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Alamethicin Pore Formation: Voltage-Dependent Flip-Flop of α-Helix Dipoles

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Abstract. The voltage-dependency of alamethicin pore formation is explained by a flip-flop gating mechanism of single alamethicin molecules. The energetically preferred aggregate structure is changed from antiparallel to parallel molecule orientation by membrane voltage application. The electrical field is sensed by the permanent dipole of the α-helical molecule part which spans the hydrophobic membrane core. Ion conducting pore and pore states result from electrostatic repulsion of a varying number of parallel dipoles which arrange circularly. This model is consistent with published data and with two additional experimental facts, that pore state distributions are ionic strength dependent and pore state conductances depend on ionic current direction.

Key words: Alamethicin pore – Voltage-dependent conductance – α-helical structure – Dipole moment – Lipid bilayers

Introduction

Alamethicin, a nonadecapeptide antibiotic (Fig. 1), forms voltage-dependent pores in artificial (Mueller and Rudin 1968; Gordon and Haydon 1972; Eisenberg et al. 1973) and biological (Sakmann and Boheim 1979) membranes. Although its primary and secondary structures are known (Jung et al. 1975, 1981), the nature of the voltage-dependent gating process remained obscure. In view of recent results on the crystal structure (Butters et al. 1981) and pore forming properties (Hanke et al. 1983) of peptide analogues we propose a flip-flop gating mechanism. In membranes, the behaviour of alamethicin molecules is largely determined by their dipole moment, which is an intrinsic property of the α-helix (Hol et al. 1981; Yantorno et al. 1982; Schwarz and Savko 1982). In particular, aggregates of antiparallel dipoles may form. The voltage-gated transition of one or several molecules into a parallel orientation leads to electrostatic repulsion and to the formation of water filled pores

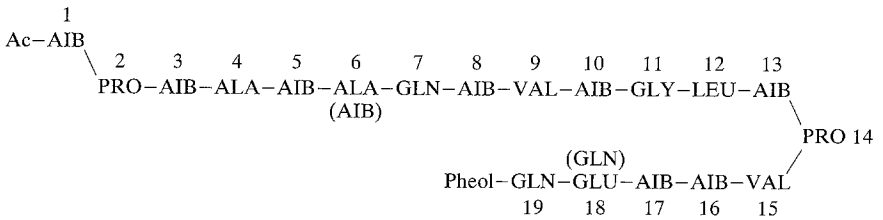

Fig. 1. Primary structure of alamethicin (Jung et al. 1981); Ac: acetyl-group; AIB: α-aminoisobutyric acid; Pheol: phenylalaninol

consistent with the barrel stave model (Baumann and Mueller 1974; Boheim 1974). In this paper we will show that electrochemical data on alamethicin pore formation (Boheim 1974; Boheim and Kolb 1978; Kolb and Boheim 1978) agree with this flip-flop gating model even in subtle details.

Materials and Methods

1-stearoyl-3-myristoyl-glycero-2-phosphocholine (1,3-SMPC) was kindly provided by Dr. H. Eibl, MPI Göttingen (Boheim et al. 1980); 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine (1,2-POPC) and bacterial phosphatidylethanolamine (bac PE) were purchased from Avanti, Birmingham, USA, Lipids were $\gtrsim 99\%$ pure.

The carboxy group bearing fraction AL30 of the natural alamethicin mixture (Jung et al. 1981) which had been purified by column chromatography on DEAE cellulose and Kieselgel H was purchased from Microbial Products Development and Production Laboratory, Porton/Salisbury, England.

Planar bilayer membranes were formed from a 2 mg/ml solution of lipid in hexane/ethanol (9/1) either on a hexadecane pretreated teflon sandwich septum with a hole $\sim 2 \cdot 10^4$ μm^2 in area (Schindler and Feher 1976) or on the tip of a non-pretreated fire-polished glass pipette with $\sim 1-2$ μm tip diameter (Neher et al. 1978). Since hexane partitions into the aqueous phase and evaporates at the air/water interface, the lipid bilayer may be considered virtually solvent-free.

