Biophysical Chemistry 20 (1984) 157–173
Elsevier

BPC 00874

MODEL CALCULATIONS OF POLARIZATION EFFECTS IN ELASTIC MEMBRANE CHANNELS

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Received 15th July 1983
Revised manuscript received 15th February 1984
Accepted 2nd March 1984

Key words: Polarization; Membrane channel; Model calculation; Ion-channel interaction

Molecular channels embedded in biological membranes are extremely well balanced systems, because the dielectric barrier imposed on an ion's self-energy, which would make the membrane practically impenetrable, is locally cancelled by the interaction of the ion with the channel up to a few kT at room temperature. This purpose can serve only highly specialized systems with a certain ligand configuration and appropriate properties. In this article two different models are tested with respect to their polarization properties and discussed in detail, one for ionic polarization and the other for dipolar polarization. The channel-mediated attractive forces between two ions are also investigated in both cases.

1. Introduction

The interaction of ions with their environment in biological systems is strongly determined by mutual Coulomb forces due to the presence of other charges and by the polarization of neutral particles. The potential energy of a single ion can be expressed in terms of its self-energy in the presence of a given charge distribution and of the polarizability of the environment which may vary rather drastically. A typical system usually consists of different regions of aqueous solutions specified by different concentrations of different ion species and of other particles, separated by membranes which are rather impermeable for charged particles. On the other hand, a selective and more or less steady transport of particles across the membranes takes place, maintaining the necessary communication between different regions throughout the system. The transport of ions across the membranes may be mediated by 'carrier' molecules and 'pores', which offer an energetically favourable passage for the respective ions. Whereas the self-energy of an ion would increase significantly upon entering a lipid bilayer membrane coming from the aqueous phase and thus prevent the crossing of the membrane, a molecular channel, e.g., gramicidin A, is expected to modify the ion's self-energy only slightly. This behaviour requires certain polarization properties which are the subject of investigation in this article.

In principle one must distinguish contributions to the self-energy of a single ion from the charge distribution of the system, and from electronic, ionic, and dipolar polarizations. Whereas the Coulomb forces are additive, the forces exerted on the ion due to the polarization of elements of the inhomogeneous environment by the ion are not. Using a macroscopic description with the aid of the spatially varying dielectric constant $\epsilon(\vec{r})$, the self-energy can be expressed by means of the corresponding Green's function $G(\vec{r}, \vec{r}')$ for the system, which is a solution of the differential equation:

$$\nabla\epsilon(\vec{r})\,\nabla G(\vec{r},\vec{r}') + \epsilon(\vec{r})\,\nabla^2 G(\vec{r},\vec{r}') = -4\pi\delta(\vec{r}-\vec{r}') \qquad (1)$$

$G(\vec{r}, \vec{r}')$ may also be understood as the solution of an equivalent integro-differential equation

$$G(\vec{r}, \vec{r}') = \frac{1}{\epsilon(\vec{r}')|\vec{r} - \vec{r}'|} + \frac{1}{4\pi} \int \frac{\partial}{\partial \vec{r}''} \epsilon(\vec{r}'') \frac{\partial}{\partial \vec{r}''} G(\vec{r}'', \vec{r}') \times \frac{1}{\epsilon(\vec{r}'')|\vec{r} - \vec{r}''|} d^3\vec{r}'' \quad (2)$$

which clearly demonstrates the non-linearity of the problem. From eq. 2 iterative solutions $G_n(\vec{r}, \vec{r}')$ can be obtained starting with $G_0 = 1/(\epsilon(\vec{r}')|\vec{r} - \vec{r}'|)$. This procedure can be useful for systems with rather smoothly varying ϵ. For systems with discontinuous changes in ϵ there are some elegant methods presented in the modern literature [1,2] yielding the exact Green's functions.

For a given charge distribution $\rho(\vec{r})$ the electrostatic potential $\phi(\vec{r})$ is

$$\phi(\vec{r}) = \int d^3\vec{r}' G(\vec{r}, \vec{r}') \rho(\vec{r}').$$

Hence, the desired self-energy is

$$E_s = \tfrac{1}{2} \int d^3\vec{r} \int d^3\vec{r}' \rho(\vec{r}) G(\vec{r}, \vec{r}') \rho(\vec{r}'). \quad (3)$$

For example, considering an ion as a spherical cavity with radius R, carrying charge q in an infinitely extended dielectric medium, the self-energy is:

$$E_s = \frac{q^2}{2\epsilon R} \quad (4)$$

Neglecting the boundary effects between two different media, the change in self-energy required by the transport of the ion from medium 1 into medium 2 is given by [3,4]:

$$\Delta E_s = \frac{q^2}{2R} \cdot \frac{\epsilon_1 - \epsilon_2}{\epsilon_1 \epsilon_2} \quad (5)$$

where $\epsilon_1 = 80$ for water, $\epsilon_2 = 2$ for the lipid, $R = 1$ Å, and $\Delta E_s > 100\ kT$ at room temperature. The magnitude of this barrier reflects the insulator-like character of a lipid membrane. As presented here, ΔE_s is the difference between the self-energies of the ion in the respective media in an infinite distance from the interface, i.e., image forces have been neglected.

There have been several attempts on the basis of a macroscopic description to incorporate the presence of a membrane pore. Parsegian [5] and Jordan [6] have shown that the barrier height is significantly reduced if a pore is defined as a cylindrical region with a larger ϵ than that of the surrounding membrane. Jordan also gives an estimation for the effect of finite membrane thickness and ion radius/pore radius ratio. He shows that dielectric pores may reduce the barrier height to about 11 kT, where ΔE_s is rather insensitive to a variation of the ion radius. The limitations of the application of continuum electrostatics become very obvious here. Once a pore is defined by some local dielectric properties of the membrane, the only remaining parameter to distinguish different monovalent ion species is their radius. Thus, one cannot expect any selectivity effects from such an approach. This deficiency finds its cause in the suppression of intrinsic degrees of freedom, which a channel possesses due to its molecular structure – if a macroscopic picture is used. The continuum approach is only justified if the distance between the ion and the constituent parts of the medium is large compared to the average separation among the constituents.

Another detailed investigation on the basis of the continuum approach has been carried out by Levitt [7]. His results are in general agreement with the findings of other authors, however, due to the lack of intrinsic degrees of freedom in his channel model he cannot find an attractive interaction of two ions in a channel, as discussed section 3.

However, with respect to the ion in a molecular channel the situation is clearly reversed. Here the continuum approach must be replaced by a microscopic description in which polarization appears due to separated distinct charges individually 'seen' by the ion. Consequently, electronic polarization is ruled out. Its contributions from the channel are in principle not different from those of the rest of the background, the electronic polarization of the lipid membrane. Therefore, one has to take into account ionic and dipolar polarization effects. An appropriate model of the system can be obtained if, for example, a distribution of elastically bound charges representing the non-electronic polarizable

part of the channel is embedded in the membrane, which in turn is described by the macroscopic quantity ϵ.

A proper description must also include the concept of image forces. So far only the interaction of a single ion with its dielectric environment has found attention in the relevant literature. However, if the channel is represented by an assembly of charges within the membrane then there are image charges of both the channel and the ion which interact mutually and contribute to the self-energy of the ion. Moreover, one wants to avoid divergence of the self-energy at the membrane/water interfaces, which requires the proper treatment of an ionic sphere penetrating the interface. A solution of this mathematically non-trivial problem has not yet been given. Nevertheless, if the intrinsic properties of a molecular channel are known, it is a standard procedure to evaluate the Green's function of the dielectric system and to incorporate the channel by virtue of its charge distribution. The choice of an appropriate channel model depends on its effectiveness in lowering the dielectric energy barrier and the ability to act selectively upon different ion species.

Another important criterion is the behaviour with respect to the presence of two ions in the channel. Strong experimental evidence [8,9] indicates the appearance of non-linear effects as to be expected from the simultaneous polarization of the channel by two ions. Also of considerable interest are effects of divalent ions, e.g., Ca^{2+}, as described by Urry [10]. In sections 2 and 3 these properties are discussed for two different channel models, based on ionic and dipolar polarization, respectively. The general problem which includes the effect of the channel on the ion in the dielectric medium will be the subject of a future communication.

