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Electrostatic modeling of ion pores

Multipolar sources

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We present calculations of the polarization energy required when a multipolar source enters a transmembrane ion channel. The polarization energy for polar, but uncharged, sources is nearly independent of channel length if the length/diameter ratio is greater than 1.25; however, it is strongly dependent on channel radius. All significant changes in the polarization energy occur within a distance of ±one channel radius of the entrance to the channel. Our calculational method also provides a means of estimating the change in polarization energy that occurs when an ion is not located axially; this contribution can be significant for smaller ions, for which the binding sites may be far from the axis.

1. Introduction

The aqueous channels which span lipid membranes form a primary pathway for regulated membrane transport. Among the features which significantly affect their permeation properties are the electrostatic interactions due to the proximity of the slightly polarizable lipid to the highly polarizable aqueous pore. Electrostatic calculations of the polarization energy of an ion in a transmembrane channel have been presented for a number of highly idealized models [1–5]. Parsegian [1] considered an infinitely long cylindrical pore containing a highly polarizable dielectric, embedded in low dielectric constant surroundings. Levitt [2], recognizing that the length/diameter ratio in the narrow portion of physiological channels is far from infinite (in fact it is rarely greater than 6 or 7), analyzed right circular cylindrical pores spanning membranes of finite thickness; not unexpectedly, the polarization energy for an ion in such a pore was significantly less than that for an ion in an infinite pore. Jordan [3–5] has developed methods of studying more general pore geometries and shown that vestibule geometry can significantly affect the polarization energy [4,5].

The water molecules which form the polarizable fluid of the pore interior are also influenced by the presence of the low dielectric constant lipid. While the energies associated with the entry of a multipolar molecule into the channel are far smaller than those associated with ion entry, the polarization energy profile turns out to exhibit qualitatively interesting differences from that of an ionic source. The same calculational approach can be used to answer another question: how rapidly does the polarization energy of an ion increase as it moves away from the channel axis?

A complete electrostatic treatment of the water molecules in the simplest model channel, a right circular cylinder, would require the study of a three-dielectric model, such as illustrated in fig. 1. The membrane is a low dielectric constant domain

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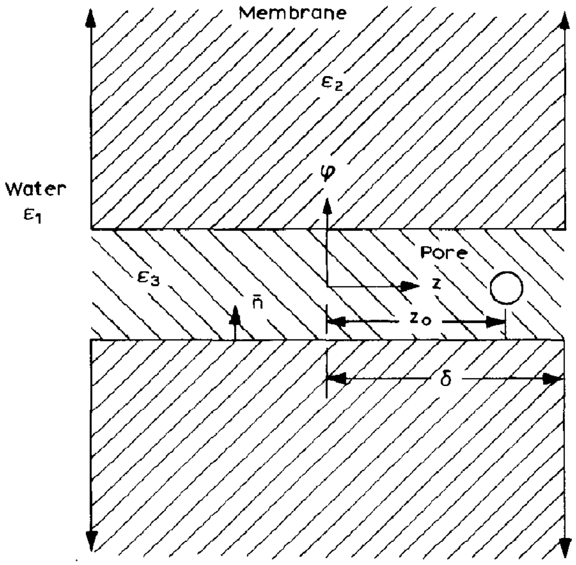

Fig. 1. Cross-section of a cylindrical pore, of length/diameter ratio δ, piercing a membrane slab of dielectric constant ϵ_2. The aqueous electrolyte and the pore interior may have different dielectric properties. Distances are scaled in terms of the pore radius, a_0. A general multipolar point source is located at z_0.

($\epsilon_2 = 2$); the bathing electrolyte is a high dielectric constant region ($\epsilon_1 = 80$). Electrostatic interaction of the polarizable molecules within the pore should be treated exactly in which case the dielectric constant (ϵ_3) in this region would be unity. Rather than pursue such a complex analysis, we have studied a much simpler model which singles out one of the water molecules within the pore. The others are assumed to form a continuum dielectric with $\epsilon_3 = 80$. In this fashion we can simulate the way in which polarization forces influence the solvent within the pore without greatly increasing the complexity of the problem.

