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Role of terminal dipole charges in aggregation of α-helix pair in the voltage gated K^+ channel

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ABSTRACT

The voltage sensor domain (VSD) of the potassium ion channel KvAP is comprised of four (S1–S4) α-helix proteins, which are encompassed by several charged residues. Apart from these charges, each peptide α-helix having two inherent equal and opposite terminal dipolar charges behave like a macrodipole. The activity of voltage gated ion channel is electrostatic, where all the charges (charged residues and dipolar terminal charges) interact with each other and with the transmembrane potential. There are evidences that the role of the charged residues dominate the stabilization of the conformation and the gating process of the ion channel, but the role of the terminal dipolar charges are never considered in such analysis. Here, using electrostatic theory, we have studied the role of the dipolar terminal charges in aggregation of the S3b–S4 helix pair of KvAP in the absence of any external field ($V=0$). A system attains stability, when its potential energy reaches minimum values. We have shown that the presence of terminal dipole charges (1) change the total potential energy of the charges on S3b–S4, affecting the stabilization of the α-helix pair within the bilayer lipid membrane and (2) the C- and the N-termini of the α-helices favor a different dielectric medium for enhanced stability. Thus, the dipolar terminal charges play a significant role in the aggregation of the two neighboring α-helices.

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1. Introduction

The building block of the ion channel protein is the α-helix. α-helices are macrodipoles, a fact that has been known for a long time [1] but has often been ignored as an important property of α-helices in a biological system. Each α-helix of the ion channel protein, having a backbone of amides all pointing in one direction, from the negative C-terminus towards the positive N-terminus, with -0.5 and $+0.5$ proton charges at the two termini, respectively, behaves like a macrodipole [1] with a length of about 1.5 N Å and a net dipole moment of about 3.5 N Debye, where N is the number of residues [2]. In an α-helix, the peptide backbones are aligned in such a fashion that nearly 97% of the peptide dipole moments point in the direction of the helix axis [3] (Fig. 1). Thus, a long α-helix can produce a considerable electrostatic field. To obtain electrostatic stabilization, it is an inherent property of electric dipoles in a multimeric aggregate to settle adjacent to each other in anti-parallel orientation, such that the electric lines of force traveling from the positive end of one dipole to the negative end of the other follow the shortest path [4]. When the α-helix dipoles are in such an anti-parallel sense, they confer significant electrostatic stabilization to the structural motifs of the protein [5].

However, the voltage dependent K^+ ion channel is a homo-tetramer with six α-helices S1–S6 in each subunit. The six transmembrane helices are primarily hydrophobic, with most of the positive charges of the amino acid side chain on S4 located at every third residue; a few other positive and negative charges are scattered on the other helices. In the structures of KvAP obtained by different methods [6–8] the S3b and S4 always stay together, while the other helices of the voltage sensor domain (VSD) present different spatial orientations. Each of these helices forms a macrodipole and can potentially contribute to the electrostatic field. In various experimental and theoretical studies, emphasis is given to the side-chain interactions [9–12] while the role of the dipolar charges is ignored. Here, we have used an S3b–S4 pair of the VSD as an example to determine the contribution of the terminal dipolar charges of the S3b–S4 pair in stabilization of their aggregation. Furthermore, since the S3b–S4 α-helices are quite mobile and the dipolar charges on either end can potentially get exposed to polar (aqueous medium) or non-polar (membrane) environments, we have considered the role of the dielectric properties of the media in such interactions.

