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VOLTAGE DEPENDENCIES OF SLOW (ms) CHEMICAL RELAXATIONS

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The exponential-relaxation rates (rate constant k) of relatively slow (ms) chemical reactions may change with applied potential. Three general cases are described which, by their dependencies on an externally applied voltage, should be experimentally separable. They are processes due to (1) permanent dipoles entirely in the field – – $(\mathrm{d}\ln k)/\mathrm{d}V \propto V^2$; (2) surface charge change – – $(\mathrm{d}\ln k)/\mathrm{d}V \propto V$; and (3) charge transport – – $\mathrm{d}k/\mathrm{d}V \propto V$ (or a delay proportional to $1/V$). The general analysis presented may be useful in analyzing biological electrical processes.

1. Introduction

Numerous biological processes are sensitive to the voltage across a cell membrane [1]. The most clearly measured of these are the action potentials of nerves, muscles, and other excitable cells. In them, a specific ion permeability across the membrane may increase by five orders of magnitude within a few milliseconds. While the kinetic electrical characteristics have been determined in great detail, little information is available describing any specific structure at a chemical level and how it might change with transmembrane voltage. Since we lack detailed information on the double layers, adsorbed ions, charged surfaces, and the complex, heterogeneous lipid-protein mosaic membrane, a more general analysis of the voltage dependence of chemical kinetics as presented here may be useful.

The kinetic data used in analyses are determined primarily by using the "voltage clamp" technique which is a potentiostat with current follower. The experiments consist of applying potential jumps of the order 10–100 mV across the cell membrane and observing the kinetic response by monitoring the ion currents flowing across the membrane. The technique is equivalent to chemical voltage jump experiments [2–4] with the millivolt jumps producing a wide range of large field changes across the 10 nm cell membrane.

Most kinetic analyses of the relaxation involve assumed details of molecular structure and/or reaction paths. A number of these have been reviewed by Roy [5].

We show below that a modest extension of Eyring's absolute rate theory as applied to reactions occurring over milliseconds in electric fields allows clear classification of the general types of reactions. The classification may then possibly serve as a self-consistency test for detailed models.

For a voltage jump experiment, the membrane is held at a fixed transmembrane potential between electrodes and perpendicular to the current flow. After a step potential jump, a relaxation will occur between the initial and final equilibrium states. This chemical response will follow the field increase or decrease and results from either a change caused by (1) the "rotation" of permanent dipoles as in a homogeneous dielectric or (2) polarization of charge at the membrane surface such as a change in the surface concentration or polarization of a double layer [6] or (3) charge translation due to simple conduction mechanisms. Each of these has a voltage dependence which is diagnostic for it. The changes due to higher order (in field) processes may contribute but the effects should be smaller.

We will not discuss the final equilibrium values of any quantities such as internal field, ion concentration, or average dipole orientation. These have been considered extensively both in thermodynamic and molecular structural terms [7]. We wish to discuss only the rates of change between the initial and final states of the system for large field jumps over a broad range. And we consider only relatively slow chemical changes that are seen to occur in biomolecules [8] and biomembranes; the energy states will be Boltzmann distributed.

We make the following, simplifying assumptions in all three cases.

(1) There is a single rate controlling step and this is much slower than all other molecular processes. The assumption is reasonable since most ion atmosphere or solvent dipole reorientation relaxations are far faster (nsec or faster) than the chemical changes we see (ms).

(2) If the rate is dependent on the change in potential, then the energy controlling the difference will be electrical as opposed to thermal. The other extreme is either that no charge is involved so the field has no effect or that the field effect is small and the process is thermally controlled [7,9].

(3) The internal field (or voltage) change is proportional to the applied external potential. As has been pointed out, a large part of the difficulty in dielectric calculations arises from determining the "internal" or microscopic field (see ref. [10]). For materials as complex as physiological membranes, we have little choice but to assume the pertinent internal potential is proportional to that applied. A prime (′) will be used to signify internal quantities.

2. Theoretical

2.1. Dipoles entirely in the field

As has been clearly shown [9] the rate of a physical or chemical process in an electric field can be expressed using the formalization of absolute reaction rate theory as

$$k = (\kappa T/h)\exp(-\Delta G^{\ddagger}/RT). \qquad (1)$$

In the preexponential, κ is the Boltzmann constant. The basis for using the thermodynamic formula is that the reactant and activated complex are treated as if they are in equilibrium except for the special "reaction coordinate".

More recently, it has been shown that in solution the preexponential as written in equation (1) is not valid [11]. However the free energy of activation $\Delta G^{\ddagger}$, is still a good function. The basis of this more recent analysis rests on postulating the existance of a fluctuating steady state and requires only that a Boltzmann equilibrium exists among the microstates of the reacting molecules [11]. Within this framework, the analysis presented here may possibly be extended to faster reactions ($\gtrsim$ ns) in solution. This is beyond the scope of this paper, and, for the slower reactions considered here, we shall use the language and concepts of the earlier, classical form of the transition state theory.

