Is Flexoelectricity the Coupling Factor between Chemical Energy and Osmotic Work in the Pump? A Model of Pump

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Abstract. The following pump model is proposed. A gate is responsible for pump specifity. The actual driving force of the transport of ions against the electrochemical potential gradient is the electric field originating from an altered curvature of the phospholipid bilayer around the pump. The physical origin of this curvature-induced electric field arises from a basic liquid crystal property of lipid bilayers called flexoelectricity. Alterations occurring in phospholipid bilayer arrangement are due to changed conformation of protein; the main energy source of this change is ATP. Consequently, the energy of ATP is transformed, in our pump model, into osmotic work in following steps: ATP + protein (conformation I) → protein (conformation II) → alterations in phospholipid bilayer arrangement → electric field → active transport of ions. This model is the most simple one. In Na, K-pump there is a bidirectional ion transport. In our model of Na, K-pump three conformational states of pump proteins and two different electric fields formed sequentially in opposite directions are supposed.

Key words: Model of pump — Flexoelectricity — Active transport of ions — Na, K-pump — Electric field

Introduction

In the last two decades much progress has been achieved in studying active ion transport. Enzymes responsible for this transport, termed ATPases, were thoroughly studied. It has been shown that ATP is, without any doubt, the energy source for active ion transport against their electrochemical potential gradient (for review, see Dunham and Hoffman 1980; Boldyrev and Tverdislov 1978; Skou and Nørby 1979).

Several steps can be distinguished in active transport: "recognition" of the respective ion by the pump, translocation of the ion across the membrane, and release of the ion from the membrane. Our considerations were focused on the way

in which the ion is transported across the membrane. To answer this question, a model implicating a physical phenomenon called flexoelectricity, has been proposed.

Flexoelectricity

Flexoelectricity is a term coming from the physics of liquid crystals (de Gennes 1974). It is used to describe flexion-induced polarization, a phenomenon occurring in a liquid crystal body (a body with long range orientational molecular order). The existence of curvature-induced (flexoelectric) polarization of biomembranes in their liquid crystalline state was postulated by Petrov (1975) and has already been considered to function in some transport processes (Petrov 1977, 1978; Petrov et al. 1978). The flexoelectric phenomenon in biomembranes is briefly described in the present paper, for more details see Petrov et al. (1979) and Petrov and Bivas (1984).

From the phenomenological point of view the curvature of a membrane is a symmetry-breaking operation. Even if nonpolar in flat state, the curved membrane can be electrically polarized. The electric polarization vector of the curved membrane can be directed towards or from the centre of the curvature, depending on the sign of the flexoelectric coefficient. The quantitative expression of curvature-induced polarization P_s per unit area (Petrov 1975) is:

$$P_s = e\left(\frac{1}{R_1}+\frac{1}{R_2}\right), \tag{1}$$

where R_1 and R_2 are the two principial radii of the membrane curvature at a given point, and e is the flexoelectric coefficient in coulombs (C). Positive sign of e corresponds to P_s directed from the centre of the curvature, and a negative e corresponds to P_s directed oppositely.

The polarization per unit area can be calculated by integrating the distribution of volume membrane polarization $P(z)$ over the whole membrane thickness including polarized water layers adjacent to both polar groups surfaces. In a lipid bilayer, major contributions to $P(z)$ come from dipolar moments of polar head groups, ester linkages of fatty acid residues, small dipoles at $-CH_3$ end groups of each chain, and from polarization of structured water molecules around each head group.

In a flat symmetrical bilayer, $P(z)$ is an antisymmetric function (dipolar moments of lipids in both monolayers have opposite directions) so that its integral is zero. Several mechanisms that destroy the antisymmetry of $P(z)$ in curved bilayers and give rise to non-zero P_s, have been analyzed. A brief description of these mechanisms is given in Appendix.