The principle of the mechanical setup and electronic equipment is described elsewhere (Boheim and Kolb 1978). Membrane voltage is designated positive, if the more positive potential is applied on the cis-side of the membrane. Current is designated positive, if cations are transferred from the cis- to the trans-side.

Results and Discussion

The secondary structure of alamethicin in organic solvents is α-helical between proline (2) and proline (14) (Jung et al. 1975, 1981; Mayr and Jung 1980). Recently, a synthetic undecapeptide analogue was crystallized, and structural

analysis revealed antiparallelly arranged rods of α-helices (Butters et al. 1981). For an α-helix of 13 amino acids one would expect a macrodipole of $\sim$ 65 D assuming a dipole moment of $\sim$ 5 D per peptide bond in the case of cooperative interaction (Hol et al. 1981). Under conditions of no cooperative interaction a dipole moment of $\sim$ 3.5 D per peptide bond is found (Hol et al. 1981). Direct measurements of the molecular dipole moment of alamethicin reveal 67 D (solvent: 25% ethanol in dioxane, Yantorno et al. 1982) and 75 D (solvent: 50% ethanol in dioxane, Yantorno et al. 1982; solvent: octanol, Schwarz and Savko 1982), respectively. Since the C-terminal amino acids (15–19, Fig. 1) are found to adopt nonhelical structure (Jung et al. 1975, 1981), this dipole moment mainly originates from the α-helical part. The length of an α-helix consisting of 13 amino acids amounts to $\sim$ 20 Å.

Several investigators have attempted to localize alamethicin during its interaction with a lipid bilayer. Circular dichroism experiments on lipid vesicles doped with alamethicin (Jung et al. 1977) or alamethicin analogues (C. Methfessel and H. Schmitt, unpublished results) revealed a high α-helical content. Infrared attenuated total reflection spectroscopy on lipid multilayers modified by alamethicin found the antibiotic within the bilayer (Fringeli and Fringeli 1979). These authors reported that helix unfolding to membrane spanning β-structures occurred after contact of the alamethicin containing membrane with an aqueous environment. However, this result has not been confirmed by other techniques (Jung et al. 1981). Alamethicin-phospholipid conjugates with a crosslink at the N-terminal part were detected after UV-irradiation of vesicles made from alamethicin and a phosphatidylcholine analogue with a carbene precursor. These conjugates showed alamethicin-like pore fluctuations (Latorre et al. 1981). These data lead to the suggestion that the alamethicin molecule is located within the lipid in α-helical conformation (Boheim and Kolb 1978).

Further experiments were done in order to compare several alamethicin analogues. Whereas alamethicin and suzukacillin A (Boheim et al. 1976) showed voltage-dependent pore formation with stable pore states, trichotoxin A40 and a synthetic nonadecapeptide induced voltage-dependent bilayer conductivity, but no pore states could be resolved (Hanke et al. 1983; Jung et al. 1979). However, trichotoxin A40 modified by a dansyl-group at the C-terminal part exhibited stable pore state fluctuations (Hanke et al. 1983). Furthermore, it was shown that melittin, the main constituent of bee venom, forms multi-level pores (Hanke et al. 1983). Its hemolytic properties (Irmscher and Jung 1977) as well as its primary and secondary structures reveal striking similarities to those of alamethicin (Hanke et al. 1983). Thus it was concluded that an α-helical part at the N-terminal side and a hydrophilic part at the C-terminal side are the prerequisites for voltage-dependent pore formation. The peculiar amino acid α-amino-isobutyric acid (AIB) and the C-terminal phenylalaninol are not essential for activity (Hanke et al. 1983).

