DIPOLE MOMENT, ENTHALPY, AND ENTROPY CHANGES OF HODGKIN-HUXLEY TYPE KINETIC UNITS

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ABSTRACT Dipole moment, enthalpy, and entropy changes were calculated for hypothetical structural units which control the opening and closing of ionic channels in axon membranes. The changes of these thermodynamic functions were calculated both for activation (transition to intermediate complex) and for the structural transformation as a whole. The calculations are based on the experimentally determined Q_{10} values and the empirical formulae for the rate constants (α's and β's) as functions of membrane potentials in Hodgkin-Huxley type models. From the calculated thermodynamic functions we suggest that the specific structural units of the axon membranes are probably of macromolecular (possible protein-like) dimensions with large dipole moments (hundreds of debyes). The calculated dipole moment changes of a single structural unit indicate that in many cases these dipole moments saturate at strong depolarizations or hyperpolarizations. The transitions in structural units show substantial activation enthalpies and entropies but the net enthalpy and entropy changes are practically negligible for the transition as a whole, i.e. the structural units presumably undergo displacements. While the calculated dipole moment changes associated with structural transformations in *Loligo* and *Myxicola* show similar potential dependencies, those for *Rana* usually show a different behavior. The relevance of the dipole moment changes to gating currents is discussed.

INTRODUCTION

One of the possible interpretations of the Hodgkin-Huxley axon model is that the kinetic parameters describe "gating" processes which can be related to some structural or conformational changes in specific areas in the membrane. These transformations are field or potential-dependent and only indirectly current dependent. Only recently experimental evidence which supports this interpetation has been forwarded (Keynes and Rojas, 1973, 1974; Bezanilla and Armstrong, 1974; and Armstrong and Bezanilla, 1974).

The main experimental manifestation of the membrane processes at present are the membrane ionic currents. Because of the macroscopic nature of the available information its direct physical interpretation must inevitably be thermodynamic. The description of the system in thermodynamic terms on the other hand makes it possible to extend further the physical interpretation of the data and to check the internal consistency of models.

The energies and entropies of activation (or the corresponding Q_{10}) were estimated on the basis of the Hodgkin-Huxley type models for the various membrane processes (Hodgkin et al., 1952; Cole, 1968; Tsien and Noble, 1969; Moore, 1971; Schauf, 1973). To characterize the effect of membrane potential on the "gating" processes the value of the effective charge transferred during an elementary structural change was estimated (Hodgkin and Huxley, 1952). Recently more general functions representing the free energy changes were used by Hill and Chen (1972).

Tsien and Noble (1969) used Eyring's theory of transition state (Glasstone et al., 1941) for a thermodynamic representation of the Hodgkin-Huxley kinetic parameters (α and β). They assumed a linear dependency of the free energy of activation on the membrane potential and interpreted it as resulting from a net charge transfer across a potential barrier occupying some part of the membrane. This approach made it possible for them to estimate the effective net charge transferred during the elementary structural change associated with membrane activity. The values thus obtained agree with those of Hodgkin and Huxley (1952). More recently Keynes and Rojas (1974), and Nonner et al., (1974), based the analysis of their results on similar assumptions.

Hill and Chen (1972) assumed that the free energy changes associated with membrane "gating" processes can be expressed as a function of membrane potential by means of a second order polynom. They calculated the coefficients of these polynoms from the empirical formulae of the kinetic parameters (α's and β's) obtained from *Loligo forbesi* and *Rana pipiens*. Hill and Chen (1972) list the possible physical processes which may be responsible for the potential dependency of the free energy changes. In principle they are net charge transfer and dipole moment changes (polarizational or orientational).

In this presentation we intend to assume that the potential dependency of the free energy changes is determined only by a dipole moment change in some specific structural units which undergo an internal transformation. In other words, we assume electrical neutrality of the structural unit as a whole (including counterions if necessary). On this basis we calculate the dipole moment changes using the available empirical expressions for kinetic parameters as functions of the membrane potential. The corresponding standard enthalpies and entropies will be included.