The contribution of the different mechanisms was estimated and a value of $\frac{1}{3}\times 10^{-19}$ C was obtained for the flexoelectric coefficient (Petrov 1984), its sign

being probably negative for all the mechanisms. When flexoelectric polarization is homogeneously spread over the membrane thickness P_s/d the corresponding depolarizing electric field E^i for a spherically curved membrane sector is according to electrical displacement continuity low

$$E^i = -(P_s/d)/\varepsilon_o = -2\,e/(Rd\varepsilon_o) \tag{2}$$

where $\varepsilon_o = 8.85 \times 10^{-12}$ F/m is the absolute dielectric constant of free space and $R = R_1 = R_2$ have the same meaning as in equation (1). This field corresponds to a transmembrane potential difference

$$\Delta U = -2\,e/(\varepsilon_o R) \tag{3}$$

At a curvature radius $R = 100$ nm $= 10$ d and $e = \frac{1}{3} \times 10^{-19}$ C a substantial electric field $E^i = 7.5 \times 10^6$ V/m arises, equivalent to a potential difference $\Delta U =$ 75 mV. This field is sufficient to move ions against their concentration gradient even at relatively small curvatures as above.

Another way of creating a polarization disbalance between the two monolayers with a resulting noncompensated depolarizing field is to change the orientation of the dipoles in one monolayer by their rotating around the axis parallel to the membrane surface. This occurs, e.g. when a half of a hydrophilic edge is formed around an integral membrane protein (Petrov et al. 1978). Our flexoelectric model of the pump makes use of both of these possibilities, suggesting that the lipid environment is most important for the pump functioning.

Proposed Model of Ion Transport across the Membrane

The pump model of Shamoo and Ryan (1975) and the known properties of Na, K- and Ca-pumps were applied to our model (Table 1, Fig. 1). The pump model, as proposed by Shamoo and Ryan (1975), consists of two major parts, a gate and a channel; the gate is responsible for the selectivity of ions transported through the channel. This model is consistent with the structure-function unitization model of biological membranes of Green et al. (1972).

A channel, or a channel and a cavity in the pump help to elucidate the problem of flexoelectricity-induced ion translocation across the membrane. In our proposed model (Fig. 1) the ion becomes translocated through the membrane via a channel (or a cavity) due to electric field which is generated in the phospholipid bilayer of the pump as a result of deformation of the bilayer. A prerequisite for the development of an electric field is a strong conformation change in the protein subunits, manifested by a change in their overall shape, e.g. from cylindrical to pear-shaped. Although similar alterations have not yet been fully recognized, they do not contradict any hitherto experimental findings. If, due to ATP and ions, the conformation of subunits and, perhaps, their energy content become changed, we may reasonably expect shape alterations of the whole protein complex and

subsequently of phospholipids bound to particular proteins in the pump as well. Finally, the orientation of phospholipids changes and an electric field arises. Thus, in our proposed model, phospholipids represent a kind of a coupling factor between conformational changes of the proteins and the actual force for translocation of ions.

The radius of the lipid bilayer curvature R around a pear-shaped protein can be estimated as follows (Fig. 1):

$$R = a/\alpha \tag{4}$$

where a is the diameter of the protein and α is the conical angle (Fig. 1). If $a = 10$ nm and $\alpha = 0.1$ rad $= 6^{\circ}$, according to equation (4) $R = 100$ nm, and with $e \sim 1/3 \times 10^{-19}$ C, a depolarizing electric field $E^{i} \sim 10^{7}$ V/m should arise. Hence even minute shape changes (~ 0.1 rad) are sufficient to produce flexoelectric polarization and a depolarizing electric field strong enough to transport ions.

