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ELECTROSTATIC ACTIVATION ENTHALPY FOR ION TRANSPORT THROUGH A MEMBRANE CHANNEL

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The temperature dependence of the conductance of a membrane channel offers a means of obtaining information about the electrostatic energy barrier that opposes the entry of ions into a channel. Quantitative calculations of the magnitude of this barrier show that it may be low enough to allow ion transport to occur at observed rates (1). However, the activation enthalpies obtained from Arrhenius plots of channel conductances are often close to zero, once they are corrected for the temperature dependence of water viscosity. The temperature dependence of channel conductance is usually only slightly steeper than that of ion mobilities in water. The temperature dependences of these mobilities all closely follow the temperature dependence of the viscosity of water with an apparent activation enthalpy near 3.8 kcal/mol (2).

This report points out that the activation enthalpy is not identical with the activation free energy and can be much lower than the total electrostatic free energy of placing an ion within an aqueous cylindrical pore surrounded by a low dielectric medium such as hydrocarbon. Previously, Hille found that a barrier model for the sodium channel was improved when entropic terms were added to the energy barriers (3). Although it is a trivial matter to differentiate a free energy with respect to temperature to obtain the entropy, it is not widely appreciated that electrostatic energies are not purely enthalpic. At 25°C the dielectric constant of water changes by a fraction of 0.0046 of itself per degree Centigrade. Differentiating with respect to temperature, the coulombic potential, G, in water gives an entropy of $S = -0.0046 \times G$. At 25°C, $TS = -1.37 \times G$. Electrostatic interactions in water are therefore entropy-driven (4).

The quantitative calculations of Levitt (1) are numerical and not easily subjected to this kind of analysis. However, Levitt has found that Parsegian's infinite cylindrical pore potential (5) can be corrected for end effects with Parsegian's finite slab potential (5) to give

$$G = \frac{e^2}{\epsilon_h b} P\left(\frac{\epsilon_h}{\epsilon_w}\right) - \frac{e^2}{\epsilon_h \ell} \ln\left(\frac{2\epsilon_w}{\epsilon_h + \epsilon_w}\right) \qquad (1)$$

where e is the charge of an electron, ϵ_h and ϵ_w are the dielectric constants of hydrocarbon and water respectively, b and ℓ are the radius and length, respectively, of the channel, and P is an integral evaluated and tabulated by Parsegian (5). This expression is 26% larger than the result of a more quantitative calculation of the free energy of placing an ion in the center of a pore with the same dimensions as gramicidin (6 Å wide, 25 Å long) (1).

Differentiating Eq. 1 with respect to temperature gives

$$-S = \frac{-e^2 P}{\epsilon_h^2 b}\frac{d\epsilon_h}{dT} + \frac{e^2 P'}{\epsilon_h b}\left(\frac{1}{\epsilon_w}\frac{d\epsilon_h}{dT} - \frac{\epsilon_h}{\epsilon_w^2}\frac{d\epsilon_w}{dT}\right) + \frac{e^2}{\ell}\left[\frac{1}{\epsilon_h^2}\frac{d\epsilon_h}{dT}\ln\left(\frac{2\epsilon_w}{\epsilon_h + \epsilon_w}\right) - \frac{1}{\epsilon_w \epsilon_h}\frac{d\epsilon_w}{dT} + \frac{\frac{d\epsilon_w}{dT} + \frac{d\epsilon_h}{dT}}{\epsilon_h(\epsilon_h + \epsilon_w)}\right]$$

With $\epsilon_h = 2$ and $\epsilon_w = 80$, the appropriate value of P is $P(0.025) = 0.17$. $P'(0.025)$ was estimated from the table of values of P to be 2.1 (5). $d\epsilon_w/dT = -0.368$; $d\epsilon_h/dT = 0.0012$ (for dodecane [6]). With $b = 3$ Å and $\ell = 25$ Å, TS is -4.5 kcal/mol. For these values of b, ℓ, ϵ_w, and ϵ_h, G is determined from Eq. 1 to be 4.8 kcal/mol, so the free energy of the barrier is almost all entropic, and the barrier enthalpy is only 0.3 kcal/mol.

