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ENERGY BARRIERS FOR PASSAGE OF IONS THROUGH CHANNELS. EXACT SOLUTION OF TWO ELECTROSTATIC PROBLEMS

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Exact solutions are given to two electrostatic problems relevant to ion permeation through pores in membranes. The first assesses the importance of the pore forming molecule as a dielectric shield. It is shown on the basis of structural and dielectric considerations alone (neglecting effects attributable to possible charge distribution at the interior surface of the pore-former) that the *minimum* electrostatic barrier for monovalent ion passage through a gramicidin-like channel is 11 kT. It is further shown that given favorable circumstances, dielectric shielding might dramatically reduce the barrier to ion passage through potassium channels. The second problem considers the error introduced by treating ions as point charges. It is shown that for structureless pores the point charge approximation introduces no meaningful error, even if the ratio of ion radius to pore radius is as great as 0.95.

1. Introduction

It has long been accepted that electrostatic interactions significantly influence the transport of ions across lipid membranes. There is an electrostatic energy barrier associated with the movement of an ion from a region of high dielectric constant (water, $\epsilon \sim 80$) through a region of low dielectric constant (lipid, $\epsilon \sim 2$). Were it not for the presence of specialized molecules such as carriers and pores, the energy required to effect such translocations would be simply enormous. A *bare* potassium ion (radius ~0.13 nm) penetrating a lipid membrane ~3 nm thick would have to surmount a barrier of ~245 kJ mole^{-1} (~100 kT at 300 K). The actual energetic impediments to ion transport are clearly orders of magnitude smaller, otherwise there could be no conduction through membranes.

The first quantitative estimate of the effect that pores and carriers have on the energy barriers to ionic transport was given by Parsegian [1,2]. His analysis was based upon continuum electrostatics. A pore was treated as a long narrow cylinder of high dielectric constant surrounded by a membrane of low dielectric constant; for the purpose of calculating the polarization energy the ion was approximated as a point charge. The barrier decreased dramatically. For channels formed by gramicidin the pore has a radius of ~0.2 nm [3]. Assuming the most favorable circumstances, that the aqueous region within the channel has the same dielectric constant as bulk water, a monovalent ion must surmount an activation barrier of ~57 kJ mol^{-1} (~23 kT) to penetrate the lipid membrane.

While a substantial improvement, this barrier is still too large to rationalize observed single channel conductance data. At low ionic concentration conductance (G) is proportional to concentration [4]. For 0.1 M solutions of monovalent cations (which is in the linear domain) the open state conductance of single gramicidin-A channels inserted into neutral membranes is ~10 pS [4,5]. An approximate expression for the single channel conductance may be determined using a Nernst-Planck approach [6]; the result is

$$G = 2\pi R^2 c \frac{\lambda}{L} \exp(-\delta E/kT) \qquad (1)$$

where λ is the ion equivalent conductance in water, c the ion concentration in water, R the channel radius, L the channel length, T the absolute temperature, k the Boltzmann constant and δE the non-diffusional activation energy. Monovalent cations have equivalent conductances ~0.006 m^2 S eq^{-1} [7]. Thus, when bathed with a 0.1 M solution of monovalent cation, the conductance of a single gramicidin channel would be ~60 $\exp(-\delta E/kT)$ pS; this suggests that the non-diffusional energy barriers may be as low as ~4.5 kJ mol^{-1} (~1.8 kT).

An alternative estimate of the non-diffusional energy barrier in gramicidin can be established by comparing the activation energy for channel conductance, ~30 kJ mol^{-1} using 1 M Na^+ as electrolyte [8], and that for Na^+ conductance in water, ~16 kJ mol^{-1} [9]. The difference, 14 kJ mol^{-1}, can be identified as a non-diffusional barrier reflecting the interactions between the ion and the gramicidin-membrane system. The barrier inferred in this fashion, ~5.6 kT, is somewhat higher than the Nernst-Planck estimate; more than likely this reflects the limitations of the Nernst-Planck procedure. In any case realistic barrier energies are far less than the 57 kJ mol^{-1} (23 kT) estimate of Parsegian [1,2].

Levitt [10] recognized that Parsegian's expression [1,2] must overestimate the barrier height for at least two reasons. The ratio of the channel length to its radius is not infinite; thus the presence of water bathing the membrane reduces the barrier to ion translocation. Furthermore the channel forming molecule may have a dielectric constant substantially greater than that of the lipid. As a result the channel former provides some dielectric shielding which also reduces the polarization energy. The effect of finite membrane thickness was treated exactly within the point charge approximation. The effect of dielectric shielding by the pore former was estimated by the introduction of an electrostatic pore radius larger than the physical pore radius. On the basis of these considerations the energy barrier to conductance through gramicidin channels was reduced to ~7 kT, almost small enough to rationalize the observed conductance data.

In this paper I consider two exactly soluble electrostatic problems in order to understand better some aspects of channel conductance. The analysis is based upon the equations of macroscopic, continuum electrostatics. The treatments are not designed to study the energetic significance of specific features of a pore's molecular architecture. Furthermore, very short range electrical interactions can not be adequately handled within this context.