Let us now assume that the alamethicin helices are oriented perpendicularly to the membrane plane, bridging the hydrophobic layer and with some probability for 'flipping'. Figure 2 shows how such dipoles can be expected to aggregate due to their electrostatic interaction. Let alamethicin be added to only

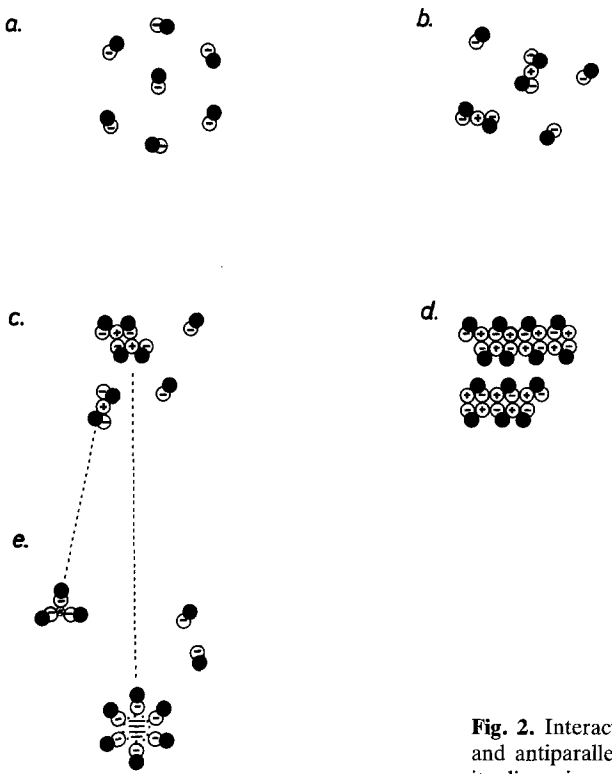

Fig. 2. Interaction scheme between parallelly and antiparallelly oriented α-helix dipoles. For its discussion see text

one aqueous compartment (cis-side of the membrane). It diffuses to the membrane and becomes incorporated with its α-helical part. The N-terminal positive pole points to the trans-side and the negative pole to the cis-side (n-dipole, $\ominus$). The C-terminal nonhelical part is indicated by a black dot. If two n-dipoles meet by lateral diffusion, they repel each other and only monomers are present (Fig. 2a). This changes, if a n-dipole flips into antiparallel orientation. It becomes a p-dipole ($\oplus$) with its positive pole pointing to the cis-side. The p-dipole attracts n-dipoles and a trimeric aggregate forms (Fig. 2b). The trimer may be favoured over the tetramer because of steric hindrance from the C-terminal part (amino acids 15–19 in Fig. 1). After some time of lateral diffusion and appearance of further p-dipoles larger aggregates establish, whereby the hexameric aggregate may be energetically and sterically preferred. It already shows the quadratic elementary unit of alternating p,n-dipoles (Fig. 2c). Finally equilibrium is reached and the aggregates show some kind of size distribution. With bilayers in the fluid state formation of large aggregates may be prevented by thermal motion. However, in case of a frozen lipid matrix extended structures may build up in form of parallelly oriented linear chains (Fig. 2d). This linear array results from the molecular asymmetry of the C-terminal part with respect to the α-helix. The interesting phenomena occur if a potential difference is applied across the membrane (Fig. 2e, we choose the

more positive potential on the cis-side). Changing to the energetically preferred orientation parallel to the electric field, p-dipoles (⊕) may flip back to n-dipoles (⊖). Within an aggregate, neighbouring n-dipoles repel each other thus creating a hole. This hole may be filled by lipid through lateral diffusive exchange or by water molecules. The latter case is possible, because dielectric screening and additional ionic screening at the partially charged poles can reduce the repulsive forces by at least one order of magnitude. The arrangement of those parallel α-helices will be a circular array in form of trimers, hexamers or other oligomers (Fig. 2e): a pore of varying diameter! (Baumann and Mueller 1974; Boheim 1974).

After voltage application and flipping of some p-dipoles to n-dipoles small aggregates consisting exclusively of n-dipoles become unstable, whereas larger aggregates do not. This leads to a shift in aggregate size distribution to monomers and larger aggregates. Generally, the type of pore fluctuations observed will reflect the distribution of aggregate sizes which depends on the concentrations of p- and n-dipoles, the flip-flop rate and the lipid environment.