GENERAL CONSIDERATIONS

For the thermodynamic interpretation of Hodgkin-Huxley's kinetic model let us assume that the membrane includes some structural units which can be in one of two different states or forms. The ratio between the numbers of these units in each state determines the magnitude of a particular ionic current. The kinetics of the transformation of the structural unit determines the rate of current changes. These considerations may be represented in symbolic form as follows:

$$1 \underset{\beta_i}{\overset{\alpha_i}{\rightleftarrows}} 2 \qquad (i = n,m,h). \tag{1}$$

Here 1 corresponds to a "closed" state, and 2 to an "open" state. *m*, *n*, *h* are the Hodgkin-Huxley kinetic variables, and α_i, β_i are the corresponding rate constants. Within this framework each transformation of an elementary unit is independent of other units. In other words, the elementary structural units in which the reaction described by Eq. 1 occurs form an ideal lattice gas.

On the basis of ordinary chemical thermodynamics and Eyring's transition state theory (Glasstone et al., 1941) the equilibrium constant of the reaction defined by Eq. 1 and the corresponding rate constants are:

$$K_i = \alpha_i/\beta_i = \exp(-\Delta G_i/RT), \tag{2}$$

$$\alpha_i = (kT/h)\exp(-\Delta G^{\ddagger}_{i\alpha}/RT), \tag{3}$$

$$\beta_i = (kT/h)\exp(-\Delta G^{\ddagger}_{i\beta}/RT), \tag{4}$$

where K_i is the equilibrium constant of the transformation, ΔG_i is the standard free energy of the transition 1 → 2, $\Delta G^{\ddagger}_{\alpha i}$ and $\Delta G^{\ddagger}_{\beta i}$ are the standard free energies of activation for the transitions 1 → 2 and 2 → 1, k, h, R, T are Boltzmann's constant, Planck's constant, the gas constant, and the absolute temperature, correspondingly.

It is obvious that

$$\Delta G_i = \Delta G^{\ddagger}_{\alpha i} - \Delta G^{\ddagger}_{\beta i}, \tag{5}$$

and since

$$\Delta G = \Delta H - T\Delta S, \tag{6}$$

the standard enthalpies and entropies of the transition can be expressed by means of the activation enthalpies and entropies in a similar way.

Let us restrict ourselves to the case when the structural units that undergo transformation have zero net electric charge and possess dipole moments. Under these conditions for a system of structural units the Gibbs free energy differential may be written as follows:

$$\mathrm{d}G = \mathrm{d}G_0 - M\mathrm{d}D, \tag{7}$$

where M is the projection of the total dipole moment of the system on the electric field direction, D is the electric displacement, $\mathrm{d}G_0$ is the free energy differential at some standard value of the external electric field intensity.

By using the effective membrane thickness (75 Å) one can pass from electric displacement D to electric potential difference across the membrane E or the membrane potential[1] which is fixed in voltage-clamp experiments.

If E is given in millivolts and M in debyes per structural unit, Eq. 7 takes the following form (dG is measured in calories per mole):

$$\mathrm{d}G = \mathrm{d}G_0 - 0.0641\, M\mathrm{d}E. \tag{8}$$

Eq. 8 can be rewritten for free energy changes:

$$\mathrm{d}(\Delta G) = \mathrm{d}(\Delta G_0) - 0.0641\, \Delta M\mathrm{d}E. \tag{9}$$

Hence

$$\partial(\Delta G)/\partial E = -\, 0.0641\, \Delta M \tag{10}$$

and

$$\begin{aligned} \Delta G &= \Delta G_0 - 0.0641 \int_{E_0}^{E} \Delta M \mathrm{d}E \\ &= \Delta H_0 - T\Delta S_0 - 0.0641 \int_{E_0}^{E} \Delta M\mathrm{d}E, \end{aligned} \tag{11}$$

where E_0 is a standard membrane potential which can be chosen arbitrarily.

Expressions similar to Eq. 11 can be written for the passage from state 1 or 2 to the transition state. In this case the standard free energies, enthalpies, entropies, and dipole moments of activation will be involved. They will be denoted by ‡.