Section 2 considers the pore former as a dielectric shield by extending Parsegian's model [1,2]. The membrane-channel former-pore-ion system is approximated by two concentric infinite cylinders containing different dielectrics. This assembly is embedded in a third dielectric, a single point charge is located on the axis of the cylinders.

In section 3 the point charge approximation, upon which all previous electrostatic calculations have been based [1,2,10] is assessed. It is far from obvious that ions, in long narrow pores such as gramicidin (~0.2 nm radius) [3] or the potassium channel (~0.15 nm radius) [11], are reasonably approximated as point charges even if interaction with specific structural features such as selectivity filters [12,13] is ignored. Limiting consideration to continuum systems, the physical model is that of an infinite cylinder embedded in surroundings with different dielectric properties; the ion is a charged, polarizable sphere located on the cylinder axis. Section 4 recapitulates the major findings of the study.

2. Pore formers as dielectric shields

2.1. Solution of the electrostatic problem

The model is illustrated in fig. 1. The interior of the pore is a cylinder of radius R_1 and dielectric constant ϵ_1. The channel former is a concentric cylinder of radius R_2 and dielectric constant ϵ_2. The whole assembly is embedded in surroundings of dielectric constant ϵ_3. A point charge is located on the axis of the system. This problem, while exactly soluble in the limit where the channel is very long, grossly simplifies the real physics. The energetic consequences of finite membrane thickness, of the accompanying electrostriction, of ion size, of molecular structure whether in the aqueous phase, pore former or membrane, etc. are all ignored. The calculation is designed to focus upon a single feature – the importance of the pore former as a dielectric.

As long as the finite thickness of the membrane may be neglected, the electrostatic problem in the central portion of the pore is characterized by the equations [14]

$$\nabla^2 V_1 = -4\pi q\delta(0)/\epsilon_1, \quad \nabla^2 V_2 = 0, \quad \nabla^2 V_3 = 0, \quad (2)$$

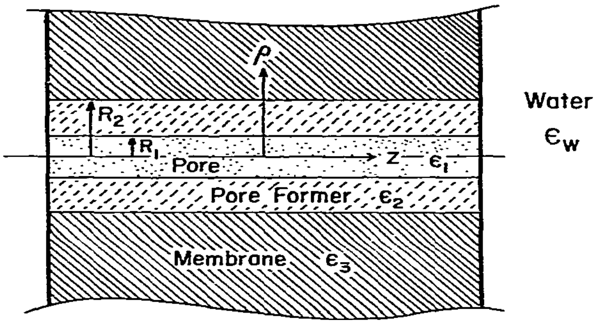

Fig. 1. Cross-section of a cylindrical "pore" in a "membrane" of dielectric constant ϵ_3. The pore interior has radius R_1 and dielectric constant ϵ_1; the pore former has outer radius R_2 and dielectric constant ϵ_2. The surrounding water has dielectric constant ϵ_w. A point charge is located at the origin. The assembly is presumed to be infinite in the z-direction.

$$V_1 = V_2, \quad \epsilon_1 \partial V_1/\partial\rho = \epsilon_2 \partial V_2/\partial\rho, \quad \rho = R_1\,, \tag{3}$$

$$V_2 = V_3, \quad \epsilon_2 \partial V_2/\partial\rho = \epsilon_3 \partial V_3/\partial\rho, \quad \rho = R_2\,. \tag{4}$$

Here V_α is the electrical potential in phase α; a charge q is at the origin. The potential and the normal component of the electric displacement are continuous across the dielectric phase boundaries. As the system has cylindrical symmetry, $V_\alpha(r)$ is

$$V_\alpha(r) = \frac{2q}{\pi\epsilon_\alpha}\int_0^\infty \mathrm{d}t\,[A_\alpha(t)K_0(t\rho) + B_\alpha(t)I_0(t\rho)]\cos tz \tag{5}$$

where I_0 and K_0 are zeroth order modified Bessel functions of the first and second kind respectively [14]. Of the six coefficients $A_\alpha(t)$ and $B_\alpha(t)$, two are fixed by the behavior of the potential near $r = 0$ and as $\rho \to \infty$. Since $V_1(r) \to q/\epsilon_1 r$ as $r \to 0$ and $V_3(r) \to 0$ as $\rho \to \infty$, A_1 and B_3 are known

$$A_1(t) = 1, \quad B_3(t) = 0.$$

The remaining four functions are found by substituting eq. (5) into eqs. (3) and (4). As the constraints at the dielectric phase boundaries are valid for arbitrary z (the system is infinitely long), the coefficients of $\cos tz$ can be equated in the four equations generated. Solving for $B_1(t)$, which determines the electric potential within the pore, yields

$$B_1(t) = \kappa_1\left\{1 + \frac{\lambda_1\varphi_1^2\kappa_2}{\kappa_1 - \kappa_2(1-\varphi_1)(1-\lambda_1\varphi_1)}\right\}. \tag{7}$$

where

$$\lambda_1 \equiv \epsilon_2/\epsilon_1, \quad \lambda_2 \equiv \epsilon_3/\epsilon_2. \tag{8a}$$

$$\varphi_\alpha(tR_\alpha) = [1 - (1-\lambda_\alpha)tR_\alpha I_0(tR_\alpha)K_1(tR_\alpha)]^{-1}, \tag{8b}$$

$$\kappa_\alpha(tR_\alpha) = (1-\lambda_\alpha)tR_\alpha K_0(tR_\alpha)K_1(tR_\alpha)\varphi_\alpha. \tag{8c}$$

Considerable algebra is needed to obtain the result, eq. (7), with repeated use being made of various properties of Bessel functions [15]

$$I_0'(x) = K_1(x), \quad K_0'(x) = -K_1(x), \quad I_1K_0 + I_0K_1 = 1/x \tag{9}$$

The expression for $B_1(t)$ agrees with Parsegian's result [1,2] in the limits where the pore former is electrostatically invisible, i.e. if it is dielectrically equivalent to the membrane or to the pore or if it is negligibly thick.