In the following discussion the unique water molecule is described as a sphere in which are embedded a point dipole and a point quadrupole. The moments are those determined experimentally [6] or from quantum-mechanical calculation [7].

2. Theory

2.1. Computational method

The computational method is an extension of the replacement charge density approach described previously [3]. However, some considerable care is required because the sources of interest are no longer axial point charges; rather, we are treating more general electrical sources (such as dipoles and quadrupoles) as well as sources which are not on the pore axis. The fundamental equations are the extensions of eqs. I.1 and I.2. *

$$\sigma(\boldsymbol{r}) = g\boldsymbol{n}\cdot[\nabla\phi(\boldsymbol{r})] \qquad 2\pi g = (\epsilon_1 - \epsilon_2)/(\epsilon_1 + \epsilon_2) \tag{1}$$

$$\phi(\boldsymbol{r}) = V_0(\boldsymbol{r},\boldsymbol{r}_0) + \int \mathrm{d}S\sigma(\boldsymbol{r}')/|\boldsymbol{r}-\boldsymbol{r}'| \tag{2}$$

We continue to use dimensionless coordinates in which length is measured in units of the pore radius, a_0, charge in units of electronic charge, e_0, and energy in units of $e_0^2/(a_0\epsilon_1)$. The model system geometry is a right circular cylindrical pore within a planar membrane and $\boldsymbol{n}$ is the outward pointing normal along the dividing surface between the electrical phases. The coulombic source $1/|\boldsymbol{r} - z_0\boldsymbol{k}|$ of eq. I.2 has been generalized to treat higher multipoles; it is replaced by the Fourier expansion

$$V_0(\boldsymbol{r},\boldsymbol{r}_0) = \sum_{n=0} [W_n(\rho,\rho_0,z-z_0) \times \cos n\nu + U_n(\rho,\rho_0,z-z_0) \sin n\nu] \tag{3}$$

where the source is located at $\boldsymbol{r}_0$ and the potential is measured at $\boldsymbol{r}$. Cylindrical polar coordinates are used throughout; the vector $\boldsymbol{r}$ has coordinates (ρ,ϕ,z), etc., and the angle ν, between the cylindrical radius vectors ρ and ρ_0, is $\phi - \phi_0$. For the problems being studied, only terms with $n \leq 2$ are needed. The electrical potential, ϕ, and the replacement surface charge densities, σ, can be ex-

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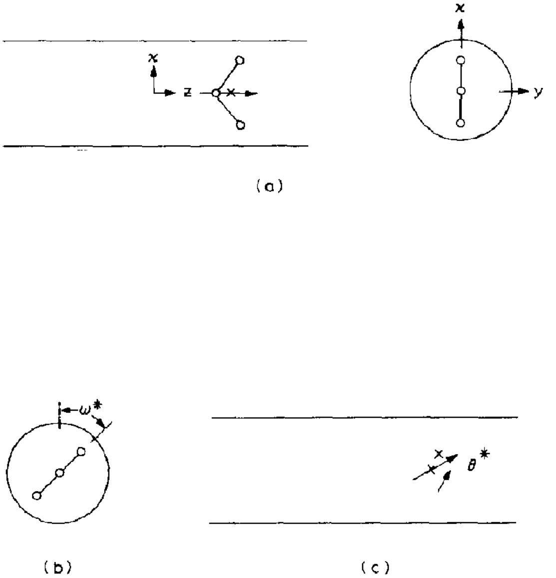
* This notation refers to eqs. 1 and 2 of ref. 3; it will be used throughout the remainder of this paper.