2. Theory

2.1. Electrostatic principle holding the macrodipoles together

On the basis of the principle of electrostatic theory, the antiparallel arrangement is best understood by dipolar interactions in which the

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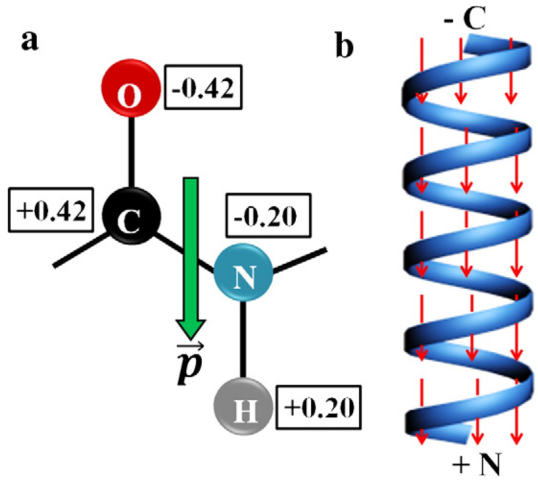

Fig. 1. Origin of macrodipoles. (a) Dipolar charges on a peptide bond. (b) Multiple peptide dipoles aligned along the axis of the α-helix summate to produce a macrodipole.

mutual potential energy (PE) of two interacting adjacent macrodipoles depends upon their dipole moment $\left(\vec{p}\right)$ and varies with their relative angular separation (θ) [4]. The two dipoles tend to orient so as to achieve the minimum PE of the system. The lower the PE, the more stable is the conformation. When they are parallel ($\theta=0°$) the PE is at the maximum; when perpendicular ($\theta=90°$) PE is zero, and when antiparallel ($\theta=180°$), the PE reaches a minimum value.

When the dipoles are very close to each other (i.e. the distance between the two dipoles is smaller than their length) the interaction of the pole charges plays a dominant role. Due to electrostatic attraction, the two opposite poles of the antiparallel dipoles possess a negative Coulombic potential energy ($\mathrm{PE_{coulomb}}$) (Eq. (1a)); while a positive potential energy is possessed by the two similar poles of parallel dipoles.

$$\text{Coulomb Energy;}\ \ \mathrm{PE_{coulomb}}=\frac{1}{2}\frac{1}{(4\pi\varepsilon_0)}\sum_{\substack{i=1\\ j=1\\ i\neq j}}^{n,m}\frac{q_iq_j}{\left(d_{ij}\right)}\left\{\frac{1}{\varepsilon_i}+\frac{1}{\varepsilon_j}\right\}. \qquad (1a)$$

When the charges are near the boundary of two different dielectric media, opposite charges are induced on the dielectric interface. These induced charges interact with the original charges by the method of image charges [13], contributing (a) self energy ($\mathrm{PE_{self}}$) (Eq. (1b)) and (b) shield energy ($\mathrm{PE_{shield}}$) (Eq. (1c)). $\mathrm{PE_{self}}$ is due to the interaction of a charge with its own (self) image charge. This image charge creates a shielding effect ($\mathrm{PE_{shield}}$) on the Coulombic interaction.

$$\text{Self Energy;}\ \ \mathrm{PE_{self}}=\frac{1}{(4\pi\varepsilon_0)}\sum_{\substack{i=1\\ j=1}}^{n,m}\frac{\left(\varepsilon_i-\varepsilon_j\right)}{\left(\varepsilon_i+\varepsilon_j\right)}\left\{\frac{q_i^{\,2}}{2\varepsilon_i\,d_i}\right\}; \qquad (1b)$$

$$\text{Sheild Energy;}\ \ \mathrm{PE_{shield}}=\frac{1}{2}\frac{1}{(4\pi\varepsilon_0)}\sum_{\substack{i=1\\ j=1\\ i\neq j}}^{n,m}\frac{q_iq_j}{\left(d_{ij}\right)}\frac{\left(\varepsilon_i-\varepsilon_j\right)}{\left(\varepsilon_j+\varepsilon_i\right)}\left\{\frac{1}{\varepsilon_i}-\frac{1}{\varepsilon_j}\right\}; \qquad (1c)$$

where q_i,q_j are the charged residues in medium of dielectric constant ε_i,ε_j respectively, d_i is the distance of the respective charge from the dielectric interface and d_{ij} is the distance between two respective charges. The 1/2 factor in the Coulombic energy and the shield energy is to eliminate the duplicity of the summation on ith and the jth particles. When the charges are in the same medium the shielding effect comes from the dielectric constant of that medium as a factor in the denominator of Coulombic interaction ($\mathrm{PE_{coulomb}}$), (Eq. (1a)). When the charges are on either side of the interface an additional shielding effect ($\mathrm{PE_{shield}}$) (Eq. (1c)) gets included due to the induced charges at the interface.