Within the channel the electric potential is, from eqs. (5) and (6),

$$V_1(r) = \frac{q}{\epsilon_1}\left\{\frac{1}{r} + \frac{2}{\pi}\int_0^\infty \mathrm{d}t\,B_1(t)I_0(t\rho)\cos tz\right\}. \tag{10}$$

The work required to bring an ion of charge Q and radius σ from the bulk water phase to the center of the channel is thus

$$\delta E = \frac{Q^2}{2}\left\{\frac{1}{\epsilon_1\sigma} - \frac{1}{\epsilon_w\sigma} + \frac{2}{\epsilon_1\pi}\int_0^\infty \mathrm{d}t\,B_1(t)\right\}. \tag{11}$$

As long as the channel interior has the same dielectric constant as water the energy barrier is, after substitution from eq. (6),

$$\delta E = \frac{Q^2}{\pi\epsilon_1 R_1}\int_0^\infty \mathrm{d}y\,\kappa_1(y) \times \left[1 + \frac{\lambda_1\varphi_1^2(y)\kappa_2(\alpha y)}{\kappa_1(y) - \kappa_2(\alpha y)(1-\varphi_1(y))(1-\lambda_1\varphi_1(y))}\right] \tag{12}$$

where $\alpha \equiv R_2/R_1$. The second term within the square brackets accounts for the correction due to the dielectric differences between the channel former and its surroundings.

2.2. *Applications and speculations*

2.2.1. *Gramicidin-A*

The effectiveness of gramicidin as a dielectric shield has been crudely estimated by Levitt [10]. A better appreciation of the effect may be obtained using the expression for δE just calculated. This requires values of the parameters $R_1, R_2, \epsilon_1, \epsilon_2$ and ϵ_3. The structural work of Koeppe, Hodgson and Stryer [3] suggests that the molecule, in its dimeric form, is roughly 1.26 nm in diameter with an axial channel 0.43 nm in diameter. The dielectric constants of water (ϵ_1) and membrane (ϵ_3) are ~80 and ~2 respectively. While the dielectric constant of gramicidin-A is not known, an estimate may be obtained from measurements on the polypeptide $(\text{Gly-Ala})_n$ which is analogous to gramicidin-A in that none of the amino acids comprising the chain has a polar residue. Measurements on $(\text{Gly-Ala})_n$ suggest that an ϵ of 4 is appropriate to crystalline gramicidin-A [16].

Some points must still be considered before these structural and electrical data can be used. The dielectric constant is an average property of the whole molecule. However, gramicidin has a polar interior and non-polar exterior. Thus its dielectric constant should vary along its cross-section, decreasing from interior to exterior. To assess whether significant error is introduced by treating gramicidin as a uniform dielectric the molecule is presumed to be formed of two concentric cylinders. The exterior is electrostatically indistinguishable from membrane hydrocarbon; the dielectric constant of the interior is determined as follows. Assuming the volume fraction of the interior cylinder to be f, the unknown dielectric constant (ϵ_2) may be estimated from the relation

$$\epsilon_2 f + \epsilon_3(1 - f) = \epsilon_{\mathrm{PF}}, \qquad (13)$$

where ϵ_3 is the membrane dielectric constant (~2) and ϵ_{PF} is the dielectric constant of the pore former, in this case ~4. The volume fraction f is fixed by the radii of the various cylindrical regions,

$$f = (R_2^2 - R_1^2)/(R_{\mathrm{PF}}^2 - R_1^2), \qquad (14)$$

where R_1 is the channel radius and R_{PF} the outer radius of the pore former.

The polarization energy for a range of values of R_2 and f is given in table 1. It is clear that the barrier height is insensitive to the choice of f as long as physically reasonable values of R_2 are used. Only when $f \leqslant 0.2$ and ϵ_2 becomes unreasonably large is there any significant dependence of the barrier height on the variation of dielectric properties within the channel former itself. As structural models suggest that the polar region of the molecule is ~0.2 nm thick ($f \sim 0.36$) it is fair to conclude that an *infinitely long* channel with the presumed physical and electrical properties would exhibit an electrostatic barrier of ~46 kJ mol^{-1}.