2. Channel model with ionic polarization

Ionic polarization of a molecule is caused by elastic deformation of the ionic skeleton due to an external field. In the absence of any perturbation the constituent atoms or charges remain in equilibrium positions $\vec{r}_\mu$ which define the geometrical structure of the molecule. Under the influence of a perturbation all mass points suffer a displacement denoted here by $\vec{u}_\mu$. Since the molecule is to be considered stable in its unperturbed form an elastic restoring force prevents the molecule from destruction. Let $W(\{\vec{r}'_\mu\})$ be the self-energy of the molecule, where the $\vec{r}'_\mu$ terms are not necessarily the equilibrium positions, then this expression may be expanded for deviations $\vec{u}_\mu$ around $\vec{r}_\mu$. In the harmonic approximation we have:

$$W(\{\vec{r}'_\mu\}) \approx W_0(\{\vec{r}_\mu\}) + \tfrac{1}{2}\sum_{\mu,\nu}\left(\vec{u}_\nu \frac{\partial}{\partial \vec{r}_\mu}\right)\left(\vec{u}_\nu \frac{\partial}{\partial \vec{r}_\nu}\right) W(\{\vec{r}_\mu\}) \quad (6)$$

In the next step of approximation we consider only nearest-neighbour interactions. Then the relevant quantity is the relative displacement $\vec{u}_\mu - \vec{u}_{\mu+1}$ and the elastic molecular energy can be written as:

$$\Delta W = \tfrac{1}{2}\sum_{\langle\mu\rangle}(\vec{u}_\mu - \vec{u}_{\mu+1})\vec{\vec{T}}_{\mu,\mu+1}(\vec{u}_\mu - \vec{u}_{\mu+1}) \quad (7)$$

Now let the molecule be subject to an external field with $\vec{F}_\mu$ at each position $\vec{r}_\mu$. In general the molecule will not be at rest as a whole. By contrast, there will be an acceleration of the centre of mass accompanied by a deformation of the mole-

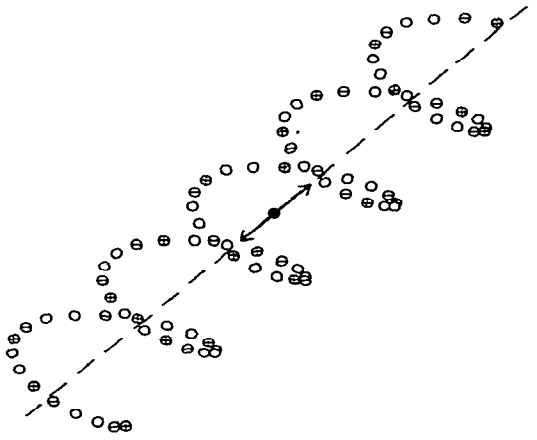

Fig. 1. The channel model for ionic polarisation. Each pair of neighbouring mass points is coupled harmonically.

cule. It is therefore recommended that one should consider the Lagrangian of the system, although we are not interested in the time-dependent problem. In order to obtain a separation between displacement of the centre of mass and true deformation of the molecule, we introduce the quantity $\vec{u}_s + \vec{u}_\mu$ as the total individual distortion, where $\vec{u}_s$ refers to the centre of mass. Then the $\vec{u}_\mu$ terms obey the constraint

$$\sum_{\mu=1}^{N} m_\mu \vec{u}_\mu = 0. \tag{8}$$

A proper variation of the $\vec{u}_\mu$ forms requires the introduction of Lagrange multipliers $\vec{\Gamma}$. Then the Lagrangian can be written as

$$L = \tfrac{1}{2}\sum_{\mu=1}^{N} m_\mu(\dot{\vec{u}}_s + \dot{\vec{u}}_\mu)^2 + \sum_{\mu=1}^{N} V(\vec{r}'_\mu - \vec{r}) - \vec{\Gamma}\sum_{\mu=1}^{N} m_\mu \vec{u}_\mu + \tfrac{1}{2} m_0 \dot{\vec{r}}^2 - \tfrac{1}{2}\sum_{\mu=1}^{N-1} \hat{u}_\mu \vec{T}_{\mu,\mu+1}\hat{u}_\mu, \tag{9}$$

where $\vec{r}'_\mu = \vec{r}_\mu + \vec{u}_\mu + \vec{u}_s$ and $\hat{u}_\mu = \vec{u}_\mu - \vec{u}_{\mu+1}$.

$V(\vec{r}'_\mu - \vec{r})$ is the interaction potential between the ion of mass m_0 and a molecular charge of mass m_μ at the actual position $\vec{r}'_\mu$.

In the present picture the molecular configuration is an arrangement of mass points representing a system of coupled harmonic oscillators. Bearing in mind, for example, the structure of gramicidin A [11], it is reasonable to assume the propagation of a perturbation mainly along a helical strand. This conception suggests a molecular model consisting of a chain of oscillators in the form of a helix (fig. 1) which represents a so-called bead-and-spring model. The molecule is assumed to be neutral, carrying neutral mass points, as well as positively and negatively charged ones, where all masses m_μ may be different. For such a configuration we want to calculate the deformation, i.e., the set of equilibrium displacements for all mass points in an arbitrary, external static field, from which the polarization energy can be obtained. For the present model a rigorous solution can be obtained.

The variational derivatives with respect to $\vec{r}$, $\vec{u}_s$ and $\vec{u}_\mu$ are:

$$\frac{\delta L}{\delta \vec{r}} = 0: \quad m_0 \ddot{\vec{r}} - \nabla \sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) = 0 \tag{10a}$$

$$\frac{\delta L}{\delta \vec{u}_s} = 0: \quad \sum_{\mu=1}^{N} m_\mu \ddot{\vec{u}}_s + \nabla \sum_{\mu=1}^{N} V(\vec{r}'_\mu - \vec{r}) = 0 \tag{10b}$$

$$\frac{\delta L}{\delta \vec{u}_\mu} = 0: \quad m_\mu \ddot{\vec{u}}_\mu + \nabla V(\vec{r}'_\mu - \vec{r}) + m_\mu \vec{\Gamma} - \vec{T}_{\mu+1}\hat{u}_{\mu-1} + \vec{T}_\mu \hat{u}_\mu = 0. \tag{10c}$$

For simplicity we write $\vec{T}_{\mu,\mu+1} \equiv \vec{T}_\mu$.

The harmonic approximation we are dealing with here allows us to use the original positions of the mass points in the argument of the force, i.e., we can write:

$$\nabla V(\vec{r}'_\mu - \vec{r}) \approx \nabla V(\vec{r}_\mu - \vec{r}) = -\vec{F}_\mu \tag{11}$$

Summation over all subscripts in eq. 10c yields the multiplier $\vec{\Gamma}$:

$$\sum_{\mu=1}^{N} m_\mu \vec{\Gamma} - \sum_{\mu=1}^{N} \vec{F}_\mu = 0$$

Hence

$$\vec{\Gamma} = \frac{1}{M}\vec{F} \tag{12}$$

with $M = \Sigma_{\mu=1}^{N} m_\mu$ and $\vec{F} = \Sigma_{\mu=1}^{N} \vec{F}_\mu$.

With the use of the result for $\vec{\Gamma}$ and the approximation in eq. 11 one obtains the expression for the total potential energy of the system:

$$V = \sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) - \sum_{\mu=1}^{N} \vec{u}_\mu\left(\vec{F}_\mu - \frac{m_\mu}{M}\vec{F}\right) + \tfrac{1}{2}\sum_{\mu=1}^{N-1} \hat{u}_\mu \vec{T}_\mu \hat{u}_\mu \tag{13}$$

Minimization of V with respect to all $\vec{u}_\mu$ yields the set of equilibrium displacements $\vec{a}_\mu$. The vector $\vec{u}_\mu$ may be decomposed and written as

$$\vec{u}_\mu = \vec{a}_\mu + \delta\vec{u}_\mu,$$

where $\delta\vec{u}_\mu$ is the deviation from equilibrium. The expansion of V (eq. 13) around the equilibrium

value of $\vec{u}_\mu$ yields:

$$V = \sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) - \sum_{\mu=1}^{N} \vec{a}_\mu \left(\vec{F}_\mu - \frac{m_\mu}{M} \vec{F} \right) + \tfrac{1}{2} \sum_{\mu=1}^{N-1} \hat{a}_\mu \ddot{T}_\mu \hat{a}_\mu + \tfrac{1}{2} \sum_{\mu=1}^{N-1} \delta\hat{u}_\mu \ddot{T}_\mu \delta\hat{u}_\mu \quad (14)$$

The vanishing coefficient of $\delta\vec{u}_\mu$ just defines $\hat{a}_\mu$:

$$\vec{F}_\mu - \frac{m_\mu}{M} \vec{F} + \ddot{T}_{\mu-1} \hat{a}_{\mu-1} - \ddot{T}_\mu \hat{a}_\mu = 0. \quad (15)$$

Eq. 15 is a difference equation in $\ddot{T}_\mu \hat{a}_\mu$ which is readily solved. Note, however, that $\hat{a}_\mu$ is the relative displacement $\vec{a}_\mu - \vec{a}_{\mu+1}$! The solution for $\hat{a}_\mu$ is:

$$\hat{a}_\mu = \ddot{T}_\mu^{-1} \sum_{\nu=1}^{\mu} \left(\vec{F}_\nu - \frac{m_\mu}{M} \vec{F} \right) \quad (16)$$