panded in similar Fourier series. An analogue to Eq. I.4 can be generated for each coefficient in the Fourier series. The F_i are determined from either the z or ρ derivative of the particular source term W_n or U_n, evaluated at the membrane water interface (for $i = 1$) or on the cylindrical surface of the pore (for $i = 2$). The K_i of eq. I.5 are also functions of the order of the Fourier term being treated. They can be constructed from the z and ρ derivatives of the following quantities:

$$\begin{aligned} M_0(a,b,c) &= 4K(k)/S, \quad n=0 \\ M_1(a,b,c) &= 2S[K(k) - E(k)]/b/c \\ &\quad -4K(k)/S, \quad n=1 \\ M_2(a,b,c) &= -M_0(a,b,c)/3 + 4(2/k^2 - 1) \\ &\quad \times M_1(a,b,c)/3, \quad n=2 \end{aligned} \tag{4}$$

where $a = \rho$, $b = \rho'$, and $c = z - z'$, S is given by eq. I.6b and $k = \sin \alpha$. The vector $\boldsymbol{r}'$ is the location of a point on the dielectric interface. The quantities $K(k)$ and $E(k)$ are complete elliptic integrals of the first and second kind, respectively [8].



(a)

(b)

(c)

Fig. 2. Rotations which define the orientation of the water quadrupole in terms of a space-fixed axis system. The water molecule, originally located in the x-z plane (a), is rotated by ω^* about the z-axis (b); the symmetry axis is then rotated by θ^* about the x-axis (c). These are two of the Euler angles; they are sufficient to define the angular position of the molecule, but are not adequate for describing kinematics.

Our major interest is the intrinsically multipolar source generated by a molecule of water. The determination of the source potential V_o is fairly complex, even if the source is located axially. The orientation of a water molecule with respect to a fixed axis system is defined by two angles θ^* and ω^*, as illustrated in fig. 2; θ^* is the angle between the permanent dipole moment of the molecule and the z-axis and ω^* the angular location of the symmetry axis of the molecule. These are two of the Euler angles defining molecular orientation (in terms of the definitions given by Goldstein [9], θ^* is θ and ω^* is ϕ). The dipole source potential is then

$$\mu[\rho \cos \phi \sin \theta^* - (z - z_o) \cos \theta^*]/D^3. \tag{5}$$

where μ is the dipole moment of the water molecule and D is given by

$$D = \sqrt{[\rho^2 + (z - z_o)^2]} \tag{6}$$

Comparing this expression to eq. 3 indicates that an axial dipole contributes to two terms of the Fourier expansion, W_0 and W_1; these can be expressed in the form $W_i = f_i(\mu,\theta^*) \cdot G_i(\rho, z - z_o)$ where the $\boldsymbol{r}$-dependent terms are

$$G_0 = (z - z_o)/D^3, \quad G_1 = \rho/D^3 \tag{7}$$

The quadrupole potential due to a source located at z_o on the channel axis at a test location $\boldsymbol{r}$ is most conveniently evaluated by first transforming to a body-fixed coordinate system, r''. In such a system the quadrupole moment tensor is diagonal with zero trace. Denoting the xx and yy components of the tensor as a and b, respectively, the quadrupole potential * is

$$\begin{aligned} &\left[a(3x''^2 - r''^2) + b(3y''^2 - r''^2)\right. \\ &\quad \left. -(a+b)(3z''^2 - r''^2)\right]/3r''^5 \end{aligned} \tag{8}$$

The components of $\boldsymbol{r}''$ can be expressed in terms

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* This definition ensures consistency with the quadrupole moment convention used by Neumann and Moskowitz [7].

of space-fixed coordinates by sequential rotations of the vector $\boldsymbol{r} - z_o\boldsymbol{k}$, separating the test point $\boldsymbol{r}$ from the location of the axial source, z_o,

$$\boldsymbol{r}'' = R_z(-\omega^*) \cdot R_y(-\theta^*) \cdot (\boldsymbol{r} - z_o\boldsymbol{k}) \tag{9}$$

here R_y and R_z are rotation matrices about the y- and z-axes, respectively. Using this prescription yields, after lengthy algebra, a five-term expression for the quadrupole potential. While there are five terms which contribute to eq. 3, there are only three distinctly different functions of $\boldsymbol{r}$. The coefficients W_i and U_i can be written in the form $W_i = g_{w,i}(a,b,\theta^*,\omega^*) \cdot H_i(\rho, z - z_o)$, with a similar expression for U_i; the independent spatial functions are simply

$$H_0 = \left[3(z - z_o)^2 - D^2\right]/D^5,$$
$$H_1 = 3\rho(z - z_o)/D^5, \quad H_2 = 3\rho^2/D^5 \tag{10}$$

with D as defined in eq. 6.