Table 1
Energy barrier for passage of a monovalent cation through an infinitely long pore with the cross-section of gramicidin-A and a mean dielectric constant of 4 as a function of R_2, ϵ_2 and f (see text)

$\frac{(R_2 - R_1)}{(R_{\mathrm{PF}} - R_1)}$	f	R_2/R_1	ϵ_2	Energy barrier (kJ mol^{-1})
0	0	1.0	"∞"	51.4
0.1	0.056	1.19	37.9	49.4
0.2	0.121	1.39	18.5	47.9
0.3	0.200	1.58	12.2	47.0
0.4	0.282	1.78	9.1	46.3
0.5	0.377	1.97	7.3	46.0
0.6	0.482	2.16	6.2	45.9
0.7	0.597	2.36	5.4	45.9
0.8	0.721	2.55	4.8	46.0
0.9	0.856	2.75	4.3	46.2
1.0	1	2.94	4.0	46.5

The calculated activation energy depends upon the value chosen for ϵ_{PF}. Denoting the barrier height for shielded and unshielded pores as E_s and E_0 respectively, the effect that variation of ϵ_{PF} has on E_s and the shielding energy, $\delta E_s \equiv E_0 - E_s$, is illustrated in table 2. Shielding is more effective as ϵ_{PF} increases, however the rate of increase drops sharply with increasing ϵ_{PF}. A change of ϵ_{PF} from 2 to 4 leads to a 9 kJ mol^{-1} drop in the activation barrier. To obtain a further 9 kJ mol^{-1} decrease would necessitate increasing ϵ_{PF} to ~11. In fact ϵ is not likely to be anywhere near that large for gramicidin since the dielectric studies on polypeptides suggest that ϵ values $\gtrsim 6$ are already associated with molecules containing some amino acids with polar residues [16]. Thus, for an *infinitely long* channel former with cross-section and dielectric constant similar to gramicidin, shielding reduces the energy barrier by ~9 kJ mol^{-1} (~3.6 kT).

The magnitude of the shielding for membranes of

Table 2
Activation (E_s) and shielding (δE_s) energies for monovalent cations in a pore with gramicidin's cross-section as a function of ϵ_{PF} (see text)

ϵ_{PF}	Infinitely long pore		3 nm long pore
	E_s (kJ mol^{-1})	δE_s (kJ mol^{-1})	Bounds on $\delta E_s(L)$ (kJ mol^{-1})
2	55	0	0
3	49.2	5.8	3.5–5.8
4	46.1	8.9	5.4–8.9
5	44.2	10.8	6.6–10.8
6	42.4	12.6	7.6–12.6
8	40.0	15.0	9.1–15.0
10	38.0	17.0	10.3–17.0

finite thickness can be estimated by noting the qualitative effect that variation of the pore former dielectric constant has on the electrostatic energy:

1) the longer the channel the larger the *absolute* change;

2) the longer the channel the smaller the *relative* change.

Denoting the activation energy for shielded and unshielded pores of length L as $E_s(L)$ and $E_0(L)$ respectively, these observations may be formulated as

$$E_0(L) - E_s(L) < E_0(\infty) - E_s(\infty), \qquad (15a)$$

$$E_s(L)/E_0(L) < E_s(\infty)/E_0(\infty). \qquad (15b)$$

An example immediately at hand is a system with the gross structural features of gramicidin: $R_1 = 0.2$ nm, $R_2 = 0.6$ nm; $L = 3$ nm; and $\epsilon_1 = 80$, $\epsilon_3 = 2$. The energies of unshielded ($\epsilon_2 = 2$) and completely shielded ($\epsilon_2 = 80$) pores have been calculated [10,17]. The results are: $E_0(\infty) = 58.9$, $E_s(\infty) = 19.6$, $E_0(L) = 37.1$ and $E_s(L) = 5.4$ with energies in kJ mol^{-1}. Since the shielding energy $\delta E_s(L)$ is $E_0(L) - E_s(L)$, eqs. (15) permit determination of the bounds

$$\delta E_s(\infty)\{E_0(L)/E_0(\infty)\} < \delta E_s(L) < \delta E_s(\infty). \qquad (16)$$

Assuming, in addition to the cross-sectional data given previously, that the gramicidin pore is 3 nm long, the activation barrier in the absence of dielectric shielding is $E_0 = 33.5$ kJ mol^{-1} [10,17]. Limits on $\delta E_s(L)$ can then be calculated from eq. (16), these are included in table 2 for a range of values of ϵ_{PF}. If ϵ is taken to be 4 for gramicidin the shielding energy is in the range 5.4–8.9 kJ mol^{-1}. It is only 30 to 50% as large as Levitt's estimate [10], which is attributable to the uncertainties in his procedure for establishing the location of an effective dielectric phase boundary. Consequentially the conductance is 35 to 150 times smaller than would be deduced on the basis of his assumptions. As pointed out in section 1 the non-diffusional energy barrier is either ~5 or ~14 kJ mol^{-1}, depending upon the estimation procedure used. For dielectric shielding alone to account for such a small electrostatic barrier in gramicidin channels the pore former would have to have an ϵ of at least 15: more than likely an $\epsilon \geqslant 30$ would be needed to effect the necessary energy reduction in a pore of finite length. Given the non-polar nature of the amino acid residues in gramicidin such ϵ values are totally unrealistic.