The appearance of both $\vec{a}_\mu$ and $\hat{a}_\mu$ in eq. 14 is an unpleasant situation. With a little manipulation it is possible to express V by the relative displacements only. Multiplication of eq. 15 with $\vec{a}_\mu$ from the left and summation over all subscripts μ yields the following identity:

$$\sum_{\mu=1}^{N} \vec{a}_\mu \left(\vec{F}_\mu - \frac{m_\mu}{M} \vec{F} \right) = \sum_{\mu=1}^{N-1} \hat{a}_\mu \ddot{T}_\mu \hat{a}_\mu \quad (17)$$

Then the desired expression for the interaction potential is:

$$V = \sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) - \tfrac{1}{2} \sum_{\mu=1}^{N-1} \hat{a}_\mu \ddot{T}_\mu \hat{a}_\mu + \tfrac{1}{2} \sum_{\mu=1}^{N-1} \delta\hat{u}_\mu \ddot{T}_\mu \delta\hat{u}_\mu \quad (18)$$

If we substitute $\hat{a}_\mu = \ddot{T}_\mu^{-1} \vec{G}_\mu(\vec{r})$ with

$$\vec{G}_\mu(\vec{r}) = \sum_{\nu=1}^{\mu} \left(\vec{F}_\mu - \frac{m_\mu}{M} \vec{F} \right),$$

the summation in the second term may be extended over N and we finally arrive at:

$$V = \sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) - \tfrac{1}{2} \sum_{\mu=1}^{N} \vec{G}_\mu(\vec{r}) \ddot{T}_\mu^{-1} \vec{G}_\mu(\vec{r}) + \tfrac{1}{2} \sum_{\mu=1}^{N-1} \delta\hat{u}_\mu \ddot{T}_\mu \delta\hat{u}_\mu \quad (19)$$

The quantity of interest for further investigations is the effective potential V_{eff}, the so-called potential of the mean force. Whereas this quantity is in general temperature dependent, it is not in the present case, because of the harmonic approximation of the intramolecular interaction.

The configurational integral

$$Q(\vec{r}) = \int e^{-\beta V} \mathrm{d}\Gamma$$

defines the restricted free energy

$$\mathscr{F}(\vec{r}) = -kT \ln \int e^{-\beta V} \mathrm{d}\Gamma,$$

where the integration has to be taken over all coordinates except for those of the ion. Then the effective potential is defined as:

$$V_{\text{eff}}(\vec{r}) = \mathscr{F}(\vec{r}) - \mathscr{F}(\infty) \quad (20)$$

where $\mathscr{F}(\infty)$ is the free energy in the absence of the ion. Hence:

$$Q(\vec{r}) = e^{-V_{\text{eff}}(\vec{r})} \int e^{-\frac{1}{2}\beta \sum_\mu \delta\hat{u}_\mu \ddot{T} \delta\hat{u}_\mu} \mathrm{d}\Gamma$$

$$V_{\text{eff}}(\vec{r}) = \sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) - \tfrac{1}{2} \sum_{\mu=1}^{N} \vec{G}_\mu(\vec{r}) \ddot{T}_\mu^{-1} \vec{G}_\mu(\vec{r}) \quad (21)$$

The first term on the right-hand side of eq. 21 is the interaction energy of the ion with the molecular charges at the original positions, the second term being the polarization energy due to the deformation of the molecular channel in the presence of the ion. The whole expression must now be used to calculate $V_{\text{eff}}(\vec{r})$ for a given molecular configuration. In its present form the restoring elastic forces can be anisotropic and inhomogeneous, i.e., $\ddot{T}_\mu$ actually varies with μ. For simplicity, it is assumed that in the present model the tensorial coupling constant is isotropic and a constant:

$$\ddot{T}_\mu = 1 \cdot \kappa$$

In this case the sum over $\vec{G}_\mu(\vec{r})^2$ has to be evaluated. This task becomes easier if we revert to the fields $\vec{F}_\mu$.

Using

$$\hat{F}_\mu = \vec{F}_\mu - \frac{m_\mu}{M} \vec{F}$$

we have:

$$\sum_{\mu=1}^{N} \vec{G}_\mu(\vec{r})^2 = \sum_{\mu=1}^{N} \sum_{\nu=1}^{\mu} \sum_{\nu'=1}^{\mu} \hat{F}_\nu \hat{F}_{\nu'} \tag{22}$$

Introducing the step function

$$\theta(\mu-\nu) = \begin{cases} 1 & \mu \geqslant \nu \\ 0 & \mu < \nu \end{cases}$$

we can write:

$$\sum_{\mu=1}^{N} \vec{G}_\mu(\vec{r})^2 = \sum_{\mu=1}^{N} \sum_{\nu=1}^{N} \sum_{\nu'=1}^{N} \theta(\mu-\nu)\theta(\mu-\nu')\hat{F}_\nu \hat{F}_{\nu'} \tag{23}$$

The summation over μ can be carried out separately:

$$\sum_{\mu=1}^{N} \theta(\mu-\nu)\theta(\mu-\nu') =$$
$$\tfrac{1}{2} \sum_{\mu=1}^{N} \left\{ \theta(\mu-\nu)^2 + \theta(\mu-\nu')^2 \right.$$
$$\left. - \left[\theta(\mu-\nu) - \theta(\mu-\nu')\right]^2 \right\} =$$
$$\tfrac{1}{2}\left\{ N-(\nu-1) + N-(\nu'-1) - |\nu-\nu'| \right\} \tag{24}$$

With the use of eqs. 23 and 24 in eq.21 the effective potential becomes:

$$V_{\text{eff}}(\vec{r}) = \sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) + \tfrac{1}{4}\kappa^{-1} \sum_{\mu=1}^{N} \sum_{\nu=1}^{N} |\mu-\nu| \hat{F}_\nu \hat{F}_\mu \tag{25}$$

In the presence of external fields one wishes to formulate the free energy with the aid of a response function, the generalized susceptibility $\ddot{\chi}_{\mu\nu}$, connecting the forces $\vec{F}_\mu$ and each individual displacement $\vec{d}_\mu$:

$$\vec{d}_\mu = \sum_{\mu=1}^{N} \ddot{\chi}_{\mu\nu} \vec{F}_\nu \tag{26}$$

This can be achieved by a simple rearrangement of the double sum in eq. 24:

$$V_{\text{eff}}(\vec{r}) = \sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) - \tfrac{1}{2} \sum_{\mu=1}^{N} \sum_{\nu=1}^{N} \vec{F}_\mu \ddot{\chi}_{\mu\nu} \vec{F}_\nu \tag{27}$$

In the present case the susceptibility is found to be:

$$\ddot{\chi}_{\mu\nu} = -\tfrac{1}{2}\kappa^{-1} \cdot \left\{ \sum_{\alpha=1}^{N} \sum_{\beta=1}^{N} |\alpha-\beta| \frac{m_\alpha m_\beta}{M^2} \right.$$
$$- \sum_{\alpha=1}^{N} |\mu-\alpha| \frac{m_\alpha}{M}$$
$$\left. - \sum_{\alpha=1}^{N} |\nu-\alpha| \frac{m_\alpha}{M} + |\mu-\nu| \right\} \tag{28}$$

The forces exerted on the molecular charges are caused by the electrostatic field of the ion:

$$\vec{F}_\mu = q_\mu \vec{E}_\mu \tag{29}$$
$$\vec{E}_\mu = q \frac{\vec{r}_\mu - \vec{r}}{|\vec{r}_\mu - \vec{r}|^3}$$

Thus, $\ddot{\alpha}_{\mu\nu} = q_\mu \ddot{\chi}_{\mu\nu} q_\nu$ defines the molecular ionic polarizability and we finally have:

$$V_{\text{eff}}(\vec{r}) = \sum_{\mu} V(\vec{r}_\mu - \vec{r}) - \tfrac{1}{2} \sum_{\mu} \sum_{\nu} \vec{E}_\mu \ddot{\alpha}_{\mu\nu} \vec{E}_\nu \tag{30}$$

where q is the ionic charge.