Looking at the literature on alamethicin pore formation we find striking and convincing similarities in behaviour to the dipole flip-flop gating model as outlined above.

1. Insertion as monomers (Fig. 2a): A large excess of monomeric polypeptide over aggregates was found in adsorption experiments of alamethicin at the interface between glyceryl-monooleate in n-decane and NaCl solutions (Gordon and Haydon 1975). A change in dipole orientation is not possible under these conditions.

2. The weakly-voltage-dependent conductance (Boheim and Kolb 1978; Kolb and Boheim 1978; Cherry et al. 1972; Roy 1975): For this conductance path a second to third power dependence on alamethicin concentration was found (Roy 1975). Figure 2c, e illustrates the formation of a short-lived trimeric pore by a spontaneous dipole reorientation.

3. Aggregate size redistribution after a voltage-jump: In the case of a small weakly-voltage-dependent conductance a delay period for pore formation is observed (Baumann and Mueller 1974; Boheim and Kolb 1978). Noise analysis indicates a decrease of the number of conducting units with increasing voltage within this conductance range, whereas the mean conductance value per unit increases (Kolb and Boheim 1978). This corresponds to the redistribution in aggregate size described above.

4. The voltage-dependent conductance: The barrel stave model (Baumann and Mueller 1974; Boheim 1974; Boheim and Kolb 1978; Hanke and Boheim 1980) exactly describes the circular array of identical units around an aqueous pore and the gating of monomeric units. The voltage-dependent flip-flop of α-helix dipoles is consistent with this model.

5. Voltage-dependence of pore state distributions: Under conditions of no cooperative interaction, which applies to small aggregates, the effective charges at the α-helix poles are $+^1/_2$ and $-^1/_2$ elementary charge, respectively (Hol et al. 1981). The flip-flop of such a dipole is consistent with the single-pore (Boheim 1974) and multi-pore (Boheim and Kolb 1978; Kolb and Boheim 1978) data, if

the alamethicin dipole sees ~ 90% of the applied voltage. Since the thickness of the hydrocarbon core of a solvent free bilayer is about 22–25 Å (Boheim et al. 1980), the effective dipole should have a length of 20–22 Å.

We want to stress this point in more detail, because it demonstrates the quantitative agreement of the experimental results of alamethicin pore formation with the predictions of the flip-flop gating model. In a 'note added in proof' (Boheim and Kolb 1978) we concluded that orientational changes of the alamethicin dipole moment in an electric field between orientations parallelly and vertically to the membrane plane (insertion into the bilayer) would account for only about 50% of the voltage dependence which was expected to originate from a single alamethicin molecule (Boheim 1974). Consequently the flip-flop of single dipoles accounts *quantitatively* for the voltage-dependence of pore state distributions. This means that a flip-flop of single alamethicin molecules seems to occur if the pore undergoes transitions between any distinct pore state and the next neighbouring one.

The torque for such a flipping process is given by the vector product between the electric field and the helix dipole. This is zero for an antiparallel alignment of electric field and dipole. However, the helix-breaking property of the proline in position 14 causes a bend in molecule structure and because of this asymmetry process initiation.

Model calculations of Hol et al. (1981) estimate for the difference in electrostatic energy between a pair of parallel and a pair of antiparallel α-helices composed of 13 residues at a mutual distance of 10 Å a value of ~ 63 kJ · mol^{-1} (dielectric screening was neglected). In the case of a dipole moment of 65 D in an electric field this electrostatic energy is achieved at a potential difference of ~ 1 V over a distance of 20 Å. This seems to be a reasonable value.

6. Voltage-dependence of the pore formation rate (Boheim and Kolb 1978; Kolb and Boheim 1978): From alamethicin concentration dependency of the pore formation rate a preaggregate of six alamethicin molecules inserted with their α-helical part into the hydrophobic membrane core was proposed (Boheim and Kolb 1978). Voltage-dependent gating of two molecules then should initiate pore formation. Figures 2c, e illustrate this behaviour of the hexameric aggregate.