The measured activation enthalpy for the conductance of the gramicidin channel is 1–3.5 kcal/mol larger than that for the viscosity of water. (7, 8). For the excitability-inducing material channel (9), for the acetylcholine channel (10), and for the sodium and potassium channels (11, 12), there is no significant activation enthalpy in excess of that of the free ion mobility. Though precise dimensions are available only for gramicidin, the above calculation suggests that low activation enthalpies of channel conductances do not indicate the absence of an electrostatic barrier.

In conclusion, the low activation enthalpies of channel conductances are consistent with a naive model of a cylindrical water-filled pore through a slab of hydrocarbon, in which macroscopic properties of electrolyte solutions and hydrocarbon are applied. It is not clear whether a more molecular picture would preserve the qualitative predictions of this model, but it is worth bearing in mind

that measurements of channel conductances and their activation enthalpies provide two useful independent tests for any theory.

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ELECTROSTATIC MODELS OF THE GRAMICIDIN AND THE DELAYED RECTIFIER POTASSIUM CHANNEL

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I have treated an ion-pore former-membrane–water system as an electrostatic problem involving a set of distinct dielectric phases. The effect that reasonable variation of the system's physical and electrical structure has on the energy barrier to ion permeation and on the voltage profile generated by an applied potential is used to show that: (*a*) a parameter-free model is consistent with gramicidin channel properties that are clearly dependent on coulombic interactions; and (*b*) electrostatic considerations severely limit the range of possible structures for the delayed-rectifier potassium channel.

GRAMICIDIN A

The gramicidin channel is treated as a uniform cylinder of length 2.6 nm with binding sites 0.25 nm from each end (see reference 1), embedded in membranes of variable width. The aqueous solutions and the water within the pore form a dielectric phase with $\epsilon = 80$. The pore former and the lipid form another dielectric phase with $\epsilon = 2$. To compensate for dielectric shielding by the polar groups lining the pore interior, the pore's effective electrical radius is 0.25 nm (2), larger than its physical radius. Membrane dipole potentials are estimated from surface potential measurements of lipid monolayers on water (3). A mean charge distribution for gramicidin is determined from atomic coordinates found by computer modeling of the β-helical structure (4) and partial charge parameters representative of atoms in amino acids (5). It is equivalent to a uniform dipole density of 8×10^{-12} C m^{-1} smeared out on a cylinder of radius 0.37 nm; the negative end of the dipoles points inward. The model suppresses local variation.

The total electrical potential due to the ion image, the membrane potential and the pore-former charge distribution is calculated for membranes of variable width by an extension of my previous work (2, 6). This establishes the electrostatic potential energy profile and the additional repulsive energy when both binding sites are occupied. The electrostatic contribution to the energy barrier at the channel center, ϵ^*, to the energy barrier to translocation, ϵ_t, and the ratio of the binding constants for single and double occupancy, K_1/K_2, are plotted in Fig. 1 as functions of membrane width for phosphatidylcholine (PC) and glyceryl monooleate (GMO) bilayers.

In addition to electrostatic energy, the total potential contains a term reflecting differences in the solvating ability of water and of polar groups lining the pore. In bilayers ~5 nm wide the activation barrier to Na^+ conductance is ~31 kJ/mol^{-1} in PC (7) and ~20 kJ/mol^{-1} in GMO (8). Because ϵ^*, for a 5-nm GMO membrane, is ~28 kJ/mol^{-1}, the local solvation energy must be < -8 kJ/mol^{-1}. If binding in the channel is slightly exothermic (1, 9) this energy would be more negative.

As solvation energy varies little within the pore[1], ϵ_t is

[1]W. K. Lee and P. C. Jordan. Unpublished results.

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