A closed expression for the double sum in eq. 30 cannot be given, especially not for a finite system. All summations have to be carried out numerically, which has been done for a particular model. For simplicity, all masses m_μ have been chosen to be identical. The helical backbone of the model consists of $N_0 = 18$ equidistantly spaced mass points per turn, where the helix has a constant pitch of $P = 12$ Å and the lattice constant $z_0 = P/N_0$. The number of charges per turn is 12, six of which are positive and six negative. The arrangement corresponds to that shown in fig.1. For the present purpose it is also sufficient to calculate V_{eff} along the z-direction, which is identical with the helical axis. With the summation running over all lattice points one must bear in mind that not all of them carry charges. Therefore we, introduce

$$q_\mu = q\delta_\mu,$$

where δ_μ equals either $+1$, -1 or 0. Then the first term on the right-hand side of eq. 30 can be

written as

$$\sum_{\mu=1}^{N} V(\vec{r}_\mu - \vec{r}) = \frac{q^2}{z_0} \sum_{\mu=1}^{N} \frac{\delta_\mu}{\sqrt{\Delta^2 + (\mu - \zeta)^2}} \tag{31}$$

where $\zeta = z/z_0$, $\Delta = \rho/z_0$, and ρ is the radius of the helix. Accordingly, the forces $\vec{F}_\mu$ are given by the following expression:

$$\vec{F}_\mu = \frac{q^2}{z_0^2} \frac{\delta_\mu}{\sqrt{\Delta^2 + (\mu - \zeta)^2}^3} \begin{pmatrix} \Delta \cos \mu\varphi_0 \\ \Delta \sin \mu\varphi_0 \\ \mu - \zeta \end{pmatrix} \tag{32}$$

φ_0 is defined by $2\pi/N_0$.

In the present notation $V_{\text{eff}}(\zeta)$ may be expressed as

$$V_{\text{eff}}(\zeta) = V_0 \left\{ \sum_{\mu=1}^{N} \frac{\delta_\mu}{\sqrt{\Delta^2 + (\mu - \zeta)^2}} + \tfrac{1}{4}\epsilon \sum_{\mu=1}^{N} \sum_{\nu=1}^{N} |\mu - \nu| \phi_{\mu\nu} \right\}. \tag{33}$$

with $V_0 = q^2/z_0$ and $\epsilon = V_0/\kappa z_0^2$.

The auxiliary quantity $\phi_{\mu\nu}$ can be obtained by substitution of $\vec{F}_\mu$ (eq. 32), into eq. 25. The dimensionless parameter ϵ describes the elasticity of the molecular channel, which becomes completely rigid for $\epsilon = 0$. For our example we have chosen $\epsilon = 1$ and $\rho = 3$ Å. This value corresponds to the reasonable assumption that the elastic energy κz_0^2 is of the order of the Coulomb energy q^2/z_0. The result of the model calculation is shown in fig. 2. The potential energy profile of the channel with a length of 60 Å is symmetric, so that only one half of it has been plotted. The solid line shows $V_{\text{eff}}(\zeta)$, i.e., the total interaction energy. The dashed line is the interaction energy of the ion with the rigid channel, hence it corresponds to the first term on the right-hand side of eq. 33, whereas the dotted line is the polarization energy alone, which lowers the energy in comparison to a non-polarizable channel. The polarization term shows a much less pronounced structure than does the potential of the rigid channel. The period of the former has doubled, because the polarization energy is proportional to the square of the molecular charges, i.e., it is independent of the sign of the charges. Moreover, it also depends on the square of the ionic charge. Consequently, the polarization energy is lowered linearly by a factor of 4, if the ion is divalent. Another interesting effect appears if two ions are present in the channel. In this case the external field is a superposition of the two fields carried by the two ions.

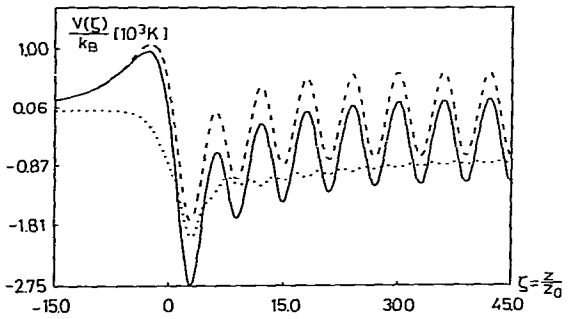

Fig. 2. The potential energy for a single ion along the z-axis (molecular axis) (— — —) Profile of the unpolarized channel. (· · ·) Polarization energy alone. (———) Total potential.

$$\vec{E}_\mu = \vec{E}_\mu(1) + \vec{E}_\mu(2).$$

From the structure of the polarization energy it is clear that it cannot be a superposition of two single polarization energies. From eq. 30 we find:

$$\sum_{\mu,\nu} \vec{E}_\mu \vec{\alpha}_{\mu\nu} \vec{E}_\nu = \sum_{\mu,\nu} \left\{ \vec{E}_\mu(1) \vec{\alpha}_{\mu\nu} \vec{E}_\nu(1) + \vec{E}_\mu(2) \vec{\alpha}_{\mu\nu} \vec{E}_\nu(2) + 2\vec{E}_\mu(1) \vec{\alpha}_{\mu\nu} \vec{E}_\nu(2) \right\} \tag{34}$$

Thus, the interaction between the two ions in the channel is given by the Coulomb term and an induced interaction

$$V(\zeta_1, \zeta_2) = V_0 \frac{1}{|\zeta_1 - \zeta_2|} - \sum_{\mu,\nu} \vec{E}_\mu(1) \vec{\alpha}_{\mu\nu} \vec{E}_\nu(2). \tag{35}$$

Since the polarization term is negative, the interaction is attractive. In the absence of the Coulomb repulsion the ions would unite, producing a divalent ion. Hence, the binding energy between two ions would be exactly twice the polarization energy of a single ion, which amounts to about

$-3kT$ at $T = 300$ K (fig. 2). However, the Coulomb energy for two ions separated by the length of the channel (60 Å) is about $+9kT$. In other words, an effective binding of two ions in this channel cannot be expected, at least not for a reasonable polarizability.

The potential energy profile of the channel for a single ion as shown in fig. 2 seems to provide a suitable object for the application of a rate theoretical formalism in order to study its transport properties. This has been done, especially under the aspect of its elasticity, and the corresponding transport rates have actually been found to be in basic agreement with experimental findings for gramicidin A [12]. However, the present model represents a channel without its dielectric environment. The polarization energy obtained here is locally significant, but can almost be neglected in comparison to the energy barrier represented by the increase of the ion's self-energy in the membrane (eq. 5). Obviously the polarization effects caused by mutually coupled displacements of molecular charges, i.e., by slight changes of orientation and magnitude of permanent dipoles, are alone insufficient to describe the actual properties of functioning membrane pores.

3. Channel model with dipolar polarization

In contrast to ionic polarization which is described by translational displacements of molecular charges, dipolar polarization is caused by reorientation of permanent rigid dipoles in an external field. The presence of permanent dipoles in a substance usually gives rise to a relatively high dielectric constant as in the case of water, for instance. A similar effect can be expected from a molecular channel where the interior is lined with elastically bound dipoles. The basic structure of a corresponding model is therefore given by an arrangement of dipoles along a rigid helix. The dipoles are viewed as hindered rotators which may be tilted in the presence of an ion. Such flexible ligands in the form of peptide carbonyl groups are present in the interior of gramicidin A, pointing with their negatively charged oxygen ends towards the helical axis of the molecule [11]. In the present model the dipoles can perform a hindered rotation in a plane spanned by the radius and the axis of the helix. The helix is assumed to be periodic with constant pitch P, carrying six dipoles per turn. In the absence of any external field the dipoles are found to be in an equilibrium orientation with respect to the molecular axis. The corresponding angle θ_μ is assumed to alternate with respect to the x-y plane in the following way (fig. 3):

$$\theta_\mu = \vartheta_0$$

$$\vartheta_{\mu+1} = 180° - \vartheta_0$$

$$\theta_\mu = \theta_{\mu+2}$$

Then the self-energy of the empty channel is given

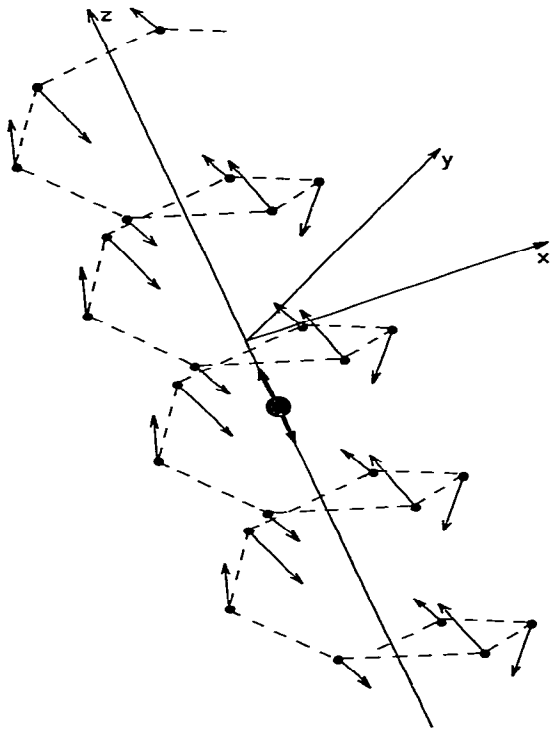

Fig. 3. The channel model for dipolar polarization. Each dipole (arrow) can rotate statistically independent from all others in the absence of an ion in the plane with the z-axis.

by

$$V_s = -\kappa p \sum_{\mu=1}^{n} \{\cos(\vartheta_\mu - \theta_\mu) - 1\}, \tag{36}$$

where κ is the coupling constant for the restoring force and $p = q'd$ the dipole moment with effective charge q'. The actual orientation of each dipole is determined by ϑ_μ which equals θ_μ in equilibrium. The equilibrium self-energy $n\kappa p$ has been subtracted so that the harmonic approximation yields:

$$V_s \approx \tfrac{1}{2}\kappa p \sum_{\mu} (\vartheta_\mu - \theta_\mu)^2. \tag{37}$$

However, in the present case all calculations will be carried out with the full anharmonic expression (eq. 36 for the hindered rotation. This procedure guarantees a bounded displacement

$$-\pi \leqslant \vartheta_\mu - \theta_\mu \leqslant \pi,$$

and a correct treatment of the actually temperature-dependent effective potential.