All the structural features that have been mentioned play a role in reducing the non-diffusional activation energy in the gramicidin channel. The residual barrier, after accounting for finite channel length and dielectric shielding, is still ~25 kJ mol^{-1} which is larger than the conductance data permit. If a Nernst-Planck estimate of conductance is made the result, using eq. (1), is ~0.002 pS in 0.1 M electrolyte, nearly four orders of magnitude smaller than that observed experimentally, ~10 pS. If only activation energies were considered, the calculated G's would be 100 times to small. These discrepancies must reflect features of the gramicidin channel that have been ignored in all attempts to calculate the activation barrier. One feature that might significantly stabilize positive ions in the channel is the carbonyl groups which line the interior pore wall [18]. Since the oxygen atoms head into the channel there are negative surface charges [19] or surface dipoles at the pore-pore former interface. Whether the resulting interaction can quantitatively account for the low energy barrier to cation passage awaits further investigation.

2.2.2. *Potassium channel*

The potassium channel, as deduced from blocking and permeability studies [11], is supposed to contain a long narrow portion of radius ~0.15 nm through which motion is essentially single file [20,21]. The activation energy for channel conductance and aqueous K^+ conductance are essentially the same [9,22], implying that there is no non-diffusional energy barrier. Open state conductance, for 0.1 M K^+ solutions, is in the 1–10 pS range [11,23,24] which is roughly what

Table 3
Range of energy barriers for monovalent ion passage through a pore with structural features similar to those of the potassium channel as a function of L, R_{PF} and ϵ_{PF} (see text)

ϵ_{PF}	Bounds on $E_S(L)$ (kJ mol^{-1})					
	$L = 3$ nm R_{PF} (nm)			$L = 1$ nm R_{PF} (nm)		
	0.5	0.6	0.7	0.5	0.6	0.7
8	33–39	29–37	22–34	4–19	<18	<17
16	23–32	18–29	15–26	<16	<14	<13
24	18–29	12–24	9–22	<14	<12	<11
32	14–26	9–22	5–19	<13	<11	<9

is expected for free diffusion through a narrow channel after friction [25] (the single file property) is taken into account.

A channel such as that described would exhibit an enormous activation barrier to ionic transport if it were uncharged and had a sharp dielectric discontinuity at the pore wall. With these assumptions, the polarization energy calculated by Levitt's method would be 57 kJ mol^{-1} if the pore were 3 nm long; if the narrow part of the pore were only 1 nm long the barrier would still exceed 28 kJ mol^{-1} [10,17]. Such barriers are clearly contradicted by the conductance data. As a result it is presumed that the channel interior is lined with multiple, negatively charged binding sites [13,26].

While dielectric shielding probably can not eliminate the energy barrier completely, it may nonetheless be an important factor, particularly if the channel former has a high dielectric constant. The dielectric properties of the potassium channel are unknown; however measurements of ϵ for polypeptides containing some polar amino acid residues suggest that values of ϵ_{PF} as large as 24 are not ridiculous [16]. To indicate how significant this effect might be, bounds on the residual activation energy, calculated from eq. (15), are given in table 3 for two values of L as a function of ϵ_{PF} and R_{PF}. The values of ϵ_1, ϵ_3 and R_1 are held fixed at 80, 2 and 0.15 nm respectively. The results are quite surprising. While the energy barrier is not eliminated it may be greatly reduced. For a pore former with $\epsilon = 24$ and with an external diameter of 1.2 nm (roughly the dimensions needed for a channel former with a hydrophilic interior and a lipophilic exterior) the activation energy would be between 12–24 kJ mol^{-1} if the narrow segment of the channel were 3 nm long; even if the channel had a minimal external diameter of 1 nm the activation energy would only be 18–29 kJ mol^{-1}. If the narrow part of the channel were short, ~1 nm long, the activation energies would be further reduced: for the thicker pore former <12 kJ mol^{-1}, for the thinner one <14 kJ mol^{-1}. Even if ϵ_{PF} were as small as 8 there would be a substantial reduction in the activation barrier due to dielectric shielding.

The significance of such shielding for channel conductance is great. Using eq. (1), noting that $\lambda_K = 0.0074\ m^2S\ mol^{-1}$ [7], and assuming a pore radius of 0.15 nm, Nernst-Planck estimates of the conductance can be calculated. For 0.1 M electrolyte G, in the absence of dielectric shielding, would be $\sim 4 \times 10^{-9}$ pS and $\sim 10^{-3}$ pS for pores with narrow segments 3 nm and 1 nm long respectively. For a pore former with 1.2 nm external diameter and $\epsilon = 8$, the corresponding G values, when shielding is included, are 10^{-5}–3×10^{-4} pS and >0.07 pS respectively; for $\epsilon = 24$ the bounds are 0.002–0.3 pS and >0.8 pS respectively. Given that open state conductance in the potassium channel is in the 1–10 pS range [11,23,24], it is clear that dielectric shielding, while not eliminating the energy barrier completely, may nonetheless be a crucial determinant of the open state conductance. Better estimates of the importance of the shielding await accurate electrostatic calculations for membranes of finite thickness. One point is already clear. Shielding can drastically reduce the number of negatively charged binding sites needed to stabilize positive ions within the potassium channel.