When the expressions for free energy changes of the type represented in Eq. 11 are substituted into Eqs. 2–4 we get:

$$\begin{aligned} K_i = \alpha_i/\beta_i &= \exp[\Delta S_{0i}/R - \Delta H_{0i}/RT + (0.0641/RT) \int_{E_0}^{E} \Delta M_i \mathrm{d}E] \\ &= K_{0i} \exp[(0.0641/RT) \int_{E_0}^{E} \Delta M_i \mathrm{d}E] \end{aligned} \tag{12}$$

$$\begin{aligned} \alpha_i &= (kT/h) \exp[\Delta S^{\ddagger}_{0i}/R - \Delta H^{\ddagger}_{0i}/RT + (0.0641/RT) \int_{E_0}^{E} \Delta M^{\ddagger}_{\alpha i} \mathrm{d}E] \\ &= \alpha_{0i} \exp[(0.0641/RT) \int_{E_0}^{E} \Delta M^{\ddagger}_{\alpha i} \mathrm{d}E], \end{aligned} \tag{13}$$

$$\begin{aligned} \beta_i &= (kT/h) \exp[\Delta S^{\ddagger}_{\beta i}/R - \Delta H^{\ddagger}_{\beta i}/RT + (0.0641/RT) \int_{E_0}^{E} \Delta M^{\ddagger}_{\beta i} \mathrm{d}E] \\ &= \beta_{0i} \exp[(0.0641/RT) \int_{E_0}^{E} \Delta M^{\ddagger}_{\beta i} \mathrm{d}E], \end{aligned} \tag{14}$$

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[1] Defined by ascribing zero potential to the external electrode.

where K_{0i}, α_{0i}, and β_{0i} are the equilibrium constant and the rate constants at the standard membrane potential.

The standard entropies depend on the choice of the standard concentrations.[2] The standard enthalpies depend on the choice of the standard membrane potential E_0, but for an ideal system they do not depend on the choice of standard concentrations of the reactants and products. The dipole moments of transition or activation do not depend on the choice of standard concentration or potential. It can be easily seen from Eqs. 12–14 that the enthalpies of transition or activation for any membrane potential E' are expressed by means of the standard enthalpies in the following way:

$$\Delta H' = \Delta H_0 - (0.0641/RT) \int_{E_0}^{E'} \Delta M \mathrm{d}E. \tag{15}$$

This equation may be used to determine the positive direction of ΔM. Note that when E is close to E_0 and ΔH_0 is small the temperature dependence of K_i is weak.

For the dipole moment changes an equation analogous to Eq. 5 can be written.

$$\Delta M_i = \Delta M^{\ddagger}_{\alpha i} - \Delta M^{\ddagger}_{\beta i} \tag{16}$$

The standard enthalpies and entropies of transition and activation can be evaluated from experimentally determined K_{0i}, α_{0i}, β_{0i} at various temperatures in the usual way. The potential dependent part of the enthalpy and the corresponding dipole moments can be calculated from the empirically determined α_i's and β_i's as functions of the membrane potential.

From Eqs. 12–14 it follows directly:

$$(0.0641/RT) \int_{E_0}^{E} \Delta M_i \mathrm{d}E = \ln (K_i/K_{0i}), \tag{17}$$

$$(0.0641/RT) \int_{E_0}^{E} \Delta M^{\ddagger}_{\alpha i} \mathrm{d}E = \ln (\alpha_i/\beta_{0i}), \tag{18}$$

$$(0.0641/RT) \int_{E_0}^{E} \Delta M^{\ddagger}_{\beta i} \mathrm{d}E = \ln (\beta_i/\beta_{0i}). \tag{19}$$

By differentiation of Eqs. 17–19 we get:

$$\Delta M_i = (RT/0.0641)\mathrm{d}(\ln K_i)/\mathrm{d}E, \tag{20}$$

$$\Delta M^{\ddagger}_{\alpha i} = (RT/0.0641)\mathrm{d}(\ln \alpha_i)/\mathrm{d}E, \tag{21}$$

$$\Delta M^{\ddagger}_{\beta i} = (RT/0.0641)\mathrm{d}(\ln \beta_i)/\mathrm{d}E. \tag{22}$$

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[2] In the case of an ideal system the standard concentrations may be chosen as $m_0 = h_0 = n_0 = 1/2$, because the variables m, h, n are molar fractions and the reaction given in Eq. 1 is monomolecular.