For a dielectric in which part of the new surface charge may arise from chemical changes, the value for the free energy of activation must include the electric field and chemical potential terms [12]. That is

$$\mathrm{d}G^{\ddagger} = -S^{\ddagger}\,\mathrm{d}T + v^{\ddagger}\,\mathrm{d}p - M^{\ddagger}\,\mathrm{d}E - A^{\ddagger}\,\mathrm{d}\xi, \qquad (2)$$

where $M^{\ddagger}$, in analogy with the usual equilibrium expressions [12,13], is the polarization of activation, $A^{\ddagger}$ the affinity, and ξ the "extent of reaction" [12]. $M^{\ddagger}$ is the first derivative of the free energy with electric field and, as such, is the extensive variable characterizing the change.

We operate with the isothermal state change operator on equation (2); at fixed T, p, and ξ we recover

$$\frac{\mathrm{d}\,\Delta G^{\ddagger}}{\mathrm{d}E} = -\Delta M^{\ddagger}, \quad \text{or} \quad \frac{\mathrm{d}\ln k}{\mathrm{d}E} = \frac{\Delta M^{\ddagger}}{RT}, \qquad (3)$$

where k is the rate constant, and $\Delta M^{\ddagger}$ is the molar polarization of activation. An alternate derivation of equation (3) is shown in the appendix.

$\Delta M^{\ddagger}$ is, in analogy with the equilibrium case, the difference in polarization between the reactants and the activated complex (see appendix). It is a macroscopic parameter and depends on the competition between the thermal disordering and electric field ordering of the system. Assuming the frequency factor and transmission coefficient of the absolute rate theory [9] are field independent, the change of rate may be seen as a change in the free energy of activation with a change in field. Alternately, it can be conceptualized as a change in the reaction coordinate as it goes over a different area of the thermal energy-electric energy surface. The polarization of activation is a general quantity; only with further assumptions can microscopic data be derived from the experimental results. However certain other activation parameters

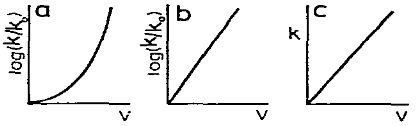

Fig. 1. The general voltage dependencies of the three general cases presented: (a) permanent, independent dipoles in moderate fields; (b) surface charges with one "end" of the dipole outside of field and K_{eq} about ten or greater; (c) charge transport. Here k is the rate constant and k_0 the constant without external voltage. The internal voltage (or field) in all cases is assumed proportional to the applied voltage.

follow directly, and some are shown in the appendix.

The simplest and most commonly used microscopic model for dielectrics assumes the solid to be composed of harmonically bound charges although the method seems to hold for deviations from this binding [14]. Then, in analogy with the equilibrium case,

$$\Delta P^{\ddagger} = v\Delta M^{\ddagger} = \Delta\chi^{\ddagger}E'v$$

$$= N[\Delta\alpha^{\ddagger} + (\Delta\mu^{\ddagger})^2/3\kappa T]E'v, \qquad (4)$$

where v is the system volume, $\Delta\alpha^{\ddagger}$ the polarizability of activation, and $\Delta\chi^{\ddagger}$ and $\Delta\mu^{\ddagger}$ the susceptibility and dipole moment of activation respectively. These are partial molar quantities defined in the same way as $\Delta M^{\ddagger}$ in the appendix. With k_0 the rate constant in the absence of field and with E' assumed proportional to V, a plot of the rate versus the voltage will then be parabolic as shown in fig. 1a.

General considerations of the problem with the naive equilibrium models have been reviewed recently [15,16]. Also, significantly different equilibrium behavior may occur for real rate processes as functions of applied potential.

2.2. *Interface activation*

The second major functional form of the dependence of the rate on voltage is similar to the rates derived for electrode processes [17]. This behavior in the membrane arises from interfacial polarization or interfacial concentration changes. The general requirement for this behavior to be realized is that one "end" of the changing dipole remain in an unchanging field. In the case of electrodes, this is the "free solution". In addition, for membrane systems, the "end" could be in the center of the lipid if the potential drops occur mainly across the double layer and interfaces.

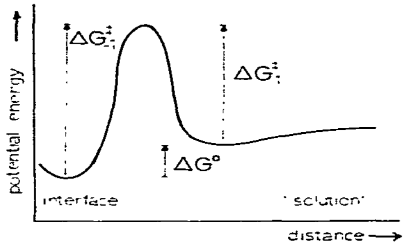

Fig. 2. Free energy-reaction coordinate diagram for an interface in the absence of external potential.

Referring to fig. 2 which illustrates the reaction coordinate for an interface, and following the derivation of Frohlich [18] (but ignoring any special degeneracy factors) we write

$$k = (\kappa T/h)[\exp(-\Delta G^{\ddagger}_{1}/RT) - \exp(-\Delta G^{\ddagger}_{-1}/RT)]. \qquad (6)$$

If $\Delta G^0 = \Delta G^{\ddagger}_{1} - \Delta G^{\ddagger}_{-1}$ is larger than about -6 kJ/mole, or equivalently if K_{eq} is larger than about ten, one of the exponentials of equation (6) will predominate (see below). And the behavior will become quite simple with

$$\frac{\mathrm{d}\ln(k/k_0)}{\mathrm{d}V} = \text{constant}. \qquad (7)$$

See fig. 1b.