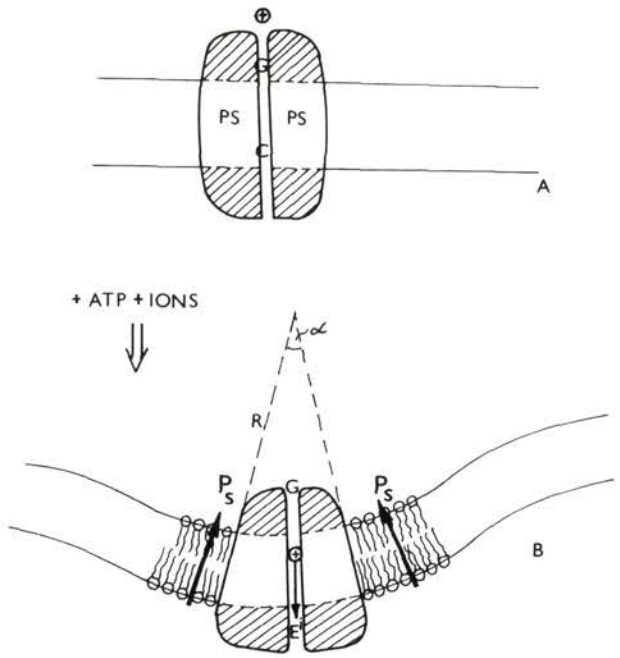

Fig. 1. Proposed model of a pump performing unidirectional ion transport: The pump is composed of protein subunits and lipids. Due to conformation changes of the protein subunits induced by ATP and ions, the phospholipid bilayer becomes curved. This curvature induces flexoelectric polarization and an electric field which represents the actual driving force for ion translocation. The direction of the flexoelectric polarization corresponds to the negative flexocoefficient. (A) basic state of the pump, (B) state of the pump during the translocation of ion (s), (⊕) the ion transported, (G) gate, (C) channel, (PS) protein subunits, (P_s) flexoelectric polarization, (E^i) depolarizing electric field.

To produce a spherically curved bilayer sector, a small amount of chemical energy of ATP is necessary to overcome the bending stiffness of the lipid bilayer. The elastic energy density is given by the formula (Helfrich 1973)

$$g = \frac{1}{2} K \left(\frac{1}{R_1} + \frac{1}{R_2} \right)^2 \tag{5}$$

where K is the elastic modulus of bending, R_1 and R_2 are the radii of the membrane curvature. It can be estimated that a small membrane sector of a sphere with a radius R, with the radius of the sector $r_1 < R$, will store a total elastic energy

$$G \approx \frac{1}{2} K \left(\frac{2}{R} \right)^2 \cdot \pi r_1^2 = 2\pi K \left(\frac{r_1}{R} \right)^2 \tag{6}$$

With $r_1/R \sim 1/10$ and $K \sim 10^{-19}$ J (Helfrich 1973) this energy is 6×10^{-21} J, while the free energy of enzymatic hydrolysis of one molecule of ATP is 7×10^{-20} J (49.4 kJ/mol; Boldyrev and Tverdislov 1978); a part of this energy can be used to curve the membrane. The energy necessary to produce the above curvature of the lipid bilayer is of the order of the thermal motion energy ($kT = 4 \times 10^{-21}$ J).

Indeed, biomembranes are subjected to intense thermal curvature fluctuations of a similar magnitude (Brochard and Lennon 1976; Petrov and Bivas 1984). This means that shape transformations of the pump proteins utilizing ATP energy may not be used to just mechanically drive the lipid bilayer into a bent configuration, but rather to "clamp" one of the signs of the fluctuating curvature, making it energetically more advantageous than the other one. In this way, one direction of flexoelectric polarization persists for a short time sufficient to transport the ion across the membrane. Our model is thus getting a dynamical character.

According to our hypothesis, the process of ion translocation across the membrane can be expressed in terms of energy conversion by several steps shown in Table 2. The most simple model for ion transport is the one mentioned above. In Na, K-pump the situation is more complicated since the pump transports Na^+ and K^+ ions in opposite directions. We suppose that Na, K-pump contains two channels, one specific for Na^+ and another for K^+, or, which is less probable, one channel with two specific gates (for Na^+ and K^+) that alternatively "open" and "close".

In order to generate a driving force for the transport of Na^+ and K^+ ions in opposite directions, two different electric fields formed sequentially have to be anticipated. This idea is in no contradiction to the known states of Na, K-ATPase (Albers 1967; Post et al. 1969). Post and Sen (1965) on the basis of experimental results believe, that 2—3 phosphate intermediates of the enzyme with higher and lower energy are formed during ATPase reactions; Albers (1967) and Post et al. (1969) suggested two phosphorylated enzyme states to occur during Na, K-ATPase reaction.