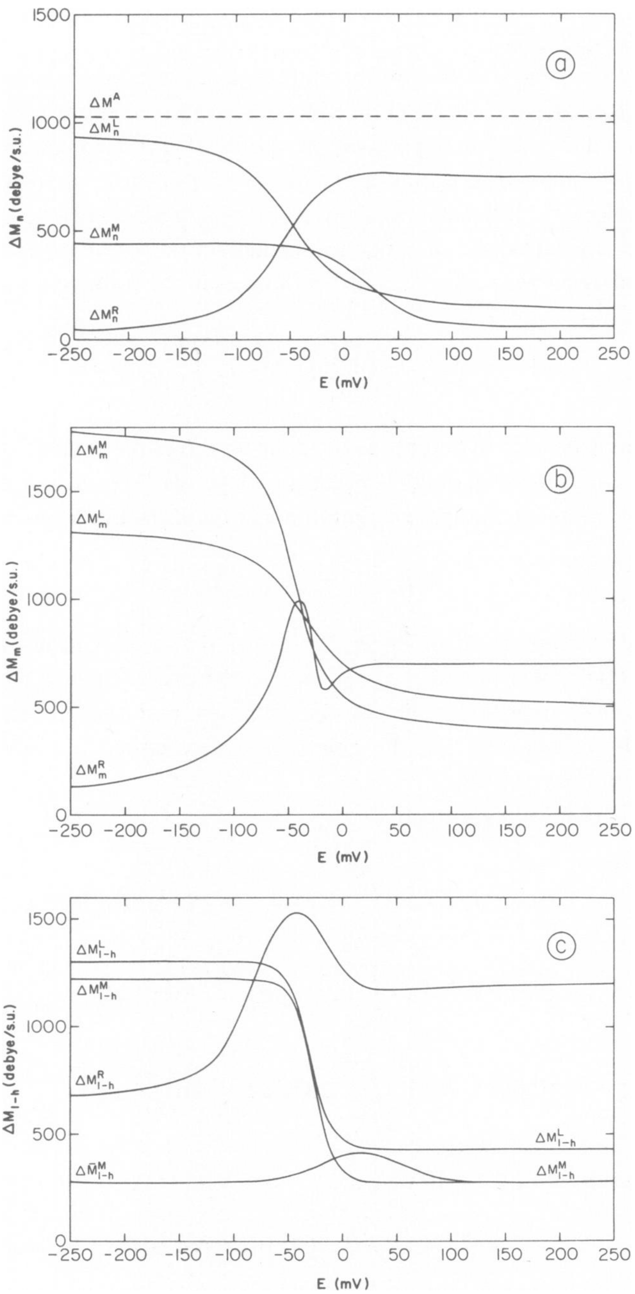

FIGURE 1 The transition dipole moments (in debye per structural unit) for *Loligo (L)*, *Myxicola (M)*, *Rana (R)*, and artificial membrane *(A)* for the processes *n* (*a*), *m* (*b*), (1 − *h*) (*c*) at various membrane potentials (*E*). $\overline{\Delta M}^{M}_{1-h}$ corresponds to a version of the potential dependence of β_h (Goldman and Schauf, 1973).

From equations of the type 13 and 14 it is easy to obtain expressions for Q_{10}, e.g.

$$\begin{aligned} Q_{10\alpha i} &= \alpha_i(T + 10)/\alpha_i(T) \\ &= [(T + 10)/T]\exp[10\,\Delta H_{0i}/RT(T + 10)] \\ &\quad \exp[-10 \times 0.0641/RT(T + 10) \int_{E_0}^{E} \Delta M^{\ddagger}_{\alpha i}\mathrm{d}E]. \end{aligned} \tag{23}$$

Note that the potential dependency of $Q_{10\alpha i}$ (Eq. 23) is substantially smaller than that of α_i (Eq. 13). This explains the experimentally established weak dependence of Q_{10}'s on the membrane potential as against the strong dependence of the α's and β's.

RESULTS

The empirical expressions for the α's and β's as functions of the membrane potential for *Loligo, Myxicola, Rana,* and oxidized cholesterol (EIM) bilayer were taken from Palti (1971), Goldman and Schauf (1973), Hille (1971), and Ehrenstein et al. (1974), respectively. These expressions were inserted into Eqs. 20–22 for all types of processes (m, n, h). In this way explicit expressions for the dipole moments of transition and activation were obtained. Since these expressions are mostly simple but lengthy algebraic formulae they are presented graphically in Figs. 1–3. Note that the dipole moments were calculated for the same temperatures for which the empirical formulae were written by their authors.