3. Ions of finite volume

3.1. Solution of the electrostatic problem

The effect that ionic size has on the activation energy can be assessed by consideration of the model illustrated in fig. 2. It is designed to probe the importance of *non-specific* electrical effects, not the consequences of specialized features of channel architecture such as selectivity filters [12,13]. The ion is taken to be a sphere of radius σ and dielectric constant ϵ_0 with a point charge at its center located on the axis of a pore

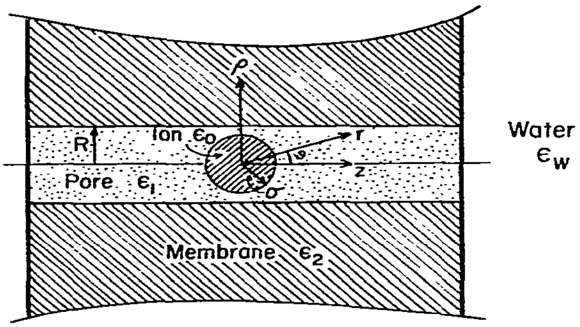

Fig. 2. Cross-section of a cylindrical "pore" of radius R and dielectric constant ϵ_1 in a "membrane" of dielectric constant ϵ_2. A spherical, polarizable ion of radius σ and dielectric constant ϵ_0 is located at the origin. The surrounding water has dielectric constant ϵ_W. The assembly is presumed to be infinite in the z-direction.

of radius R and dielectric constant ϵ_1. The assembly is embedded in surroundings of dielectric constant ϵ_2. Exactly as in section 2, the problem, while exactly soluble in the limit when the channel is infinitely long, is an extreme simplification. It too is constructed to focus upon a single feature of the system, in this case the error introduced by treating the ion as a point charge.

Neglecting the finite thickness of the membrane the electrostatic problem is characterized by the equations [14]

$$\nabla^2 V_0 = -4\pi q\delta(0)/\epsilon_0, \quad \nabla^2 V_1 = 0, \quad \nabla^2 V_2 = 0, \tag{17}$$

$$V_0 = V_1, \quad \epsilon_0 \partial V_0/\partial r = \epsilon_1 \partial V_1/\partial r, \quad r = \sigma, \tag{18}$$

$$V_1 = V_2, \quad \epsilon_1 \partial V_1/\partial \rho = \epsilon_2 \partial V_2/\partial \rho, \quad \rho = R. \tag{19}$$

Because there are boundary constraints on both a spherical and a cylindrical surface, the electrostatic problem is more difficult than that of section 2. In regions 1 and 2 the potential still has the form of eq. (5). Within the sphere an expansion in terms of Legendre polynomials is more useful

$$V_0(r) = \frac{q}{\epsilon_0}\left\{\frac{1}{r} + \sum_{n=0} d_n \left(\frac{r}{\sigma}\right)^{2n} P_{2n}(\cos\theta)\right\}, \tag{20}$$

where P_n is the Legendre polynomial of order n.

Following the procedure outlined in section 2, noting that $B_2(t) = 0$ in order that $V_2(r)$ behave properly as $r \to \infty$, and using the boundary conditions at $\rho = R$, $V_1(r)$ may be simplified to yield

$$V_1(r) = \frac{2q}{\epsilon_1 \pi} \int_0^\infty \mathrm{d}t\, A_1(t) \times [K_0(t\rho) + \kappa(tR) I_0(t\rho)] \cos tz \tag{21}$$

with $\kappa(tR)$ given by eq. (8c) and $\lambda = \epsilon_2/\epsilon_1$. Further progress requires using two expansion theorems relating Bessel functions and Legendre polynomials [14]

$$I_0(t\rho)\cos tz = \sum_{n=0} \frac{(-)^n (tr)^{2n}}{(2n)!} P_{2n}(\cos\theta), \tag{22a}$$

$$\frac{2}{\pi}\int_0^\infty \mathrm{d}t\, t^{2n} K_0(t\rho)\cos tz = \frac{(-)^n (2n)! P_{2n}(\cos\theta)}{r^{2n+1}}. \tag{22b}$$

Expanding $A_1(t)$ in powers of t,

$$A_1(t) \equiv \sum_{n=0} a_n (\sigma t)^{2n}/(2n)! \tag{23}$$

combining eqs. (18) and (20)–(23) yields, after equating coefficients of $P_{2n}(\cos\theta)$, a set of simultaneous equations to be solved for a_n and d_n,

$$\frac{\delta_{n,0}}{\sigma} + d_n = \frac{(-)^n \epsilon_0}{\epsilon_1}\left\{\frac{a_n}{\sigma} + \frac{\gamma^{2n}}{(2n)! R}\sum_{m=0} \frac{\beta_{n+m}\gamma^{2m} a_m}{(2m)!}\right\} \tag{24a}$$

$$-\frac{\delta_{n,0}}{\sigma} + 2n d_n = (-)^n \left\{-\frac{(2n+1)}{\sigma} a_n + \frac{2n\gamma^{2n}}{(2n)! R}\sum_{m=0} \frac{\beta_{n+m}\gamma^{2m} a_m}{(2m)!}\right\} \tag{24b}$$

where $\gamma \equiv \sigma/R$ and

$$\beta_j \equiv \frac{2}{\pi}\int_0^\infty \mathrm{d}t\, t^{2j} \kappa(t). \tag{25}$$