The problem of an ion displaced from the axis is much more readily analyzed. If the ion is located at the point $\boldsymbol{r}_o$, the terms (of order n ≤ 2) contributing to the multipole expansion of V_o are

$$1/D + \rho\rho_o \cos \nu/D^3$$
$$-\rho_o^2(1/D^3 - 3\rho^2 \cos^2\nu/D^5)/2 \tag{11}$$

where D is defined in eq. 6. Using these expressions the source terms W_0, W_1 and W_2 can be generated using the definition implicit in eq. 3. In addition to the axial coulombic term, W_0 contains a contribution from H_0 and W_1 and W_2 are proportional to G_1 and H_2, respectively; the functions G_i and H_i are defined in eqs. 7 and 10.

Using the functions just defined, it is comparatively straightforward to solve the fundamental integral equations of the replacement charge density approach (eqs. 1 and 2). It is of significance that the corner singularities described in ref. 3 are a function only of the model geometry and the dielectric dissimilarity of the two phases. The kernels generated from the M_i of eq. 4 all have the same singularities at the entrance to the pore. Thus, the methods described previously [3] can be used without modification to solve for the replacement charge density functions σ which determine the potential from each of the multipolar sources.

2.2. The polarization energy

The quantity of major interest is the polarization energy. For multipolar sources, this can be written as

$$\delta E = [q\delta V + \boldsymbol{\mu} \cdot \nabla\delta V + \boldsymbol{Q} : \nabla\nabla\delta V]/2 \tag{12}$$

where q, $\boldsymbol{\mu}$ and $\boldsymbol{Q}$ are, respectively, the charge, dipole moment vector and quadrupole moment tensor of the source; δV is the change in the electrical potential due to polarization, determined at the position of the source, in this case z_o. For water, the problem of specific interest to us, eq. 12 can be expressed as a sum of five terms,

$$\delta E = \sum_{n=1}^{2} \sum_{m=0}^{2} \{P_{n,m}(\theta^*,\omega^*) \cdot \delta E(n,m)\}/2 \tag{13a}$$

$$\delta E(n,m) \equiv \partial^n \delta V_{n,m}/\partial\rho^m \, \partial z^{n-m} \tag{13b}$$

where $\delta V_{n,m}$ are the polarization potentials due to the sources G_i and H_i for $n = 1$ and 2, respectively. The derivatives are evaluated at $z = z_o$ and $\rho = 0$. The functions $P_{n,m}$ are

$$P_{1,0} = (\mu \cos \theta^*)^2, \; P_{1,1} = (\mu \sin \theta^*)^2 \tag{14a}$$

$$\begin{aligned} P_{2,0} = 9\{ & a(\cos^2\theta^* - \sin^2\theta^* \cos^2\omega^*) \\ & + b(\cos^2\theta^* - \sin^2\theta^* \sin^2\omega^*)\}^2/4 \\ P_{2,1} = \{ & [a + 2b + (a - b) \cos^2\omega^*] \sin^2\theta^*\}^2 \\ & + \{(a - b) \sin \theta^* \sin^2\omega^2\}^2 \\ P_{2,2} = \{ & [(a - b)(\cos^2\theta^* \cos^2\omega^* - \sin^2\omega^*) \\ & - (a + 2b) \sin^2\theta^*]^2 \\ & + [(a - b) \cos \theta^* \sin^2\omega^*]^2\}/2 \end{aligned} \tag{14b}$$