The potential dependent part of the enthalpy or free energy can be calculated by means of Eqs. 17–19. The results for *Loligo* and *Rana pipiens* are equivalent to those presented by Hill and Chen (1972). The corresponding curves for Myxicola are quite close to those for *Loligo.* However, they are not represented here because the dipole moment curves already contain this kind of information.

With the potential dependent part of the free energy known, the potential dependence of Q_{10} on E may be evaluated by means of Eq. 23. Some Q_{10} values thus obtained are presented in Table I. The standard potential chosen is −40 mV and the Q_{10}'s for this potential are assumed to be equal to 1. Note the difference between $(Q_{10})_{\beta h}$ and $(\bar{Q}_{10})_{\beta h}$ at hyperpolarization from the two types of β_h functions in the case of *Myxicola* (Goldman and Schauf, 1973).

The standard enthalpies of activation can be calculated on the basis of the experimentally established Q_{10}'s (at given temperature and potential) by Eq. 23, since the potential dependent factor is already known. The standard entropies can be now calculated by means of Eqs. 12–14.

The calculated standard enthalpies and entropies are presented in Table II. The same table also gives the results for *Xenopus laevis* as calculated by Tsien and Noble (1969) from experimental data of Frankenhauser and Moore (1963).

In the computations −40 mV was taken as standard potential. This value was chosen since at this potential there were always enough experimental points on the

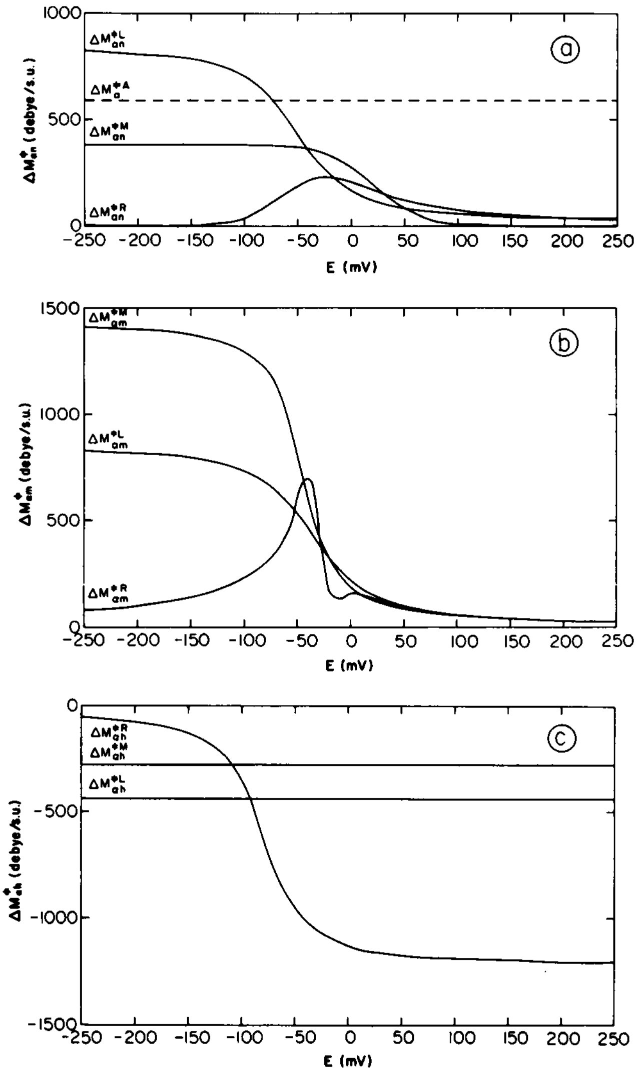

FIGURE 2 Dipole moments of activation (in debye per structural unit) for the direct transitions (described by α_i rate constants). *L*, *Loligo*; *M*, *Myxicola*; *R*, *Rana*; *A*, artificial membrane. (*a*) for the *n* processes; (*b*) for the *m* processes; (*c*) for the *h* processes.

empirical curves for the α's and β's. One can relate the values of Q_{10} to this potential since all authors report that Q_{10} is practically independent of membrane potential.