For the purpose of the present investigation it is sufficient to calculate the interaction potential along the molecular z-axis. Then all repulsive forces can be omitted, and the main contribution to the interaction arises from Coulomb forces. For an arrangement of dipoles in the field of an ion one has:

$$V_c = -q \sum_{\mu=1}^{n} \frac{\vec{p}_\mu (\vec{r} - \vec{r}_\mu)}{|\vec{r} - \vec{r}_\mu|^3} \tag{38}$$

where $\vec{r}$ is the position of the ion. With

$$\vec{r} = \begin{pmatrix} 0 \\ 0 \\ z \end{pmatrix} \text{ and } \vec{r}_\mu = \begin{pmatrix} \mu z_0 \\ \vec{\rho}_\mu \end{pmatrix}$$

eq. 38 can be written as:

$$V_c = -qp \sum_{\mu=1}^{n} \frac{(z - z_0\mu)\cos\vartheta_\mu + \rho \sin\vartheta_\mu}{\sqrt{\rho^2 + (z - z_0\mu)^2}^3} \tag{39}$$

Since all dipoles are positioned on a cylinder with radius ρ, we can use $\rho = |\vec{\rho}_\mu|$ for all μ terms. In eq. 39 ϑ_μ is positive for dipoles pointing towards the molecular axis. If one adopts the view that the θ_μ terms are a given set for the empty channel, then κ has to be considered as an effective coupling constant, i.e., the dipoles are in equilibrium under the influence of all acting forces including their mutual Coulomb forces. Thus, the dipole-dipole interaction does not appear explicitly and the total potential is:

$$V = -qp \sum_{\mu=1}^{n} \frac{(z - z_0\mu)\cos\vartheta_\mu + \rho \sin\vartheta_\mu}{\sqrt{\rho^2 + (z - z_0\mu)^2}^3} - \kappa p \sum_{\mu=1}^{n} \left[\cos(\vartheta_\mu - \theta_\mu) - 1\right] \tag{40}$$

This model is identical with that used previously by the author [13] for rate-theoretical investigations. It differs, however, in two points from the model used by Fischer et al. [14] for molecular dynamics calculations. The latter has used the harmonic approximation (eq. 37) and taken into account dipole-dipole interaction, which is needed for a rapid thermalization process.

Collecting terms in eq. 40 with $\cos\vartheta_\mu$ and $\sin\vartheta_\mu$, one obtains

$$V = -V_0 \sum_{\mu=1}^{n} \{A_\mu(\zeta)\cos\vartheta_\mu + B_\mu(\zeta)\sin\vartheta_\mu - \epsilon\} \tag{41}$$

with $V_0 = pq/z_0^2$ and $\epsilon = \kappa z_0^2/q$. The coefficients A_μ and B_μ are

$$A_\mu(\zeta) = \epsilon \cos\theta_\mu + \frac{\zeta - \mu}{\sqrt{\Delta^2 + (\zeta - \mu)^2}^3}$$

$$B_\mu(\zeta) = \epsilon \sin\theta_\mu + \frac{\Delta}{\sqrt{\Delta^2 + (\zeta - \mu)^2}^3},$$

where we have used $\zeta = z/z_0$ and $\Delta = \rho/z_0$.

Here the calculation of the equilibrium energy for a given position of the ion is much easier than in the previous case of ionic polarization, because the chiral skeleton is rigid and the oscillators are independent (Einstein oscillators).

The actual orientation is readily decomposed into an equilibrium angle $\hat{\vartheta}_\mu$ and a deviation from that:

$$\vartheta_\mu = \hat{\vartheta}_\mu + \alpha_\mu$$

The $\hat{\vartheta}_\mu$ terms satisfy the equilibrium condition

$$\frac{\partial V}{\partial \vartheta_\mu} = 0 = V_0\{-A_\mu \sin \hat{\vartheta}_\mu + B_\mu \cos \hat{\vartheta}_\mu\}, \qquad (43)$$

whence:

$$\cos \hat{\vartheta}_\mu = \frac{A_\mu}{\sqrt{A_\mu^2 + B_\mu^2}}, \sin \hat{\vartheta}_\mu = \frac{B_\mu}{\sqrt{A_\mu^2 + B_\mu^2}}. \qquad (44)$$

Using eqs. 43 and 44, eq. 41 takes the following simple form:

$$V = -V_0 \sum_{\mu=1}^{n} \left\{\sqrt{A_\mu^2 + B_\mu^2} \cos \alpha_\mu - \epsilon\right\}. \qquad (45)$$

Since the coefficients A_μ and B_μ depend on the position ζ of the ion, the equilibrium angle also does. Thus, the dipolar orientation follows the respective position of the ion. If no other perturbations are present, all α_μ terms vanish and the effective potential is:

$$V_{\text{eff}}(\zeta) = -V_0 \sum_{\mu} \left\{\sqrt{A_\mu^2 + B_\mu^2} - \epsilon\right\} \qquad (46)$$

Being part of a multi-particle system, the channel can assumed to be subject to a temperature bath. With that the dipoles are exposed to temperature-induced fluctuations, i.e., at a given instant the α_μ terms have finite and distinctive values and the actual orientations appear 'smeared out'. For calculation of the temperature-dependent quantities it is appropriate to introduce the configurational integral with $\chi_\mu = \cos \alpha_\mu$:

$$Q(\zeta) = e^{-\beta V_0 n\epsilon} \prod_{\mu=1}^{n} \int_{-1}^{+1} \mathrm{d}\chi_\mu e^{\beta V_0 \sqrt{A_\mu^2 + B_\mu^2}\chi_\mu} \qquad (47)$$

$$Q(\zeta) = \prod_{\mu=1}^{n} \left\{e^{-\beta V_0 \epsilon} \cdot \frac{\sinh\left(\beta V_0 \sqrt{A_\mu^2 + B_\mu^2}\right)}{\beta V_0 \sqrt{A_\mu^2 + B_\mu^2}}\right\}$$

According to the procedure in section 2 (see eq. 20 the temperature-dependent effective potential is defined by

$$V_{\text{eff}}(\zeta) = -kT \ln \frac{Q(\zeta)}{Q(\infty)}, \qquad (48)$$

where $Q(\infty) = \{e^{-\beta V_0 \epsilon}[\sinh(\beta V_0 \epsilon)/\beta V_0 \epsilon]\}^n$.

The temperature dependence is a direct consequence of the anharmonic binding forces (eq. 36) of the ligands. It is possible to discuss some general trends of V_{eff} with respect to the temperature without going into numerical detail. First it can be checked easily that the expression for the zero-temperature potential (eq. 46) indeed follows from the general expression (eq. 48) in the limit $T \to 0$. A direct measure of the temperature influence is the value of the effective dipole moment $\langle p_\mu \rangle$, which is obtained from the mean of $\cos \alpha_\mu$,

$$\langle p_\mu \rangle = q' \mathrm{d} \langle \cos \alpha_\mu \rangle$$

where

$$\langle \cos \alpha_\mu \rangle = \coth \chi_\mu - \frac{1}{\chi_\mu}, \qquad (49)$$

with $\chi_\mu = \beta V_0 \sqrt{A_\mu^2 + B_\mu^2}$.

For finite temperatures $\langle \cos \alpha_\mu \rangle$ is less than unity and vanishes, as does V_{eff}, in the limit $T \to \infty$. For sufficiently low temperatures we have

$$\langle \cos \alpha_\mu \rangle \approx 1,$$

so that eq. 46 can be used. This implies that entropy effects are small. In a previous publication dealing with transport mechanism of this channel model [13], the temperature dependence has been tested over a wide range, and it has been found that entropy effects in general are small for realistic temperatures ($T \approx 300$ K).

