \\ &= D\,c_0[e^{\psi_1} - e^{\psi_2}] \Big/ \int_1^{24} e^{(\psi+\phi-\phi_0)}\,\mathrm{d}x, \end{aligned} \tag{17}$$

where the following boundary conditions have been used:

$$c_1 = c_2 = c_0; \qquad \phi_1 = \phi_2 = \phi_0$$
$$\psi_1 = (24/25)\psi_0; \quad \psi_2 = (1/25)\psi_0$$

where c_0 is determined by the overall partition (μ_0), ψ_0 is the applied potential difference, and the potential drop is assumed to be linear (Fig. 3). In the limit where the applied potential (ψ_0) is small relative to one and the image potential (ϕ):

$$J = Dc_0(23/25)\psi_0 \Big/ \int_1^{24} e^{(\phi-\phi_0)}\,\mathrm{d}x. \tag{18}$$

If it is assumed that there is one ion per channel when the conductance is a maximum ($G_{\max}$) then c_0 can be estimated by assuming that there is a Boltzman distribution in the channel:

$$\frac{c}{c_0} = e^{-(\phi-\phi_0)} \quad \text{and} \quad \int_1^{24} c\,\mathrm{d}x = 1 \rightarrow c_0 = \left[\int_1^{24} e^{-(\phi-\phi_0)}\,\mathrm{d}x\right]^{-1}. \tag{19}$$

Finally, writing the flux in terms of the electrical conductance and solving for the diffusion coefficient in the pore:

$$D = \frac{25\,\mathrm{kT}}{23\,q^2}\left[\int_1^{24} e^{(\phi-\phi_0)}\,\mathrm{d}x\right]\left[\int_1^{24} e^{-(\phi-\phi_0)}\,\mathrm{d}x\right]G_{\max}. \tag{20}$$

Evaluating the integrals in Eq. 20 numerically (using Fig. 2):

$$D = 4.2 \times 10^4\,G_{\max}. \tag{21}$$

The maximum observed conductance for gramicidin A is about 5×10^{-11} ohm^{-1}cm^{-1} and corresponds to a D of 2.1×10^{-6} cm^2/s, about 10% of the bulk value. This calculation implies that transport over the image potential does not present an unreasonably high barrier and may actually be the rate-limiting step.

APPENDIX

Details of Calculation of Applied Potential Profile

In analogy to Eq. 9 one can write the following pair of coupled integral equations:

$$\frac{\gamma}{2\epsilon_1}\sigma_s(r) = \frac{\partial\phi_s'}{\partial n} = \int_a^{\infty}\sigma_s(y)h_1(y,r)\mathrm{d}y + \int_0^{d/2}\sigma_c(t)h_2(t,r)\mathrm{d}t + \frac{\sigma_f}{\epsilon_1}. \tag{1A}$$

(The equation for σ_c is similar and will not be shown.) The first term on the right is the contribution of the induced surface charge on one side (σ_s) of the membrane to the normal component of the field on the other side. (There is no normal component for charges on the same side.) The second term is the contribution from the induced surface charge (σ_c) on the channel wall (as the system is now antisymmetric, only the charge on one half of the channel need be calculated). The last term is the normal field due to the applied (fixed) charges (σ_f) on the two plates. For the previous case when the source was a point charge in the pore, it was clear that σ_s should go to zero at large values of r, and the upper limit of the first integral could be approximated by some large R. For this case, however, σ_s does not go to zero at large r. To overcome this, σ_s is written in the form:

$$\sigma_s(r) = \sigma(r) + \sigma_0, \tag{2A}$$

where σ_0 is the value that would be found if there were no pore and the membrane were pure lipid. It is easy to show that:

$$\sigma_0 = (K - 1)\sigma_f. \tag{3A}$$

Then, substituting Eqs. 2A and 3A into Eq. 1A and using the fact that the integral from 0 to infinity of h_1 is $(2\epsilon_1)^{-1}$:

$$(\gamma/2\epsilon_1)\sigma(r) = \int_a^\infty \sigma(y)h_1(y,r)\mathrm{d}y - \sigma_0 \int_0^a h_1(y,r)\mathrm{d}y + \int_0^{d/2} \sigma_c(t)h_2(t,r)\mathrm{d}t.$$

Because σ_s approaches σ_0 for large r, σ must go to zero at large r, and the upper limit in the first integral can now be approximated by some large R.

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