DISCUSSION

In all cases the calculated transition dipole moments were shown to be large: from a few hundred debyes per structural unit to 1,000 and more. This finding indicates that

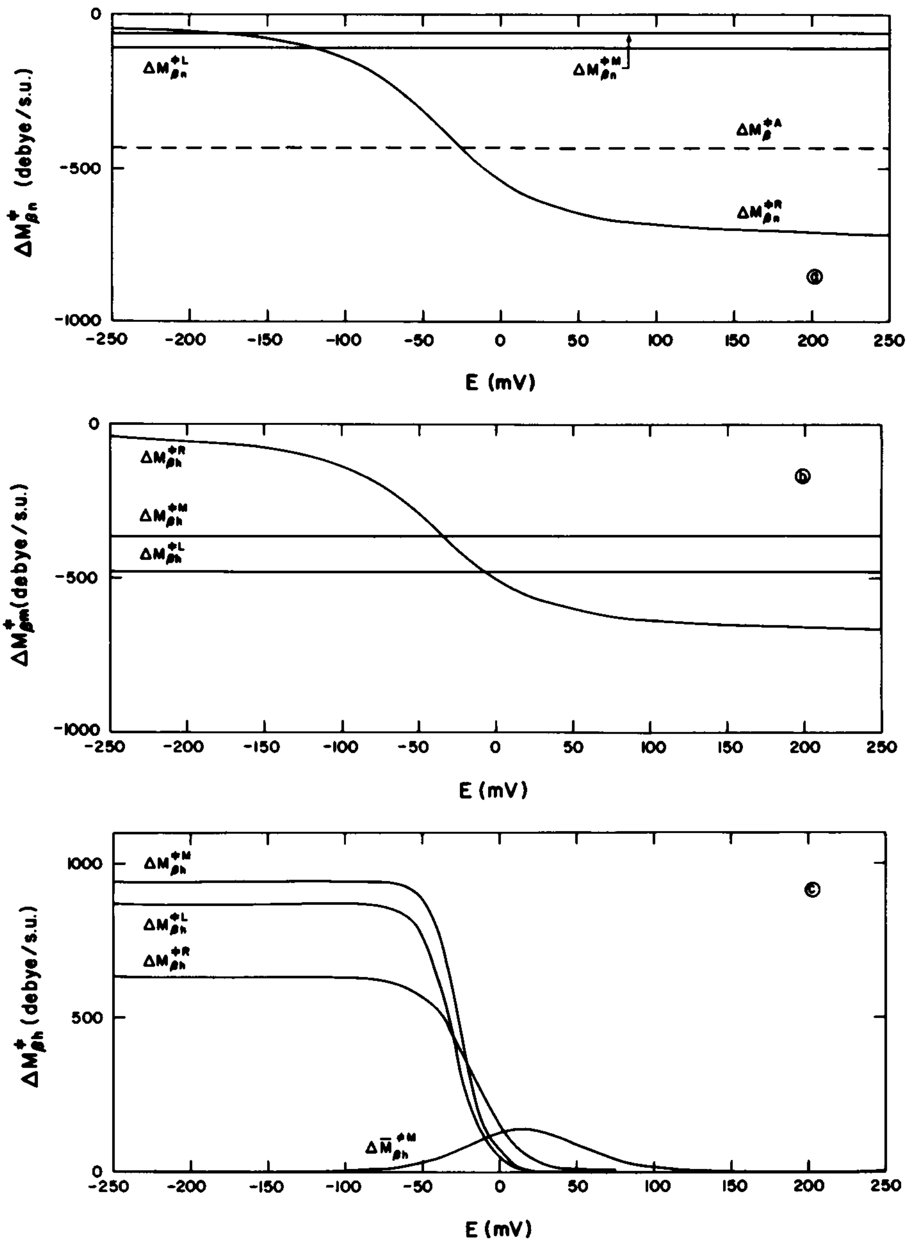

FIGURE 3 Dipole moments of activation for the reverse transitions (described by β_i rate constants). *L*, *Loligo*; *M*, *Myxicola*; *R*, *Rana*; *A*, artificial membrane. (*a*) for the *n* processes; (*b*) for the *m* processes; (*c*) for the *h* processes. $\overline{\Delta M}^{\ddagger M}_{\beta h}$ corresponds to a version of the potential dependence of β_h (Goldman and Schauf, 1973).