Due to the anharmonic character of the restoring forces the interaction energy in both eqs. 46 and 48 does not appear as a sum of two terms as in eq. 21, where the second one is the polarization energy. In order to obtain the polarization energy alone, one would have to subtract the result for the 'rigid' Coulomb contribution

$$V = -V_0 \sum_{\mu=1}^{n} \frac{(\zeta - \mu)\cos \theta_\mu + \Delta \sin \theta_\mu}{\sqrt{\Delta^2 + (\zeta - \mu)^2}^3}$$

from eqs. 46 and 48, respectively. However, this procedure is neither necessary nor desirable, since the only relevant quantity is the total energy.

The data for the channel model used here are again: $\rho = 3$ Å, $P = 12$ Å and $n = 30$. The dipole moment $p = q'd$ is given by $d = 1{,}24$ Å and $q' =$

0,40, which are the same values as in refs. 13 and 14. The two remaining parameters to be adjusted are the dimensionless coupling constant ϵ and the equilibrium angle ϑ_0, to both of which the potential is very sensitive. $V_{\text{eff}}(\zeta)$ has been calculated and plotted for $\epsilon = 5$ and $\epsilon = 0.5$ for three different values of ϑ_0 in each case, namely, for -20, 0 and $+20°$, respectively. $\epsilon = 5$ corresponds to almost rigidly fixed dipoles. For $\vartheta_0 < 0$ the dipoles are pointing outward, thus the channel interior is charged positively and the channel itself represents a barrier (fig. 4a). For $\vartheta_0 = 0°$ the dipoles are oriented parallel to the molecular axis in equilibrium (fig. 4b). The potential profile here is very similar to that found for the preceding model. For $\vartheta_0 = 20°$ the dipoles are oriented towards the molecular axis and the channel interior is charged negatively. This circumstance leads to a binding energy of about $30kT$ at $T = 300$ K for a single ion (fig. 4c).

For a weaker coupling of the dipoles ($\epsilon = 0.5$) the situation is very different. This is already seen in the case of $\vartheta_0 = -20°$ (fig. 5a). In comparison to $\epsilon = 5$ the barrier is much lower, due to the fact that the dipoles are pulled inward by the ion. This effect already leads for $\vartheta_0 = 0°$ to a significant binding energy of about $20kT$ (fig. 5b). Finally, $\vartheta_0 = 20°$ and $\epsilon = 0.5$ lead to about $50kT$ for the binding energy (fig. 5c).

All these values have been calculated from eq. 46. They are clearly of the order of what is needed to compensate for the dielectric barrier. It is clear that molecular channels with dipoles pointing off the axis are not appropriate to lower the barrier significantly. Obviously nature has produced and selected the proper molecules. Moreover, the ability to bind an ion depends on the flexibility of the ligands, i.e., it increases with decreasing ϵ. Thus, $\epsilon = 0$ gives an upper bound for the binding energy. From eq. 46 one obtains with $\epsilon = 0$:

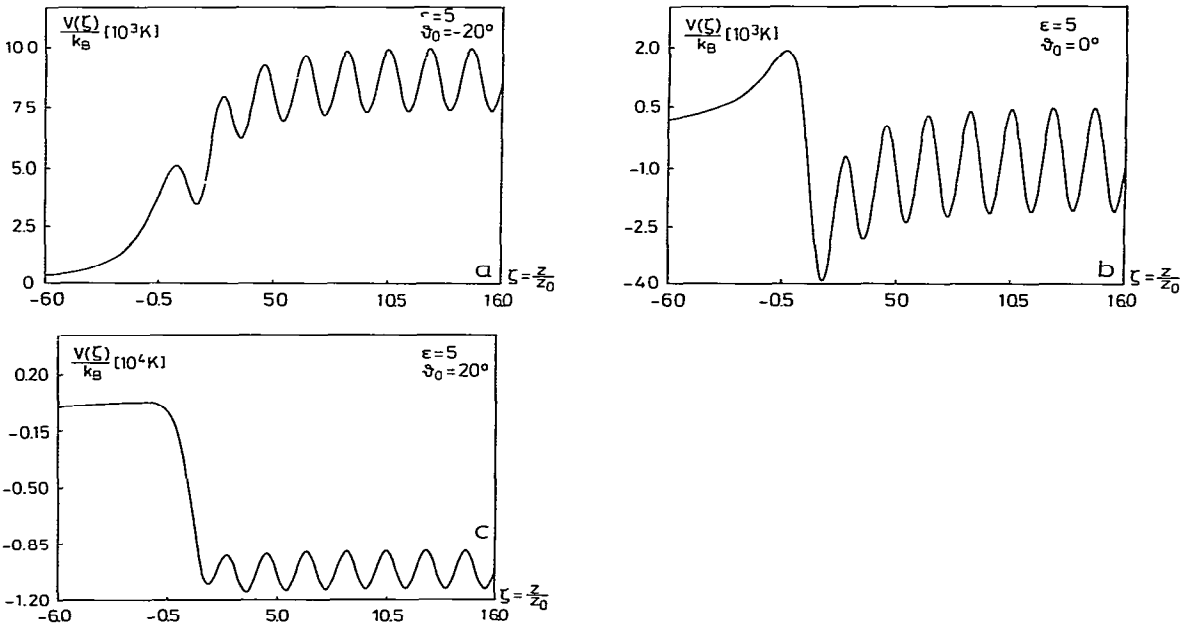

Fig. 4. The potential energy for a single ion in a channel with practically rigidly bound dipoles ($\epsilon = 5$). The different curves show the strong dependency of the energy on the equilibrium tilt angle ϑ_0. (Note the change in scale.)

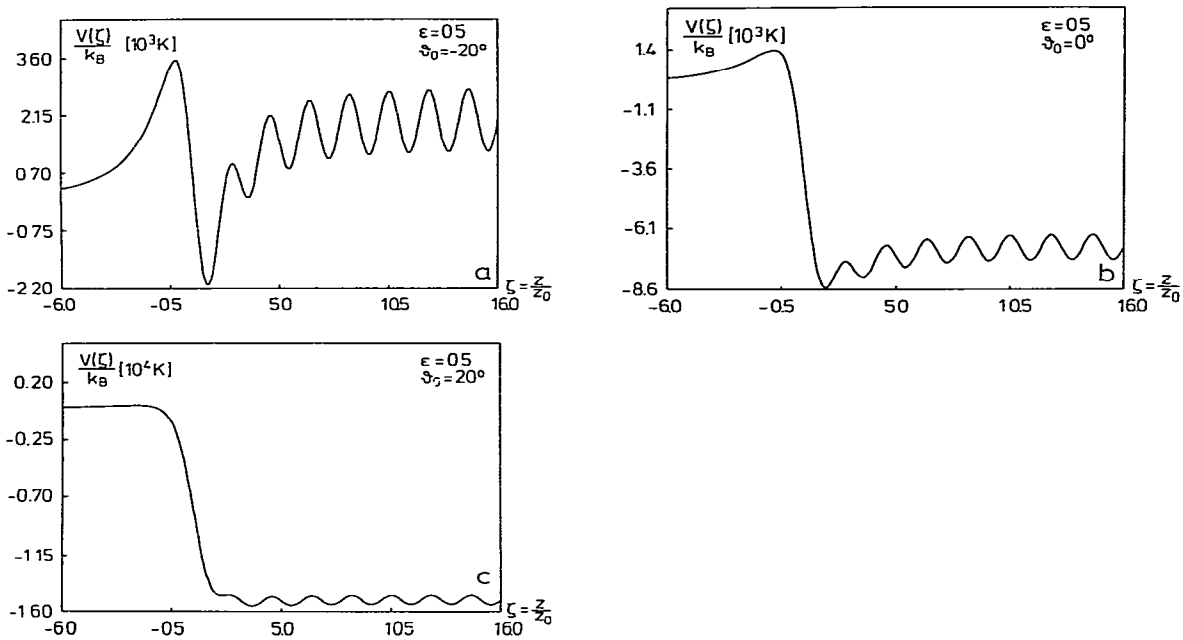

Fig. 5. The potential energy for a single ion in a channel with dipoles of higher mobility ($\epsilon = 0.5$) and different equilibrium tilt angles ϑ_0. (Note the change in scale.)

$$V_{\text{eff}}(\zeta) = -V_0 \sum_{\mu=1}^{n} \frac{1}{\Delta^2 + (\zeta - \mu)^2} \qquad (50)$$

In this case the dipoles are practically freely rotating. For the present data eq. 50 yields a binding energy of about $65kT$. So far, we have considered monovalent ions only, denoted by charge q. The next question is how V_{eff} behaves with respect to an arbitrarily variable parameter q. To answer this question we must recall the dependence of the quantities A_μ, B_μ and ϵ on q. They are given explicitly as:

$$A_\mu = \frac{\zeta - \mu}{\sqrt{\Delta^2 + (\zeta - \mu)^2}^3} + \frac{\kappa z_0^2}{q} \cos\theta_\mu,$$

$$B_\mu = \frac{\Delta}{\sqrt{\Delta^2 + (\zeta - \mu)^2}^3} + \frac{\kappa z_0^2}{q} \sin\theta_\mu$$

$$\epsilon = \frac{\kappa z_0^2}{q}$$

It can be seen immediately that an increasing charge q has the effect of decreasing ϵ, i.e., a higher mobility of the ligands. For sufficiently charged ions the dipoles appear practically as freely rotating! Altogether the binding energy increases more than linearly with increasing ionic charge.