It is likely that the enzyme has somewhat different shapes in various conformation states which are energetically different. Shape changes may then induce variations in the arrangement of adjacent phospholipids, resulting in the production of different electric fields.

During ATPase reaction the exposure of some polar groups in a protein molecule may also change, and this can be important for the transport of ions as well (e.g. in "opening" the gate or in the arrangement of phospholipids).

Our proposed model of Na, K-ATPase makes use of some information concerning the molecular organization of Na, K-pump (Boldyrev and Tverdislov 1978). Fig. 2*a* shows the arrangement of two large and two small subunits of the enzyme in a tetramer seen from the outside of the cell. It may be accidental that two cavities or channels between the subunits can be recognized with such an arrangement. A transversal view is shown in Fig. 2*b*.

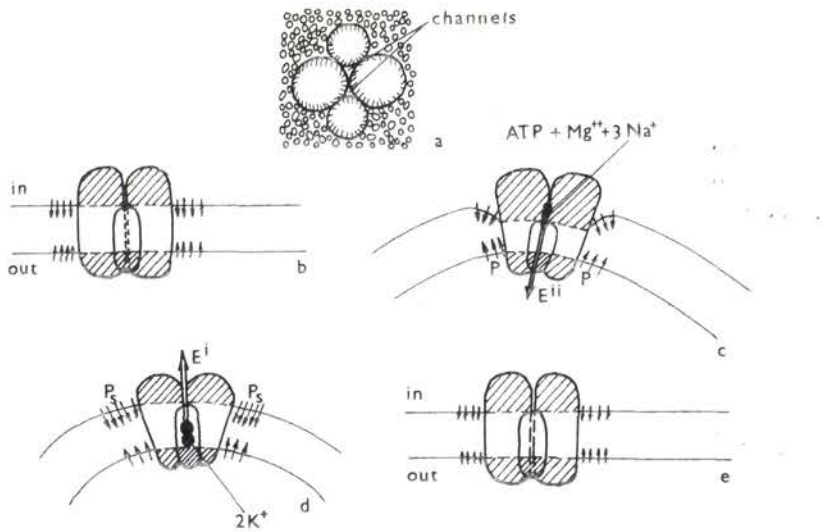

Fig. 2. Proposed model of Na, K-pump showing basic and two intermediate stages with oppositely directed electric fields being responsible for bidirectional ion transport. (*a*) Top view of the arrangement of the pump subunits (Boldyrev and Tverdislov 1978). Note that two channels can be visualized with such an arrangement. (*b*) Transversal section of the membrane and the pump in its basic state. The two monolayers in the vicinity of the pump are oppositely polarized (arrows) and balanced. (*c*) The first energized state of the pump. Due to conformational changes in the large subunits the inner monolayer forms a half edge with a corresponding rotation of its polarization. More than two ions are necessary for the edge formation (see text). Polarization (P) of the outer monolayer remains uncompensated and creates a field E^{II} which moves 3 Na^+ ions outside. (*d*) The second energized state of the pump. The edge is removed, and the overal pear-shaped form of the pump subunits remains. Flexoelectric polarization (P_s) is now due to the excess dipolar moment in the inner monolayer. The depolarizing field E^i moves 2 K^+ inside. (*e*) Restoration of the cylindrical shape of the subunits restores the basic state of the pump.

We have already suggested (Petrov 1977; Petrov et al. 1978) that during the binding of ATP and 3 Na^+ to the inner side of the pump a half hydrophilic edge is formed around the pump due to a change in the wetting of conformationally altered proteins as well as to the energetic balance between the electrostatic energy of 3 positive charges within a hydrophobic core and elastic energy necessary for the formation of a half edge (edge energy γ, see below). In addition, we assume now an overal pear-shaped transformation of the whole protein complex inducing a curvature of the surrounding lipid bilayer, as stated above (Fig. 2*c*).