From the superposition principle, the total electrostatic potential energy $\mathrm{PE_{total}}$ of the system of charges present on S3b and S4 helices will have three prominent contributions.

$$\mathrm{PE_{total}}=\mathrm{PE_{coulomb}}+\mathrm{PE_{self}}+\mathrm{PE_{shield}}.$$

2.2. The S3b–S4 pair

Here we are exploiting the role of the terminal dipolar charges (N3, C3, N4 and C4) in the stabilization of the S3b–S4 α-helix pair. Both S3b and S4 as a macrodipole have positive and negative half unit charges on each of their N- and C-termini respectively, apart from several charged side chains of residues scattered on their surfaces (Fig. 2). There are five charged arginines on S4 (+R117, +R120, +R123, +R126 and +R133) which are predominantly considered as the voltage sensor and two charged residues on S3b (histidine (+H109) and glutamic acid (−E107)). The first four positive arginines are three residue apart (i.e. apart by 300° about the axis and 4.5 Å along the axis) along the helical path on the S4 helix. However, they all lie on one hemispherical surface, making S4 an amphipathic macrodipole. The two charged residues of the S3b helix are almost diametrically (200°) apart. At physiological pH, all residues on S3b and S4 carry a unit charge, except histidine (+H107) with a half charge. The linker L34 is nonhelical with 3 nonpolar residues. The length of the 3 residue linker L34 if stretched can vary from 13.5 Å to 35 Å. The maximum allowance of the relative translation between S3b and S4 considered in our work is 24 Å which is within the expandable length of the L34 linker. These alpha helix protein, of dielectric constant $\varepsilon_p=10.0$ is embedded in a multi-dielectric environment like a lipid membrane ($\varepsilon_l=2.0$) on the side (Fig. 2) and an ionic solution ($\varepsilon_w=80.0$) on the extracellular (top) and intracellular (bottom) sides. An S3b–S4 pair is at the periphery of the VSD which is a part of the ion channel. The terminal charges being at the top and bottom end of the helices, we have considered the immediate dielectric boundary to be linear. Crevices in the calculation are introduced by considering the dielectric interface of a charge on the side to be water instead of lipid. Thus, this macrodipole pair has the probability of being partially exposed to lipid, protein and ionic media. The total interaction potential energy of the system of charges of S3b–S4 macrodipole pair is a balance between the attractive and

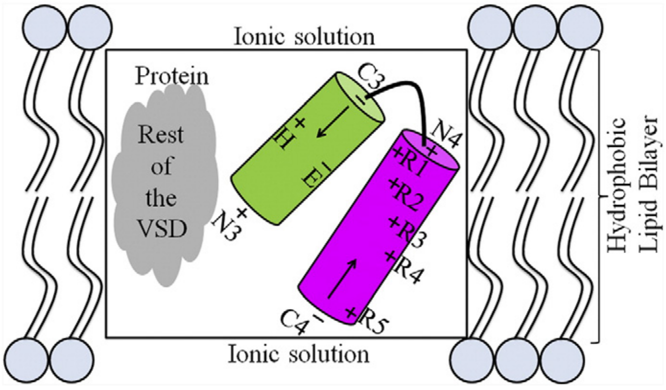

Fig. 2. The Voltage Sensor Domain of the KvAP channel. The S3b–S4 α-helix pair, with dipolar charges (N3, C3, N4 and C4) and side chain charges (R1–R117, R2–R120, R3–R123, R4–R126, R5–R133), are surrounded by the lipid bilayer and ionic solution. The rest of the VSD is shaded gray.

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