According to eq. 50 the upper limit for the binding energy of a divalent ion, e.g., Ca^{2+}, reaches about $130kT$. A closer inspection of the potential energy profile with respect to ϵ shows that especially for decreasing, small ϵ the activation energies corresponding to the barriers within the channel decrease (see also ref. 13). This finding leads to the important conclusion that, once a divalent ion has entered the channel, transportation can take place more rapidly than for a monovalent ion. This feature of the present channel

model is illustrated in fig. 6. Here the activation energy corresponding to the central well has been plotted as a function of the ionic charge q for a reasonable value of ϵ ($\epsilon = 0.5$). The activation energy happens to assume a maximum value for a monovalent ion, whereas a minimum value is assumed for a divalent ion. With a constant prefactor the jump rate for the latter ion is about 3-times larger than the former. The high value of the binding energy for a divalent ion must also be seen under the aspect of the simultaneous binding of two monovalent ions, since in the absence of Coulomb repulsion two charges would just unite. On the other hand, the Coulomb energy for two free ions separated by a distance corresponding to the length of the channel is only $9kT$, so that the binding of at least two ions per channel for this model can be expected. The potential of the mean force for two ions can be derived using the superposition principle which holds for Coulomb forces, but not for the former. According to eq. 40 the total interaction energy for two ions at positions z_1 and z_2 is, with the set of the ϑ_μ given:

$$V_{12} = -qp \sum_{\mu=1}^{n} \left\{ \frac{(z_1 - z_0\mu)\cos\vartheta_\mu + \rho \sin\vartheta_\mu}{\sqrt{\rho^2 + (z_1 - z_0\mu)^2}^3} + \frac{(z_2 - z_0\mu)\cos\vartheta_\mu + \rho \sin\vartheta_\mu}{\sqrt{\rho^2 + (z_2 - \mu z_0)^2}^3} \right\} - \kappa p \sum_{\mu=1}^{n} \left[\cos(\vartheta_\mu - \theta_\mu) - 1\right] + \frac{q^2}{|z_1 - z_2|} \quad (51)$$

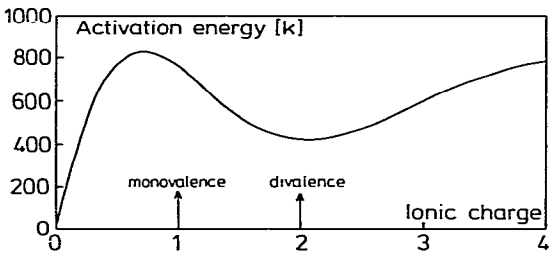

Fig. 6. Activation energy for the central well as a function of ionic charge.

The minimization procedure applied with respect to the set of ϑ_μ yields the new coefficients A_μ and B_μ:

$$A_\mu(\zeta_1, \zeta_2) = \frac{\zeta_1 - \mu}{\sqrt{\Delta^2 + (\zeta_1 - \mu)^2}^3} + \frac{\zeta_2 - \mu}{\sqrt{\Delta^2 + (\zeta_2 - \mu)^2}^3} + \epsilon \cos\theta_\mu \quad (52a)$$

$$B_\mu(\zeta_1, \zeta_2) = \frac{\Delta}{\sqrt{\Delta^2 + (\zeta_1 - \mu)^2}^3} + \frac{\Delta}{\sqrt{\Delta^2 + (\zeta_2 - \mu)^2}^3} + \epsilon \sin\theta_\mu \quad (52b)$$

The coefficients obtained from eq. 52 may now be inserted into eq. 45 or 48, respectively. The result is the potential $V^{(i)}(\zeta_1, \zeta_2)$ of the induced mean force between two ions, which is attractive. The total effective potential is then given by:

$$V_{\text{eff}}(\zeta_1, \zeta_2) = V^{(i)}(\zeta_1, \zeta_2) + \frac{q^2}{z_0} \frac{1}{|\zeta_1 - \zeta_2|}. \quad (53)$$

This expression depends on the distance between the two ions (monovalent), as well as on each of the positions. The interesting quantity in the present case, however, is the two-ion potential compared with the single-ion potential, i.e.

$$V_{\text{eff}}(\zeta_1, \zeta_2) - V_{\text{eff}}(\zeta_1), \quad (54)$$

where $V_{\text{eff}}(\zeta_1)$ corresponds to eq. 53 with the second ion at an infinite distance from both the channel and the first ion. Thus, the difference (eq. 54) tells us what energy is possibly gained, if an ion is brought from infinity into the channel to position ζ_2 with another ion present at ζ_1. If the difference (eq. 54) is negative, the second ion is likely to be bound. It is clear that only the absolute minimum with respect to both ζ_1 and ζ_2 yields the desired answer. In general eq. 54 need not be negative for any two positions within the channel, even though binding of the second ion is possible. In a symmetric channel the equilibrium positions for the two ions are also symmetric. With an appropriate choice of the coordinate system it is

therefore only necessary to vary one position, namely, $\zeta = \zeta_1 = -\zeta_2$. Let ζ_0 be the value which minimizes $V_{\text{eff}}(\zeta, -\zeta)$, if there is a minimum. Then the normalized effective interaction potential is defined by:

$$\Delta V_{\text{eff}}(\zeta) = V_{\text{eff}}(\zeta, -\zeta_0) - V_{\text{eff}}(-\zeta_0) \qquad (55)$$

This function has been calculated and plotted for different values of ϵ and ϑ_0. It should be emphasized that a rigid channel of course can represent a confinement, even for two ions, due to its finite length. In this case the only true interaction between the ions is Coulomb repulsion. In the present model we are dealing with an additional non-linear interaction due to the polarizability of the channel. In competition with the Coulomb repulsion this attractive interaction leads to a finite equilibrium separation between two ions in an

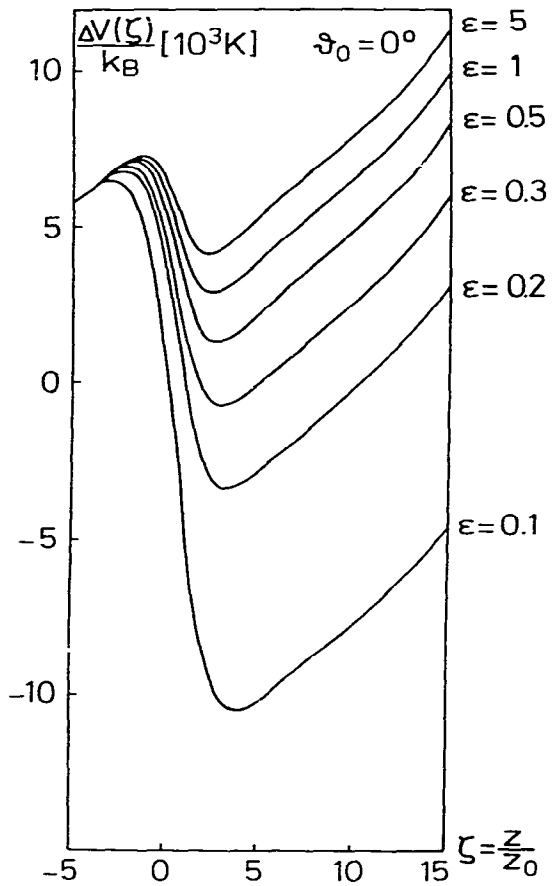

Fig. 7. The normalized effective interaction between two ions, with one ion approaching the other from the left. The equilibrium tilt angles is negative ($\vartheta_0 = -20°$). The dipolar coupling is varied from almost rigid binding ($\epsilon = 5$) to practically free rotation ($\epsilon = 0.1$).