Different biochemical and physical steps can be anticipated during active Na^+ and K^+ transport. Let us consider first the energetics of the edge formation. Approximating the large subunit as a sphere with a radius r, carrying a homogeneously distributed charge q, its excess electrostatic energy (with respect to water environment), when completely dipped into the hydrophobic core with a low dielectric constant ($\varepsilon = 2$), is $q^2/(8\pi\varepsilon\varepsilon_o r)$. When the edge is formed, the excess electrostatic energy is negligible due to the highly polar environment; in this case, however, the elastic energy for the half edge formation, $\pi\gamma r$ is quite considerable. According to Petrov et al. (1978) both energies become equal at

$$r_{max} = q/(2\pi\sqrt{2\varepsilon\varepsilon_o\gamma}) \tag{7}$$

If the protein radius r exceeds r_{max}, the formation of the edge will be energetically unfavourable. The calculation of r_{max} for one elementary charge $q = 1.6 \times 10^{-19}$ C and the measured value of $\gamma = 2 \times 10^{-11}$ J/m for egg lecithin bilayers (Harbich and Helfrich 1979) yields $r_{max} \sim 1$ nm. Because the radius of the large subunit is $r \approx 2.5$ nm, at least three charges are necessary for the edge to be formed. With two charges the edge would disappear.

The formation of the edge will simultaneously rotate the orientation of lipid dipoles in the inner monolayer (Fig. 2*c*) so that normal dipolar moments of approximately $n = 40$ molecules (within a ring with an inner radius of 2.5 nm and an outer radius 3.5 nm) will be unbalanced. Taking a mean radius $r = 3$ nm, we can calculate based on electrostatics that these dipoles create in the centre of the protein a field

$$E^{ii} = -n\mu/(4\pi\varepsilon_o r^3) \tag{8}$$

From monolayer measurements a value of $\mu \sim 2 \times 10^{-30}$ C . m was estimated (Vilallonga 1968). From these values it can be calculated that a field $E^{ii} = 2.7 \times 10^7$ V/m arises, with a direction such as to expel Na^+ ions from the cell.

According to our presumption, at the next step — transport of 2 K^+ — the edge is removed (2 charges are not sufficient to keep it, as shown above), but the overal curvature remains; now, the uncompensated dipoles of the inner monolayer give a flexoelectric polarization and a depolarizing field E^i which is directed oppositely to E^{ii} and can move K^+ ions inside (Fig. 2*d*). Finally, ADP is detached,

ions are released, and the initial protein shape and bilayer planarity is restored (Fig. 2e).

According to our hypothesis, ATP energy accumulated in the proteins and the lipids can be released step by step including two intermediate energized stages with oppositely directed flexoelectric fields; these fields can move Na^+ and K^+ ions along the specific channel (channels).

Discussion

Recent models of pumps (Tverdislov et al. 1979) are based on the assumption that the exchange of ions is accomplished by means of thermally stimulated sliding vibrations of the small subunit along the large one. Namiot and Merkulova (1980) proposed a model of active ion transport, based on direct transport of ions through the flexoelectrically polarized lipid layer surrounding the asymmetrical protein.

Consistently with the generally accepted view, we assume that the primary energy source for the pump operation is ATP. The particular steps in our proposed model are listed in Tables 1 and 2 and illustrated in Fig. 1 and 2. Conformational changes and the protein structure in the pump are now being studied using top laboratory methods. This problem has largely been discussed in a monograph on Na, K-ATPase by Boldyrev and Tverdislov (1978) and in another edited by Skou and Nørby (1979).

Table 1. The proposed model of the pump

1) The pump is an asymmetrical oligomer with a specific gate for the respective ion
2) The pump includes a channel or a channel and a cavity
3) Subunits of the pump are subject to conformational changes due to ATP and ions
4) Extensive conformational changes in protein subunits are responsible for alterations of their shape
5) Shape alterations of protein subunits induce changes in the arrangement of adjacent phospholipids
6) Structural changes in phospholipid arrangement produce an electric field
7) By the action of the electric field cations are transported through the channel (cavity) even against their electrochemical potential gradient

Table 2. Presumed way of energy transformation during active transport of ions

Chemical energy of ATP
↓
Chemical energy of protein (conformational alteration)
↓
Work causing alteration of protein shape and changes in the arrangement of phospholipid bilayer
↓
Formation of an electric field in the phospholipid bilayer
↓
Osmotic work in the transport of ions against the electrochemical potential gradient

However, we still lack understanding of how the energy released from ATP is utilized for the operation of the pump. It is very likely that the first step in the transformation of chemical energy of ATP to osmotic work during the active transport of ions is the formation of an energy rich state of ATPase accompanied by its conformational change.