7. Aggregate size limitation (Boheim and Kolb 1978; Kolb and Boheim 1978; Boheim et al. 1976): With suzukacillin and at high alamethicin induced conductances the inactivation phenomenon is observed, as even large arrays are disrupted by an inordinate excess of parallel dipoles.

8. Autocatalytic transport: Applying the more negative potential on the side of antibiotic addition leads to an autocatalytic increase in membrane conductivity (Schindler 1979). Flipped dipoles initiate the formation of larger aggregates. The preconditioning procedures of Boheim and Kolb (1978) achieve a similar speeding up of the slow dipole orientation equilibrating process.

9. Lack of alkali cation selectivity: Compared to gramicidin A the lowest conductance state of the alamethicin pore is unselective (Hanke and Boheim 1980). This may be explained by the following: Alamethicin is composed of predominantly hydrophobic amino acids. The surface of the α-helices and consequently of the inner wall of the postulated pores are expected to be rather

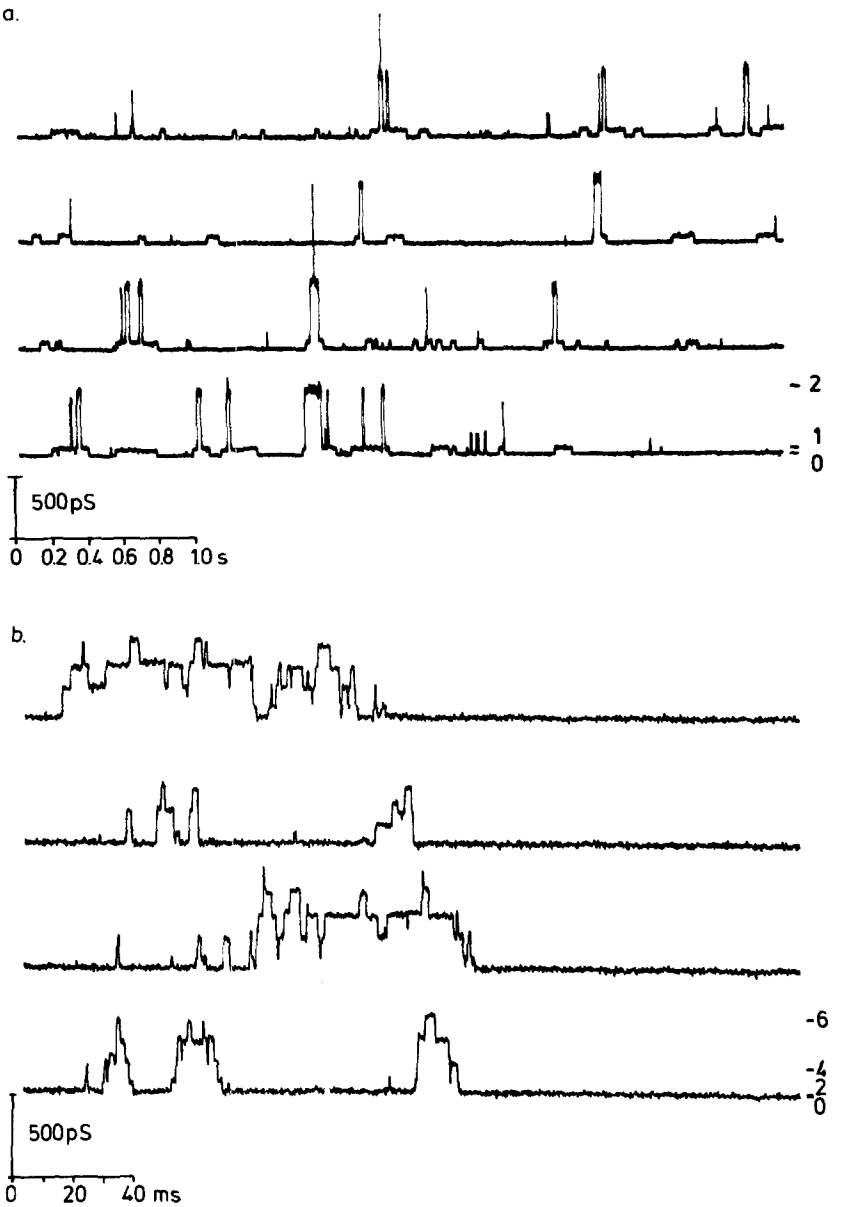

Fig. 3a and b. Alamethicin pore formation at different electrolyte concentrations demonstrating ionic strength dependence of pore state distributions. **a** At high ionic strength small pores are stable because of the reduced repulsion of parallel dipoles. The current fluctuation trace shows the first and second conductance levels as preferred pore states. The planar bilayer was formed on a hexadecane pretreated teflon sandwich septum. Lipid: 50% 1,2-POPC, 50% bac PE; salt: 5 M NaCl, pH ~ 6; alamethicin: 0.2 μg · cm^{-3} (nominally on cis-side); membrane voltage: 100 mV; temperature: 20° C. **b** At lower ionic strength only large pores are observed. The current fluctuation trace reveals the fourth to sixth conductance levels to be the mostly adopted pore states. The planar bilayer was formed on the tip of a non-pretreated fire-polished glass pipette. Lipid: 80% 1,2-POPC, 20% bac PE; salt: 0.05 M NaCl, pH ~ 6; alamethicin: 0.5 μg · cm^{-3} (nominally in bath solution); membrane voltage: 110 mV; temperature: 20° C