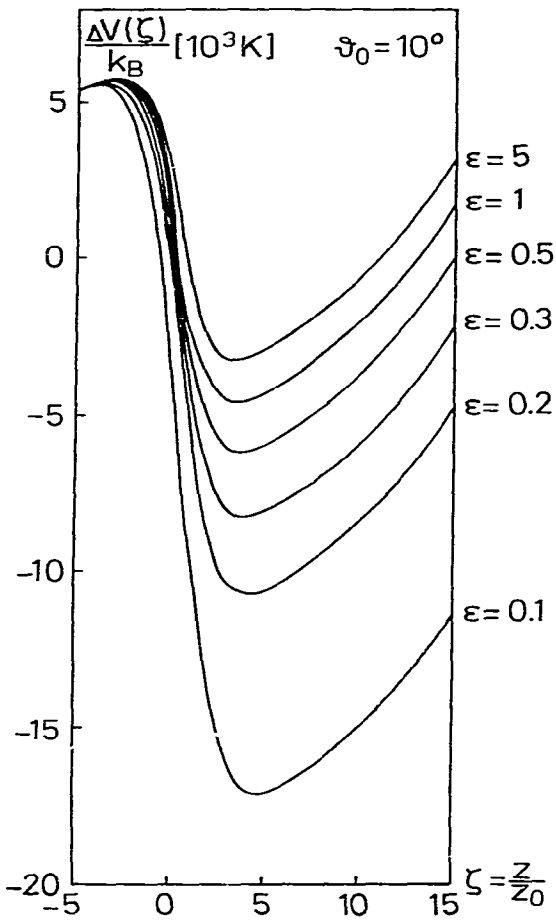

Fig. 8. As for fig. 7, but with $\vartheta_0 = 0°$.

infinitely long channel. In real systems as well as in our model, boundary effects interfere with the long-range induced interaction. It is the sum of all effects which we discuss here. In fig. 7 the results for a channel with dipolar alignment parallel to the molecular axis ($\vartheta_0 = 0°$) are shown. The value

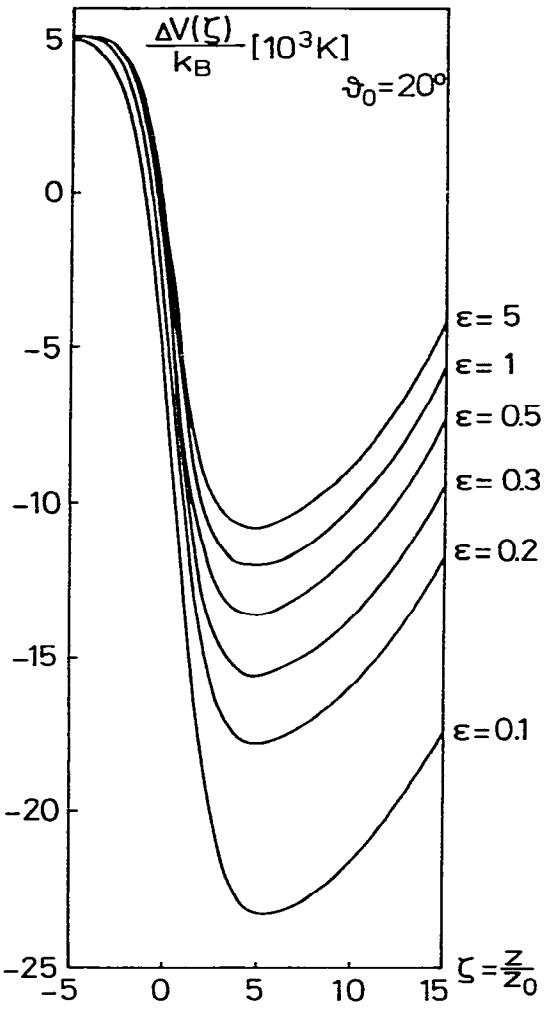

Fig. 9. As for fig. 7, but with $\vartheta_0 = 20°$.

$\epsilon = 5$ corresponds to almost rigidly bound dipoles. All potential curves show a barrier of about the same magnitude prior to the channel entrance. This barrier is caused by the Coulomb repulsion alone. For values of ϵ larger than about 0.3 the barrier is followed by a relative minimum just inside the channel. Here no energy is gained, if the second ion is transported from infinity into the channel. For values of ϵ smaller than about 0.3 the minimum of $\Delta V(\zeta)$ becomes negative in comparison with the outside, i.e., the minimum is absolute, and two-ion occupation is preferred over single-ion occupation. For channels with the dipoles tilted towards the molecular axis, the situation changes drastically in favour of the double-occupation state. In fig. 8 the corresponding results for $\vartheta_0 = 10°$ are shown. Whereas the barrier remains practically unchanged, the binding state is preferred for all values of ϵ with increasingly high binding energies. This trend is still enhanced for the channel with $\vartheta_0 = 20°$ (fig. 9) where the binding energies are remarkably high. As explained before, all minima correspond to symmetric equilibrium positions for two monovalent ions in symmetric channels. In all cases a tendency of decreasing equilibrium ion separation for decreasing dipolar binding forces can be observed. This fact reflects the contribution of molecular conformational changes to the binding force. In all cases shown here the binding energies finally have to compete with the dielectric barrier imposed by the membrane. The important result is that for appropriate dipolar tilt angles ϑ_0 and sufficiently high mobility of the dipoles a doubly occupied channel can be the preferred configuration despite Coulomb repulsion and a high dielectric barrier.

4. Conclusion

Two simple channel models based on ionic and dipolar polarization have been constructed and discussed. Both models consist, in principle, of a charge distribution along a helical backbone, accounting for the structure of polypeptides, which may serve as ionic conductors in membranes. Ionic polarizability is simulated by a quasi-linear system

of coupled harmonic oscillators, which may suffer distortions in any direction. Dipolar polarization is achieved by a system of hindered dipolar rotators, bound by anharmonic restoring forces and representing a helical arrangement of Einstein oscillators. The dipoles have only one rotational degree of freedom. In both cases the energy for ions in the channel is lowered by a distortion of the environment, as it should be. Whereas in real systems one can assume to find distortions of a molecular ionic skeleton, which are due to both ionic and dipolar polarization, it turns out that significant contributions to the polarization energy result from a tilt of permanent dipoles under the influence of ions. All other contributions, although present, are minor and can be neglected. The criterion for the effectiveness of a channel is clearly determined by the magnitude of the polarization energy in comparison to the dielectric potential barrier. The results of the present calculations demonstrate that the dipolar model must be favoured in order to explain observed transport phenomena. This also seems to be confirmed under the aspect of rate-theoretical considerations [13]. It is found that such a channel represents a well with a relatively large binding energy for an ion. This binding energy consists of two contributions which are of quantitatively and qualitatively different origin. The true polarization energy results from the mobility of the dipoles and is absent in a rigid channel. It can therefore vary between zero and an upper limit which is obtained when the dipoles can rotate freely. The second part of the binding energy is of geometrical origin. It is always present if the undistorted or rigidly fixed dipoles are tilted with their negative ends towards the molecular axis. Both contributions can be controlled independently, namely, by the equilibrium tilt angle and the dipolar coupling constant. The polarization affects not only the magnitude of the binding energy but also changes the potential energy profile locally. Potential barriers inside the channel, which result from the periodic structure of the helix, are generally lowered, if the mobility of the ligands is increased. On the other hand, a larger ionic charge has the same effect on the effective potential as that of a lower dipolar coupling constant. Therefore, divalent ions, such as Ca^{2+}, can possibly be transported even more rapidly than monovalent ones.

The general tendency of a charged particle in a polarizable environment is always to lower the free energy of the system, i.e., the charge is attracted to regions of high polarizability. This stabilizing effect seems to be a counter-effect on so-called gliding edge dislocations as proposed by Chandler et al. [15]. After all, the polarization mechanism has to be incorporated in such models for active ion transport.

Another important finding is the existence of a polarization-induced attractive interaction between two ions in a channel, which may well exceed the Coulomb repulsion within the channel length. This effect cannot be neglected and practically forbids the application of the superposition principle for more than one ion in a channel.

Recent investigations of the gramicidin A channel by Eisenman and Co-workers [8,9] have clearly demonstrated the need for such an interaction in the presence of several ions and ion species.

Since in the present model the motion of the ion is restricted to the channel axis, the only ionic parameter is the charge. In order to distinguish between different ion species, at least one parameter has to be introduced accounting for a motion off the axis. In such a model one could calculate the induced attraction between two Na^+ or K^+ or even between Na^+ and K^+, for example. The results obtained so far look very promising and will be the subject of a subsequent communication.

Acknowledgements

I am grateful to Professor P. Läuger for several discussions on the subject. Furthermore I wish to thank Professor G. Eisenman for sending me his manuscripts prior to publication. Part of the calculations presented here have been carried out at the T.H. Darmstadt. I want to thank Professor J. Brickmann and his group for their assistance. This work has been supported financially by the D.F.G. (Heisenberg-Programm).

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