2.3. The infinite channel

The polarization potential due to any multipolar source on the axis of a cylindrical channel can be expressed analytically by an extension of standard methods [1,10]. The polarization energy is then evaluated by calculating the derivatives which appear in eq. 13; in this case $z_o = 0$. The results are exceptionally simple for the sources defined by eqs. 7 and 10 (both n and $m \leq 2$),

$$\delta E(n,m) = (2/\pi)\int_0^\infty \left[B_n(t)(t^2/2)^m\right] \qquad (15a)$$

$$B_n(t) = (1-\lambda)Q_n K_n/\left[1-(1-\lambda)Q_n I_n\right],$$

$$\lambda \equiv \epsilon_2/\epsilon_1. \qquad (15b)$$

$$Q_n \equiv nK_n + tK_{n-1} \qquad (15c)$$

where I_n and K_n are modified Bessel functions of the first and second kind, respectively [8].

3. Results and discussion

3.1. General features

The major results of this study are summarized in figs. 3 and 4; all calculations presume a dielectric ratio (ϵ_1/ϵ_2) of 40. Fig. 3 illustrates the effect that changes in the length/diameter ratio, δ, have on the various terms that contribute to the energy of a multipolar source in the pore. Unlike the case of an ionic source, where the polarization energy increases quite slowly with δ, the various multipolar contributions approach their limiting values very rapidly. Only in the case of $\delta E(1,0)$, the term arising from a dipolar source oriented parallel to the channel axis, is there any significant δ dependence. Even here it is small in comparison to that exhibited by an ionic source. When $\delta = 5$, the polarization energy is 90% of that in an infinite channel. For an ionic source the 90% value is not reached until $\delta = 20$; when $\delta = 5$, the ionic polarization energy is only half the value for an ion in an infinite channel. All other terms in the multipole expansion of the polarization energy are essentially indistinguishable from the values they would have were the channel infinite, even for a δ ratio as small as 1.25. Should contributions to the polarization energy from higher multipoles ever be required, they can obviously be accurately estimated using the analytic results (eq. 15) derived for a channel for which $\delta = \infty$.

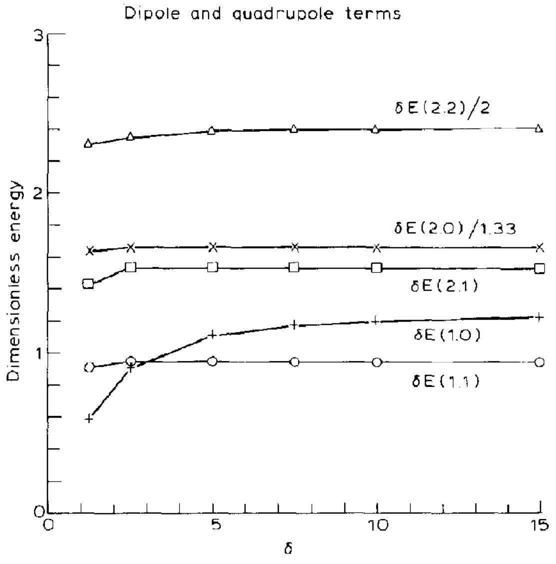

Fig. 3. Polarization energy, in dimensionless units ($e^2/2\epsilon_1 a_0$), for different multipolar sources located at the center of a cylindrical channel of length/diameter ratio δ. The dielectric ratio, ϵ_1/ϵ_2, is 40. The quantities $\delta E(n,m)$ are defined by eq. 13b. For convenience $\delta E(2,2)$ and $\delta E(2,0)$ have been scaled as indicated.