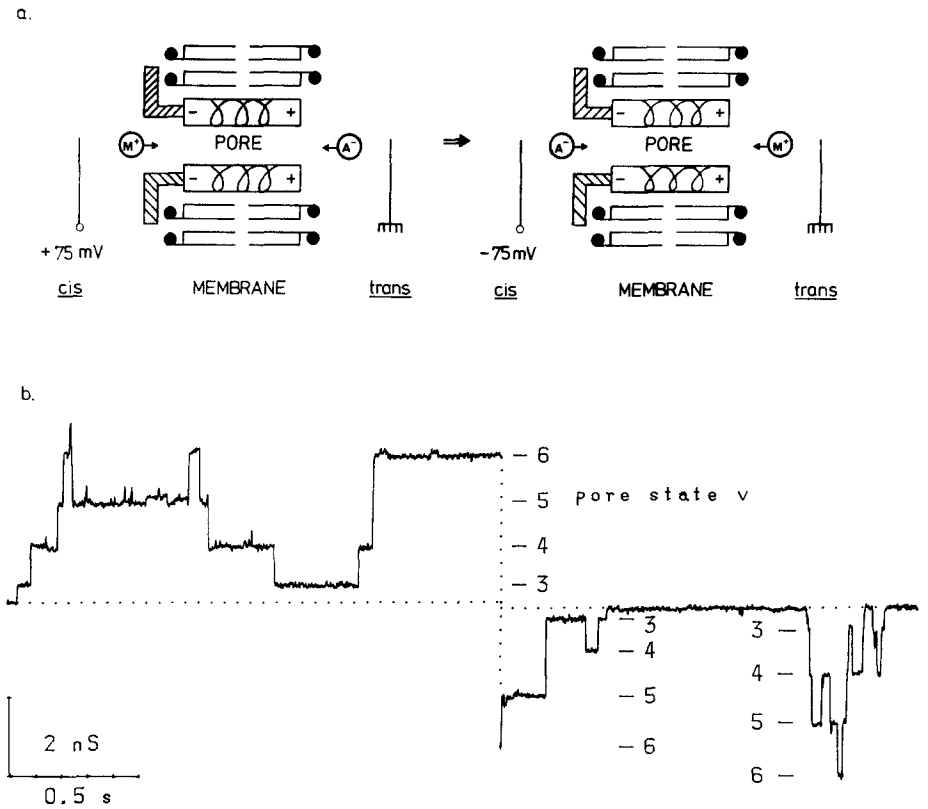

Fig. 4. a Because it is formed from parallel α-helical dipoles, the alamethicin pore exhibits asymmetric pore entrance charges as shown schematically on the left side. The negatively charged C-terminal poles are directed towards the side of positive applied potential and the positive poles point to the negative side of the membrane. The current carrying ions from both sides see attractive charges, leading to an increased pore state conductance due to the Gouy-Chapman effect. After voltage sign reversal, the pore decays as the dipoles realign to the electric field. During this stepwise closing process the current carrying ions see repulsive charges at the pore entrances which reduce the pore state conductances (right side drawing). **b** The trace shows a single pore fluctuation induced from the cis-side at +75 mV. Following a potential jump to −75 mV the pore closes in a stepwise manner. The individual pore state conductances are reduced after the jump, especially for the lowest state observed (v = 3). A short time later, a new pore induced from the trans-side appears. Since the current carrying ions now see attractive charges, the pore state conductances again assume the larger values. The planar bilayer was formed as described in Fig. 3a. Lipid: 1,3-SMPC; salt: 0.5 M KCl, pH ~ 6; alamethicin: 0.4 $\mu g \cdot cm^{-3}$ (nominally on cis-side); temperature: 14° C, or approximately 15° C below lipid phase transition temperature (Boheim et al. 1980). The capacitive "spike" was numerically subtracted for this trace

hydrophobic than hydrophilic. It is observed that the ion conductivities within large pore states are comparable to the corresponding bulk solution conductivities (Hanke and Boheim 1980). This is different in the case of the gramicidin A pore. Here the hydrophilic groups of the peptide backbone line the inner wall of the pore. Electrostatic interactions between pore and permeating ions are expected which leads to ion selectivity.

At this point we want to repeat our critique of the experimental data of Gordon and Haydon (1975) from which they concluded a size cut-off for ion permeation. It was shown by Hanke and Boheim (1980) that the large ions tris · H^+ and hepes$^-$ pass the alamethicin pore. The misinterpretation in case of Gordon and Haydon (1975) results from the fact that the contribution of the large cation to the pore state conductances is only about 5% of that of the chloride ion. This was within their limit of experimental resolution.