The equations for $n = 0$ are simple

$$a_0 = 1,$$

$$\frac{1}{\sigma} + d_0 = \frac{\epsilon_0}{\epsilon_1}\left\{\frac{1}{\sigma} + \frac{1}{R}\left[\beta_0 + \sum_{m=1} \frac{\gamma^{2m}\beta_m a_m}{(2m)!}\right]\right\}; \tag{26}$$

from eq. (20) it is clear that the second of these is proportional to the mean electrostatic potential at the surface of the ion and thereby establishes the polarization energy. To complete the solution requires determining the a_m. Eliminating d_n in eqs. (24) leads, after substantial rearrangement, to the result

$$\left\{1+\frac{1+\mu}{4n}\right\}a_n-\gamma\mu\sum_{m=1}\frac{\tau_{m+n}a_m}{(2m)!(2n)!}=\frac{\gamma\mu\tau_n}{(2n)!},\qquad(27a)$$

$$\mu\equiv\frac{\epsilon_1-\epsilon_0}{\epsilon_0+\epsilon_1},\qquad\tau_n\equiv\gamma^{2n}\beta_n.\qquad(27b)$$

These expressions may be written more compactly in matrix form

$$\boldsymbol{\Lambda}\cdot\boldsymbol{A}=-\gamma\mu\,\boldsymbol{T}\quad\text{or}\quad\boldsymbol{A}=\gamma\mu\,\boldsymbol{\Lambda}^{-1}\cdot\boldsymbol{T}\qquad(28)$$

where

$$\Lambda_{n,m}=\left\{1+\frac{1+\mu}{4n}\right\}\delta_{m,n}-\frac{\gamma\mu\tau_{m+n}}{(2m)!(2n)!}\qquad(29a)$$

$$A_n=a_n,\qquad T_n=\tau_n/(2n)!.\qquad(29b)$$

The mean potential at the surface of the ion is then, from eqs. (20) and (26)–(29)

$$\overline{V}(\sigma)=\frac{q}{\epsilon_1}\left\{\frac{1}{\sigma}+\frac{\tau_0}{R}+\frac{\Delta}{R}\right\},\qquad\Delta=\gamma\mu\,\boldsymbol{T}\cdot\boldsymbol{\Lambda}^{-1}\cdot\boldsymbol{T}\qquad(30)$$

and the work required to bring an ion of charge Q from bulk water to the channel center is

$$\delta E=\frac{Q^2}{2}\left\{\frac{1}{\epsilon_1\sigma}-\frac{1}{\epsilon_w\sigma}+\frac{\tau_0}{\epsilon_1 R}+\frac{\Delta}{\epsilon_1 R}\right\}.\qquad(31)$$

The first three terms in the expression are precisely Parsegian's result [1,2]; the final term accounts for finite ionic size.

A few general observations can be made. Since ions are not very polarizable ϵ_0 is much less than ϵ_1 and μ, from eq. (27b), is positive. As a result ionic size effects *increase* the electrostatic barrier. However, unless σ is comparable to R, the effect is very small. The leading term in the size correction factor is, from eqs. (27)–(31),

$$\frac{Q^2}{2\epsilon_1 R}\left(\frac{\mu}{5+\mu}\right)\gamma^5\beta_1^2.\qquad(32)$$

Assuming that $\epsilon_1 = 80$ and $\epsilon_2 = 2$, $\beta_1 = 1.23$. Under these circumstances the size correction is only 0.06% of the point ion term, $Q^2\beta_0/2\epsilon_1 R$, when the ionic radius is half the pore radius.

3.2. Applications

In order to evaluate the size correction term estimates of ion dielectric constant are required. Since the outer electrons of monovalent cations form a closed shell (rare gas structure), they are tightly bound and, as a consequence, not very polarizable. While the electric field induced when the ion is within the pore alters the electronic structure of the ion, the effect is not likely to be large. Were the ions macroscopic, the magnitude of the change would be measured by knowing the ionic dielectric constant, ϵ_0. While not strictly applicable since the system of interest is microscopic, the Clausius-Mosotti equation [27] should provide an estimate of ϵ_0

$$\epsilon_0=(1+2\xi)/(1-\xi),\qquad\xi=4\pi\alpha/3v=\alpha/\sigma^3;\qquad(33)$$

here α and v are ionic polarizability and volume respectively. Values of α, σ and ϵ_0 for monovalent cations are given in table 4. The values of ϵ_0 are admittedly uncertain; however this ambiguity, as will be apparent, is of little physical consequence.

The size correction factor in eq. (31) can now be computed. The only problem is that the calculation requires inversion of the infinite order matrix $\boldsymbol{\Lambda}$. However, this difficulty is circumvented for all $\gamma < 1$ by successive approximations; $\boldsymbol{\Lambda}$ is truncated and only the $M \times M$ upper left hand block of the matrix inverted. For a given value of γ, M is increased by unit steps until the correction term Δ changes by less than 0.01% at a step. The results are illustrated in fig. 3 as a function of γ and of the dielectric ratio ϵ_1/ϵ_0. For

Table 4
Polarizability [a], radius [b] and dielectric constant for monovalent cations

Ion	α (10^{-3} nm^3)	σ (nm)	ϵ
Li^+	0.025–0.031	0.06	1.4–1.5
Na^+	0.17–0.196	0.095	1.7–1.9
K^+	0.8–0.88	0.133	2.5–2.8
Rb^+	1.4–1.56	0.148	3.3–3.8
Cs^+	2.35–2.56	0.169	3.8–4.4

[a] Data from Landolt-Börnstein [28].
[b] Data from Pauling [29].