According to Yamada and Tonomura (1972), the production of a phosphorylated energy-rich intermediate of Ca-ATPase is associated with Ca^{2+} transport. An "energized" conformation has already been proposed in a model of Na, K-pump by Charnock et al. (1971) and in a general model by Blondin and Green (1975). The latter authors believed that during both the transport of ions and muscle work, the chemical energy of ATP becomes transformed into energy-rich states of the respective proteins.

Considering experimental results obtained so far we are unable to decide whether the strong conformational changes within the ATPase molecule result in shape and function variations only or whether they eventually lead to a kind of "contraction" of the whole pump. Most probably it is not just accidental that the molecular masses of large and small subunits of Na, K-ATPase are similar to those of heavy meromyosin and G-actin (Boldyrev and Tverdislov 1978).

The role of lipids and phospholipids in transport ATPases has long been known (Schatzmann 1962; Ohnishi and Kawamura 1964). Changes in membrane lipid states control the ATPase activity (Priestland and Whittam 1972; Boldyrev and Tverdislov 1978) and induce alterations in the conformation of its active center (Boldyrev et al. 1977; Tabak et al. 1977).

Boldyrev and Tverdislov (1978) mentioned that the protein subunit may become deformed during the transport of ions, and lipids enclosing the pump protein may be rearranged while simultaneous changes in orientation of polar heads of phospholipids occur. The alterations assumed in the phospholipid arrangement due to conformational changes of proteins in the pump are also consistent with the view of Raikhman and Moshkovsky (1975) that conformational changes of proteins are responsible for viscosity changes of lipids.

Phospholipids easily bind cations (Solomon et al. 1956; Kirschner 1958) and they were thus considered to participate in the active transport of ions as "carriers" (Wheeler and Whittam 1970). In our model phospholipids do not figure as "carriers" in the biochemical sense; however they are considered "carriers" from the physical point of view, i.e. they represent membrane material which performs the actual transport of ions across the membrane as a result of flexoelectricity.

In a recent model by Tverdislov et al. (1979) two ion exchange cavities were supposed on both subunits (the large and the small one) instead of channels. The contact and exchange of ions between these cavities is accomplished by means of thermally stimulated sliding vibrations of the small subunit along the large one. The energy necessary to dip the small subunit into the hydrophobic core (edge

formation in the outer monolayer) is well above the kT level (5—10 kT according to Tverdislov et al. 1979). The probability is proportional to exp $(-U/kT)$ and contacts between the subunits permitting exchange of ions may not occur frequently enough. However, the idea of flexoelectricity can well be applied to this particular model as well. We suggest that the inside sliding of the (positively charged) small subunit can be promoted by a flexoelectric field E^i corresponding to the second energized stage (Fig. 2*d*). A slight pear-shaped conformation of the large subunits must be assumed. After the restoration of the cylindrical shape of the latter, the small subunit will occupy its original position by simple elastic spring mechanism, due to elastic energy stored in the edge.

In our view the role of lipids in the pump is twofold: 1) Some lipids, including phospholipids, condition the activity of transport ATPase while other control it. 2) Phospholipids are virtually the driving force in the transport of ions since changes in their arrangement give rise to an electric field. To fullfil this function, phospholipids around the pump have to be arranged in a form of a bilayer; such an arrangement has already been suggested by Singer and Nicolson (1972) and by Simpkins and Hokin (1973). Moreover, flexoelectricity can only be operative if phospholipids exist in liquid crystal state. This state, according to Steim et al. (1969), is also a prerequisite for the normal function of various biological transport systems.

It can be concluded that, according to our hypothesis, proteins as well as phospholipids and flexoelectricity should play an important role in the active transport of ions.