The voltage dependence of the free energies of activation is given by

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{0} + \alpha'\Delta z^{\ddagger}FV,$$

where $\Delta G^{\ddagger}_{0}$ is the activation free energy at zero voltage and α' is the electrode "transfer coefficient". Its properties are discussed by Audubert [19]. The difference between the internal and external voltage is accounted for by using α' instead of α.

Since both forward and reverse charge movements involve the same α' and $\Delta z^{\ddagger}$, the relative changes of the forward and reverse rates with potential will be approximately the same. (Any difference in α' for forward and reverse reactions can be considered a measure of anisotropy in inner sphere kinetics as a function of potential.)

Using the simplified form as seen in equation (7), the descriptive equation becomes

$$\frac{\mathrm{d}\ln(k/k_0)}{\mathrm{d}V}=\frac{\Delta z^{\ddagger}F\alpha'}{RT}. \tag{8}$$

In this special case we note that the change for a voltage jump of $+\Delta V$ will be equal and opposite to one of $-\Delta V$. The simple form of equation (8) is seen in the behavior of the rapid turnoff of nerve axon sodium currents: the β_m process [20]. However the expected reversal is only seen when the heterogenity of the kinetics is accounted for [21].

2.3. Kinetics due to charge conduction

A third, general class of rate change with voltage arises from processes which result from ion mobility. That is, the charge-field forces only slightly perturb the random, thermal motion of the charges. At all but the highest fields, the well known equation describing the ion velocity is $v = uf$ where the force $f \propto zV$. Here v is the velocity, u the mobility, and V the applied voltage.

If the observed reaction rate is proportional to v, then it is directly proportional to the voltage, V. We may then write for the rate constant's dependence on voltage

$$\mathrm{d}k/\mathrm{d}V = \gamma z \tag{9}$$

γ is a simple proportionality constant. This equation is illustrated in fig. 1c. Onsager showed that weak electrolyte equilibria in an electric field could be explained by a dissociation step described by equation (9) together with a voltage-independent ion recombination [22].

As a corollary to this third type of process, a delay time may arise due to the migration of a (sheet of) charge over some distance, d. Since $d = vt$, we see that $t_{\mathrm{delay}} = d/v$. From the mobility equation, we see that the delay will be inversely proportional to the applied voltage.

3. Conclusions

We have shown how the exponential relaxation of relatively slow (msec) chemical reactions may change with applied potential. Three general cases are described which, by their voltage dependencies, should be experimentally separable. They are processes due to (1) permanent dipoles entirely in the field – $(\mathrm{d}\ln k)/\mathrm{d}V \propto V^2$; (2) surface charge change – $(\mathrm{d}\ln k)/\mathrm{d}V \propto V$; and (3) charge transport – $\mathrm{d}k/\mathrm{d}V \propto V$ (or a delay proportional to $1/V$). In a future paper [21], we will show that the currents arising in nerve membrane can be described using these general forms.

Appendix

Using Maxwell's relation on equation (2) we derive

$$(\partial A^{\ddagger}/\partial E)_{\xi,T,p} = (\partial M^{\ddagger}/\partial \xi)_{E,T,p}$$

and

$$(\partial A^{\ddagger}/\partial T)_{\xi,p,E} = (\partial S^{\ddagger}/\partial \xi)_{T,p,E}.$$

Differentiating the equation on the left with regard to T and the equation on the right with regard to E, we obtain

$$(\partial A^{\ddagger}/\partial E\partial T)_{\xi,p} = (\partial M^{\ddagger}/\partial \xi\partial T)_{E,p}$$

and

$$(\partial A^{\ddagger}/\partial T\partial E)_{\xi,p} = (\partial S^{\ddagger}/\partial \xi\partial E)_{T,p}.$$

Noting that $(\partial M^{\ddagger}/\partial \xi) \equiv \Delta M^{\ddagger}$ and $(\partial S^{\ddagger}/\partial \xi) \equiv \Delta S^{\ddagger}$, we find

$$(\partial \Delta M^{\ddagger}/\partial T)_{E,p} = (\partial \Delta S^{\ddagger}/\partial E)_{T,p}.$$

Similarly

$$(\partial \Delta M^{\ddagger}/\partial p)_{E,p} = (\partial \Delta v^{\ddagger}/\partial E)_{T,p}.$$

Another commonly used relation is the rate dependence on the volume of activation,

$$(\partial \ln k/\partial p)_{E,T} = -\Delta v^{\ddagger}/RT.$$

For an order of magnitude calculation see ref. [23]. Similar expressions can be written for the charge of activation, $\Delta z^{\ddagger}$.

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