TABLE I

SOME Q_{10} VALUES AT VARIOUS MEMBRANE POTENTIALS

Q_{10}	E_m: −100 mV	−40 mV	0 mV	+50 mV
$(Q_{10})^L_{\alpha n}$	1.14	1	0.961	0.948
$(Q_{10})^M_{\alpha n}$	1.09	1	0.949	0.916
$(Q_{10})^R_{\alpha n}$	1.03	1	0.969	0.941
$(Q_{10})^L_{\alpha m}$	1.20	1	0.948	0.920
$(Q_{10})^M_{\alpha m}$	1.29	1	0.944	0.920
$(Q_{10})^R_{\alpha m}$	1.09	1	0.957	0.934
$(Q_{10})^L_{\alpha h}$	0.901	1	1.07	1.17
$(Q_{10})^M_{\alpha h}$	0.935	1	1.04	1.10
$(Q_{10})^R_{\alpha h}$	0.836	1	1.14	1.40
$(Q_{10})^M_{\beta h}$	1.25	1	0.943	0.941
$(\overline{Q_{10}})^M_{\beta h}$	1.004	1	0.987	0.963

TABLE II

STANDARD ACTIVATION AND TRANSITION ENTHALPIES AND ENTROPIES*

	Loligo	*Myxicola*	*Rana*	*Xenopus*§
n				
$\Delta H^{\ddagger}_{\alpha;\beta}$	17	17	19	19; 16
ΔH_0	0	0	0	3
$\Delta S^{\ddagger}_{\alpha}$	12.6	8.4	18.7	18.9
$\Delta S^{\ddagger}_{\beta}$	11.6	10.4	16.2	11.8
ΔS_0	1.0	2.0	2.5	7.1
m				
$\Delta H^{\ddagger}_{\alpha;\beta}$	17	15	19	10.5; 8
ΔH_0	0	0	0	2.5
$\Delta S^{\ddagger}_{\alpha}$	15.6	15.0	24.2	−4.6
$\Delta S^{\ddagger}_{\beta}$	16.6	14.6	24.1	−14.0
ΔS_0	−1.0	0.4	0.1	9.4
h				
$\Delta H^{\ddagger}_{\alpha;\beta}$	17	14	19	16.5; 17
ΔH_0	0	0	0	−0.5
$\Delta S^{\ddagger}_{\alpha}$	8.8	7.8	9.4	12.5
$\Delta S^{\ddagger}_{\beta}$	13.6	10.2	20.6	13.8
ΔS_0	−4.8	−2.4	−11.2	−1.3

*Enthalpies are measured in kilocalories per mole and entropies in calories per degree · mole.

§Values for *Xenopus laevis* are from Tsien and Noble (1969).

TABLE III

DIPOLE MOMENTS OF SOME GLOBULAR PROTEINS

	Molecular weight	Dipole moment
		D
β-Lactoglobulin	35,500	700
Ovalbumin	45,000	250
Hemoglobin	67,000	480
Serum albumin	65,000	380

the structural change of an elementary unit occurs in a volume of macromolecular dimensions. For comparison, dipole moments of some globular proteins are given in Table III (Tanford, 1961). The calculated dipole moments of transition and activation of EIM lipid bilayers are of the same order of magnitude.

In contrast to lipid bilayers, in axon membranes the transition dipole moments vary as a function of membrane potential. The curves for *Loligo* and *Myxicola* show a close similarity. The dipole moment curves for *Rana* have a different shape; however, the signs of dipole moment changes are the same. It is difficult to decide at present whether these differences originate in the membranes themselves or from other processes and structures outside the membranes. The oscillations of some of the ΔM vs. E curves may result from peculiarities of the empirical formulae for the α's and β's which may be irrelevant for the description of their dependence on E.

As already mentioned, Hill and Chen (1972) assumed a second degree dependence of the transition free energy on membrane potential. This leads to a linear relationship between the transition dipole moment and membrane potential. Fig. 1 illustrates that such a linear part exists in all curves for *Loligo* and *Myxicola*. However, this is not the case for the m and $1 - h$ processes in *Rana pipiens*.