Appendix

Different Mechanisms Destroying Antisymmetry of $P(z)$ in Curved Bilayers, Giving Rise to Non-zero P_s

1. *Dipolar mechanism at blocked flip-flop/blocked lateral diffusion* (Petrov and Pavloff 1979; Petrov 1978). It is well known that during pure bending (without stretching) of coupled monolayers the area of the mid-plane of the bilayer remains constant, so that the outer monolayer becomes stretched and the inner one compressed. This is the case in blocked lipid exchange in both transversal and lateral direction. In this case, the number of dipolar lipid molecules with respect to the unit area of the mid-surface remains the same in both monolayers, but the magnitude of their dipolar moments changes as a result of either stretching or compression. This effect is analogical to polarization of a bimorpho-piezoelectric plate under bending. The corresponding expression for the flexoelectric coefficient is

$$e^B = -\left(\frac{d\mu}{dA}\right)_{A_0} \cdot d \qquad (A1)$$

where $d\mu/dA$ is the derivative of the dipolar moment per molecule with respect to the area per lipid head in a curved stage, A_0 is the area per lipid head in a planar stage, and d is the membrane thickness.

Information about $d\mu/dA$ can be obtained from monolayer measurements of the surface potential of different lipid monolayers, pure and mixed. It reflects changes in the polar head conformation and the configuration of the structured water at the change of packing.

2. *Dipolar mechanism at free flip-flop/free lateral diffusion* (Petrov and Derzhanski 1976; Petrov and Bivas 1984). When transbilayer lipid exchange is possible or lateral redistribution can occur, bilayer bending is equivalent to the bending of two uncoupled monolayers, each of them having its own neutral surface over which the area lipid density remains unchanged as compared to that in flat state. This means, however, that with respect to a unit area of the midsurface there will be more dipoles in the outer monolayer than in the inner one so that an imbalance of the oppositely directed dipoles will be created in the curved bilayer. The flexoelectric coefficient is now

$$e^{F} = -2\left(\frac{\mu}{A_o}\right) \cdot \delta_N \tag{A2}$$

where δ_N is the distance from the mid-plane to the monolayer's neutral surface. In general, $\delta_N \leqq d/2$. When the neutral surface does not coincide with the head group surface, a residual stretching-compression of the head groups would require an addition of the "bimorph" mechanism (1), numerically equal to that of a membrane with a thickness $2\,\delta_H$, where $\delta_H = d/2 - \delta_N$ is the distance from the head group surface to the neutral surface:

$$e^{F} = -2\left(\frac{\mu}{A_o}\right)\delta_N - 2\left(\frac{d\mu}{dA}\right)_{A_o} \cdot \delta_H \tag{A3}$$

The dipolar moment per lipid can be evaluated from the surface potential measurements in lipid monolayers (Davies and Rideal 1963). Typical values are $\sim 2 \times 10^{-30}$ C . m, the hydrophobic core being positive with respect to the ambient liquid (Vilallonga 1968).

3. *Quadrupolar mechanism* (Prost and Marcerou 1977; Petrov et al. 1979; Petrov 1984). In addition to dipolar moments, lipid molecules also posses quadrupolar moments. Curving of an array of oriented quadrupoles results in a volume polarization equal to the divergence of the quadrupolar density (Prost and Marcerou 1977). This mechanism is active at both free and blocked flip-flop. In lipid bilayers there are quadrupolar moments of $-CH_2$-groups in the hydrophobic core and quadrupolar moments of the head groups. The flexoelectric coefficient is

$$e^{Q} = -\frac{1}{3}\left(L_{zz} - \frac{2}{3}\right) N\,\bar{S}\,\Theta_a \tag{A4}$$

where $\Theta_a = \Theta_{zz} - \frac{1}{2}(\Theta_{xx} + \Theta_{yy})$ is the anisotropy of the tensor of the quadrupolar moment, $\bar{S}$ is the mean degree of the liquid crystal (uniaxial) order, N is the number of quadrupoles per unit area, L_{zz} is the component of the Lorentz local field tensor ($L_{zz} \gtrsim 1$).

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Received November 15, 1984/Accepted January 30, 1986