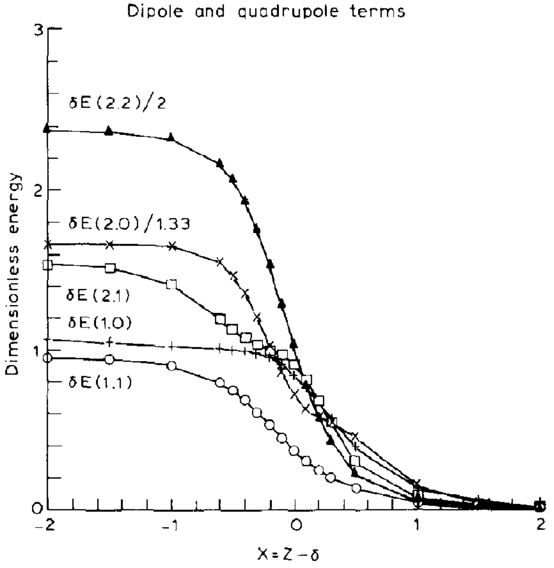

Fig. 4. Polarization energy, in dimensionless units ($e^2/2\epsilon_1 a_0$), for different multipolar sources located near the mouth of a cylindrical channel of length/diameter ratio $\delta = 5$. The distance, x, is measured from the entrance of the channel and is scaled in units of a_0. The dielectric ratio is 40; the quantities $\delta E(n,m)$ are defined by eq. 13b. Both $\delta E(2,2)$ and $\delta E(2,0)$ have been scaled as in fig. 3.

The physical implications of this unusual δ dependence are that, for channels of the same radius, the polarization energy of an uncharged source is insignificantly dependent upon the length of the channel. However, the energies are highly dependent upon channel radius because the reduced dipole moment and the reduced quadrupole moments are proportional to a_0^{-1} and a_0^{-2} respectively. As a consequence, the dipolar energy is proportional to a_0^{-3} and the quadrupolar energy proportional to a_0^{-5}.

The other interesting feature of the multipole contributions is their rapid saturation as the source enters the channel, illustrated in fig. 4. Whatever changes occur in the quantities $\delta E(n,m)$ take place within distances of $\pm a_0$ of the pore mouth. Further from the mouth, the dielectric discontinuity has no influence. Deeper into the channel polarization is essentially complete. Even $\delta E(1,0)$, the contribution from a dipolar source oriented parallel to the channel axis, exhibits this behavior; in this case the saturation limit depends slightly on δ.

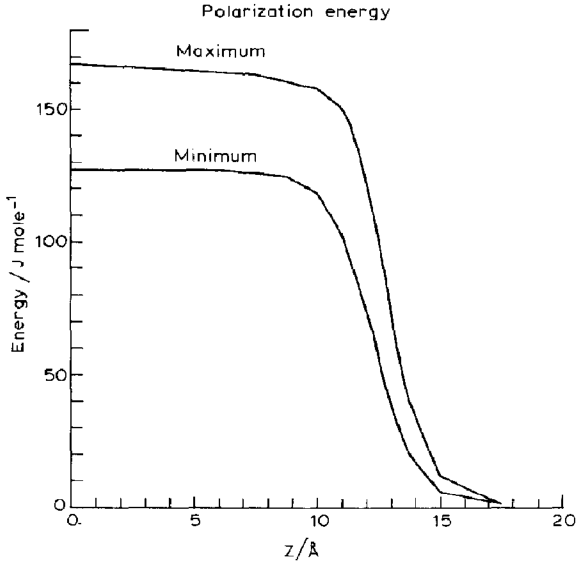

Fig. 5. Maximum and minimum polarization energy for a water molecule located on the axis of a gramicidin-like channel (length 25 Å electrical radius 2.5 Å). Distance is measured from the channel midpoint. Both energies are essentially constant until a molecule is within 2.5 Å of the channel mouth.