Some general features may be noted for the dipole moments of activation: for $\Delta M > 0$ (dipole moment change directed outwards) $\Delta M \rightarrow 0$ for strong depolarization, and for $\Delta M < 0$ for strong hyperpolarization $\Delta M \rightarrow 0$. This feature can be directly seen in the graphical representation in some cases while in the others it can be confirmed by the evaluation of the asymptotic limits of the corresponding analytical expressions. The exceptions are: $\Delta M^{\ddagger L}_{\alpha h}$, $\Delta M^{\ddagger M}_{\alpha h}$, $\Delta M^{\ddagger L}_{\beta m}$, $\Delta M^{\ddagger M}_{\beta m}$, $\Delta M^{\ddagger L}_{\beta n}$, $\Delta M^{\ddagger M}_{\beta n}$, which are constant for all membrane potentials (the last two have relatively small absolute values). $\Delta M^{\ddagger R}_{\alpha n}$ and $\Delta M^{\ddagger R}_{\alpha m}$ tend to zero at both depolarization and hyperpolarization. It should be noted here that the estimations of activation dipole moments at strong depolarizations and hyperpolarizations are not very reliable because they are based on extrapolations of the empirical formulae for the α's and β's as functions of E. Nevertheless we should like to retain, as a working hypothesis, the general property of the $\Delta M^{\ddagger}$ as mentioned above and to interpret it as a saturation phenomenon for the dipole moments of the structural units.

When the transformation of the structural unit is accompanied by a positive activation dipole moment (directed outwards) the dipole moment increment at large depolarizations tends to zero. In this case the directions of the electric field and the activation dipole moment coincide. The decrease towards zero of the activation dipole moment may be explained in terms of a saturation phenomenon, i.e. when no additional dipole moment changes of the structural units are possible. The inverse saturation at hyperpolarization obviously brings to maximal activation dipole moments.

In cases where the activation dipole moment is negative (because of the nature of the structural transformation) at hyperpolarizations the direction of the electric field coincides with that of the activation dipole moments. Under these conditions the saturation of the dipole moments of the structural units brings to zero activation moment. Inversely the saturation at depolarization brings to a maximal absolute value of the activation dipole moment.

It is well known that the polarizational displacement current is proportional to the time derivative of the polarization vector (dipole moment per unit volume). Therefore, the given calculated dipole moments as a function of membrane potential together with the Hodgkin-Huxley kinetics of the structural units makes it possible to calculate the displacement currents associated with the structural unit transitions. These currents are proportional to the dipole moment change ΔM_i and to the time derivative of the corresponding Hodgkin-Huxley kinetic parameters. Thus they should correspond to the so-called "gating" currents.

The experimental data necessary for the estimation of the standard enthalpies and entropies of activation (and of the transition as a whole) is unfortunately only available in the form of Q_{10}. Moreover the accuracy of the given Q_{10} values is very poor. As a result the accuracy of the calculated enthalpies and entropies is low. All the calculated standard enthalpies of activation are positive and their average value is about 17 Kcal/mol. The calculated standard activation entropies are also all positive. The negative activation entropies for the *m*-process in *Xenopus laevis* calculated by Tsien and Noble (1969) are probably due to the exceptionally low and uncharacteristic Q_{10} values for this process as estimated by Frankenhaeuser and Moore (1963). The average calculated activation entropy value is about 14 cal/mol·degree. The standard enthalpy and entropy changes for the whole structural transition are close to zero.

On the basis of the above the following conclusions may be reached regarding the structural units associated with the ion gating processes. The unit is of macromolecular dimensions, probably a protein-like structure with a large total dipole moment. This dipole is probably made out of many small dipoles as the saturation phenomena show. The structural unit can exist in at least two different conformations or states. As the ΔM's potential dependence shows in these states the structural unit has different radial dipole moment projections at any fixed membrane potential. The substantial activation enthalpies and entropies together with the negligible transition enthalpies and entropies indicate that the transition from one state to another may be related to displacements of the whole or big parts of the structural unit.

The importance of the dipole moment changes during the conformational transitions in the structural units lies in the fact that they make it possible for the membrane potential to influence the kinetics of the transition and the equilibrium distribution of the structural units between the two states.

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