10. Lipid bilayer morphology: In the liquid-crystalline state of a lipid bilayer alamethicin induces an irregular granular texture on the fracture faces, whereas in the crystalline state uniformly spaced rows of particles are visible (McIntosh et al. 1982) (Fig. 2d).

11. Lipid flip-flop: A voltage-dependent lipid flip-flop induced by alamethicin was observed by Hall (1981). The quantity of flipped lipid molecules increases with the pore induced membrane current, i.e., with the rates of pore formation and pore state transitions.

In addition to the literature recapitulation given above we present two further experimental facts supporting the dipole gating model. Figure 3 clearly demonstrates the ionic strength dependence of pore state distributions (Hall 1975). At high ionic strength the effective radius of electrostatic forces is strongly reduced (Debye length < 1.5 Å in 5 M NaCl). In this case small pores are stable because of the reduced repulsion of parallel dipoles. The current fluctuation trace in Fig. 3a shows the first and second conductance levels as preferred pore states. Lower ionic strength leads to a larger effective radius for electrostatic repulsion (Debye length 14 Å in 0.05 M NaCl). Small pores become unstable and only large pores are observed. The current fluctuation trace in Fig. 3b reveals the fourth to sixth conductance levels to be the mostly adopted pore states. In addition, the mean lifetime of the most probable pore state in (b) is ca. one order of magnitude shorter than that in (a).

Due to the arrangement of parallel dipoles the alamethicin pore should be asymmetric with respect to pore entrance charges. This is schematically drawn in Fig. 4a. The experimental result in Fig. 4b shows that, indeed, the pore state conductances are asymmetric in a manner consistent with this model. Unusually long pore state lifetimes and the very slow pore decay process observed after voltage-sign reversal are achieved, because the alamethicin-lipid system is almost completely frozen 15° C below lipid phase transition temperature (Boheim et al. 1980).

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