3.2. The polarization energy of a water molecule

Fig. 5 illustrates the effect of position on the maximum and minimum in the polarization energy for a single water molecule on the channel axis. This calculation assumes that the other water molecules within the pore form a uniform dielectric with $\epsilon_3 = 80$. The parameters are chosen to be representative of a fairly narrow channel, gramicidin; L = 25 Å [11], $a_0 = 2.5$ Å * and $\delta = 5$. The dipole moment of water is 1.855 Debye [6] and its quadrupole moments are $a = Q_{x,x} = -2.422$ Debye Å and $b = Q_{y,y} = 2.5030$ Debye Å [7]. The mean effect of polarization by the surrounding lipid is quite small; away from the mouth of the channel, the difference in polarization energy between the dielectrically most favorable orientation (a water molecule with its dipole perpendicular to the channel axis and the plane of the molecule at 45° to the channel axis) and the dielectrically least favorable orientation (a water molecule with its dipole oriented axially) is approx. 50 J. Even if the dipole moment is representative of water in the condensed phase (≈ 2.25 Debye [13]) the energy difference remains approx. 50 J. Naturally such differences, which are 2% of the thermal energy, have very little influence on water structure in the channel because the direct interaction of neighbouring molecules distinctly favors the axial configuration [14–16]. Assuming a mean water-water separation of 3.0 Å [15,16] and, for internal consistency a pore dielectric constant of 80, there is a 150 J energy difference per water molecule between the axial and perpendicular orientations. The fact that the polarization energy is independent of z_0 is significant. It indicates that, once inside the narrow part of a channel, the water can be described as a uniform dielectric; of course the proper dielectric constant is still unspecified.

It should be pointed out that, because the multipole terms in the polarization energy have third and fifth power dependence on the electrical radius a_0, the polarization energy estimates may be over-

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* As has been pointed out before, a_0 is an 'electrical radius' which, because of the influence of the polar regions of the pore-forming molecule itself, is somewhat larger than the physical radius of the pore, in this case 2.1 Å [12].

estimates. If, as suggested by Levitt [2], a_0 is 3.0 Å, the polarization energy for a water molecule in the channel drops by 50% and the energy differences between extrema is only approx. 20 J, far less than the difference in the direct interaction energy of neighboring dipoles, 150 J per water molecule.

3.3. *Off-axis effects*

The increase in polarization energy when an ion is not located axially can be calculated from eq. 11. The energy is determined by various derivatives of δV, the quantities $\delta E(n,m)$ defined by eq. 13b. Away from the mouth of the channel, these derivatives, as illustrated in figs. 3 and 4, are essentially equal to their values in an infinite channel. As a result, the displacement energy is quite accurately approximated by the infinite channel expression,

$$\delta E(\rho)=\sum_{n=-\infty}^{\infty}\left\{\int_0^{\infty}\left[I_n^2(t\rho)B_n(t)\right]/\pi\right\} - \int_0^{\infty}B_0(t)/\pi \tag{16}$$

where ρ is the axial displacement of the ion. For an aqueous channel (for which $\lambda = 0.025$) the first four terms in this expression are

$$\delta E(\rho)=0.7794\rho^2+0.5969\rho^4+0.5528\rho^6+0.5424\rho^8 \tag{17}$$

As long as the ion does not wander too far from the channel center, the displacement energy is quite small. In gramicidin, molecular dynamics calculations (ref. 15 and P.C. Jordan, unpublished results) suggest that in the channel interior Na^+ never gets further than 1.4 Å from the channel axis; as a result $\rho < 0.56$ and the displacement energy is no greater than 2.25 kJ mol^{-1}, about 10% of the axial contribution [17]. For larger ions the effect is even less important. Only in the case of Li^+, which may bind as far as 2.0 Å from the axis of the channel, is the displacement energy substantial; * it may be as large as 7.9 kJ mol^{-1}, approx. 35% of the axial contribution. Only here is polarization a significant force opposing the tendency of the cation to bind as close as possible to the carbonyl groups of the gramicidin helix.

It is clear that for larger channels the displacement energy may be a more significant fraction of the axial energy since for these systems ρ may approach unity more closely. An example is the acetylcholine receptor channel for which the electrical radius a_0 is approx. 3.5 Å. If gramicidin is a reliable guide, Na^+ might bind as far as 2.5 Å from the axis of the acetylcholine receptor channel in which case $\rho \approx 0.7$. The displacement energy could then be as large as 3 kJ mol^{-1}. A similar estimate for Li^+ yields a value of 12 kJ mol^{-1}, more than half the axial contribution of approx. 20 kJ mol^{-1} [17].

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* Here ρ is so large (0.8) that the four-term expression, eq. 17, is not sufficiently accurate. The additional terms in the series account for about 15% of the total displacement energy and cannot be ignored.

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