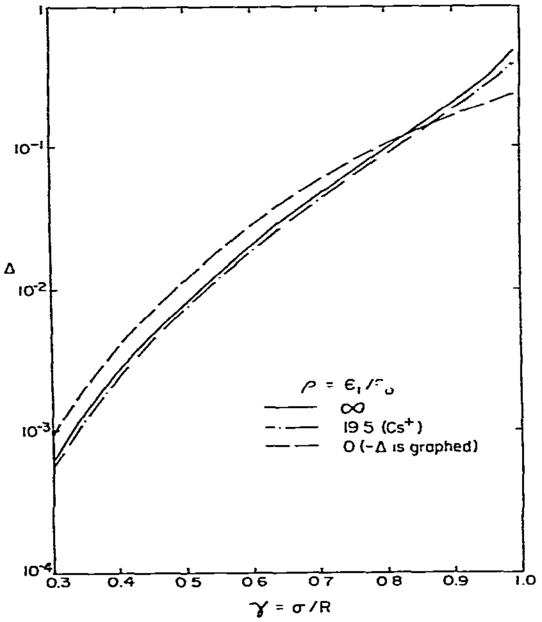

Fig. 3. Shift in polarization energy, Δ (in units of $Q^2/2\epsilon_1 R$), as a function of ionic size ratio, $\gamma = \sigma/R$, and dielectric ratio ϵ_1/ϵ_0. The dielectric constants of the pore interior and the membrane are assumed to be 80 and 2 respectively. In these units the polarization energy of a point ion is 13.56.

fixed γ the correction is largest when $\epsilon_1/\epsilon_0 \to \infty$; however the effect of varying the dielectric ratio is negligible for plausible values of the dielectric ratio. Thus uncertainties in the estimates of the ion dielectric constants introduce insignificant errors.

Only when $\gamma \gtrsim 0.8$ does the finite volume of the ion alter the activation barrier by more than 1%. Consider an extreme case: a Cs^+ ion in a pore with gramicidin's interior diameter. The corresponding value of γ is 0.79. From fig. 3 the correction function Δ is no greater than 0.09. The energy barrier is increased by ~0.35 kJ mol^{-1}, which is both negligible and an upper bound to the change that would be expected in a pore of finite length. Another case for which γ is large is for a K^+ ion in a pore with the potassium channel's interior diameter. Here $\gamma = 0.89$, Δ is less than 0.2 and the change in the energy barrier ~1.2 kJ mol^{-1}. Again the correction is negligible.

The conclusions are both gratifying and self-evident. Within the context of continuum electrostatics the activation energy is insensitive to a description of an ion in a pore as a point charge instead of as a polarizable sphere of finite volume. The approximations implicit in a continuum model pose far more serious limitations than the point charge approximation. Unless one intends to incorporate effects due to the detailed molecular structure of both the pore former and the solvent within the pore, there is no reason to abandon the point charge model for the ion.

4. Recapitulation

Continuum electrostatics has been used to study two features of the ion-pore former-membrane-solvent system that might significantly alter the activation energy for passage of an ion through a pore.

The pore former has been treated as a cylindrical sheath of dielectric constant intermediate between that of water and of lipid. Using reasonable estimates of the structural and dielectric properties of gramicidin, it was found that dielectric shielding by the gramicidin molecule itself reduces the energy barrier to ion passage far *less* than has been previously supposed. From the analysis of section 2, the non-diffusional energy barrier for a pore with gramicidin's gross physical and dielectric properties is ~10–11 kT not ~7.5 kT as has been suggested previously [10]. Since conductance measurements indicate that the non-diffusional energy barrier in the gramicidin channel is no more than 5.6 kT [8], the physico-electric model of the pore is still inadequate. Possibly ionic interaction with the negatively charged interior wall of the pore can account for the additional stabilization energy.

Consideration of a pore former with the dimensions of the potassium channel suggests that, given favorable circumstances, dielectric shielding by the channel forming molecule itself might significantly reduce the energy barrier to ion passage. Since polypeptides formed from amino acids with polar residues can have dielectric constants as high as 24 [16], it is possible that dielectric shielding by the pore forming molecule can reduce the activation energy by more than a factor of two. Given favorable, but still plausible, structural parameters for the potassium channel the barrier may be no more than ~5 kT for passage of a single ion. While not eliminating the barrier completely, dielectric shielding might, in this case, reduce it dramatically.

In addition, the energetic consequences of treating ions as point charges rather than as polarizable spheres of finite volume have been considered. Within the continuum model the conclusions are unambiguous. No error of importance is introduced by making the point charge approximation, even if the ionic radius is 95% of the pore radius. The maximum energy change, for a K^+ ion in a potassium channel, corresponds to ~0.5 kT. Given the approximations inherent to the continuum picture, this energy shift is totally insignificant.

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