Supporting Information

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SI Text

1. The Three-State Model. We define the reaction as

$$S_{\mathrm{oc}} \underset{k_3}{\overset{k_4}{\leftrightarrows}} S_3 \underset{k_1}{\overset{k_2}{\leftrightarrows}} S_2 + \mathrm{Na}, \quad \textbf{[S1]}$$

where S represents states. If P_2, P_3, *and* P_{oc} are the probabilities of being in states S_2, S_3, and S_{oc}, respectively,

$$P_2 + P_3 + P_{\mathrm{oc}} = 1. \quad \textbf{[S2]}$$

The first reaction is given by

$$\frac{dP_{\mathrm{oc}}}{dt} = P_3 k_3 - P_{\mathrm{oc}} k_4. \quad \textbf{[S3]}$$

Assuming that the last reaction is in equilibrium, we have

$$\frac{P_2[\mathrm{Na}]}{P_3} = \frac{k_2}{k_1} = K, \quad \textbf{[S4]}$$

and combining **[S2]**, **[S3]**, and **[S4]** we get

$$\frac{dP_{\mathrm{oc}}}{dt} = \frac{k_3}{1 + \frac{K}{[\mathrm{Na}]}} - P_{\mathrm{oc}}\left(k_4 + \frac{k_3}{1 + \frac{K}{[\mathrm{Na}]}}\right). \quad \textbf{[S5]}$$

The solution of **[S5]** is a single exponential with rate constant

$$k_s = k_4 + \frac{k_3}{1 + \frac{K}{[\mathrm{Na}]}}. \quad \textbf{[S6]}$$

The equilibrium constant K may be expressed as a function of the difference in free energy between the states S_3 and S_2:

$$K = C^0 \exp(-\Delta G_T/RT), \quad \textbf{[S7]}$$

where C^0 is standard state concentration of 1 mol/L (=1/1661 Å^3)—see ref. 1—and G_T is the absolute binding energy. By expanding the free energy in electrical and chemical terms,

$$K = C^0 \exp\left(\frac{z\delta FV - \Delta H_u + T\Delta S_u}{RT}\right). \quad \textbf{[S8]}$$

Separating the electrical term from all the chemical terms, we can write Eq **S8** as

$$K = K(0)\exp\left(\frac{z\delta FV}{RT}\right), \quad \textbf{[S8a]}$$

where $K(0)$ is the equilibrium constant at 0 mV. Combining **[S8a]** with **[S6]**, we obtain

$$k_s = k_4 + \frac{k_3}{1 + \frac{K(0)\exp(\frac{z\delta FV}{RT})}{[\mathrm{Na}]}}. \quad \textbf{[S9]}$$

Eq. **S9** corresponds to Eq. **2** in the main text.

Expressing k_3 and k_4 in terms of their enthalpic and entropic components and replacing K by its explicit form Eq. **S8** into Eq. **S9**, we obtain

$$k_s = A\exp\left(\frac{-\Delta H_4^{\neq} + T\Delta S_4^{\neq}}{RT}\right) + \frac{A\exp(\frac{-\Delta H_3^{\neq} + T\Delta S_3^{\neq}}{RT})}{1 + \frac{C^0}{[\mathrm{Na}]_{\mathrm{o}}}\exp(\frac{z\delta FV - \Delta H_u + T\Delta S_u}{RT})}, \quad \textbf{[S9a]}$$

where the preexponential factors are all the same and equal to A. Eq. **S9a** corresponds to Eq. **3** of the main text.

To compute the *Q-V* curve, we consider Eq. **S3** in the steady state:

$$P_3 k_3 - P_{\mathrm{oc}} k_4 = 0. \quad \textbf{[S10]}$$

The charge movement occurs between S_2 and S_3, and it is a maximum when the voltage is most negative. Then we are interested in state S_3, whose probability is obtained by combining Eqs **S2**, **S4**, and **S10**:

$$P_3 = \frac{\frac{[\mathrm{Na}]}{K}}{1 + \frac{[\mathrm{Na}]}{K}(1 + \frac{k_3}{k_4})}. \quad \textbf{[S11]}$$

At very negative V, we have the maximum charge moved (in the inward direction), and its probability is equal to

$$P_3(V \to -\infty) = P_{-\infty} = \frac{k_4}{k_3 + k_4}, \quad \textbf{[S12]}$$

and normalizing the total charge by $P_{-\infty}$ we have

$$P_{\mathrm{nor}} = \frac{P_3}{k_4/(k_3 + k_4)}, \quad \textbf{[S13]}$$

which can be written as

$$P_{\mathrm{nor}} = \frac{1}{1 + \frac{KP_{-\infty}}{[\mathrm{Na}]}}. \quad \textbf{[S14]}$$

Then P_{nor} is given by

$$P_{\mathrm{nor}} = \frac{1}{1 + \frac{P_{-\infty}C^0\exp(-\Delta G_T/RT)}{[\mathrm{Na}]}}, \quad \textbf{[S15]}$$

and, by introducing explicitly the electrical and chemical terms

$$P_{\mathrm{nor}} = \frac{1}{1 + \frac{P_{-\infty}C^0\exp(\frac{-\Delta H + T\Delta S + z\delta FV}{RT})}{[\mathrm{Na}]}} \quad \textbf{[S16]}$$

or

$$P_{\mathrm{nor}} = \frac{1}{1 + \exp(\frac{z\delta FV - \Delta H + T\Delta S + RT\ln(\frac{C^0 P_{-\infty}}{[\mathrm{Na}]})}{RT})} \quad \textbf{[S17]}$$

that can be written as

$$P_{\mathrm{nor}} = \frac{1}{1 + \exp(\frac{z\delta F(V - V_{1/2})}{RT})} \quad \textbf{[S18]}$$

from Eq. **S17**, $V_{1/2}$ is defined as

$$V_{1/2} = \frac{\Delta H - T\Delta S - RT\ln P_{-\infty} + RT\ln[\mathrm{Na}]/C^0}{z\delta F}. \qquad \textbf{[S19]}$$

Expanding the $P_{-\infty}$ term and assuming that $k_3/k_4 \gg 1$, we get

$$V_{1/2} = \frac{\Delta H - T\Delta S - RT\ln\frac{k_4}{k_3} + RT\ln[\mathrm{Na}]/C^0}{z\delta F}, \qquad \textbf{[S20]}$$

but we can replace k_4/k_3 by the exponential relation to the change in free energy in the deoccluding step:

$$\frac{k_4}{k_3} = \exp(-\Delta G_o/RT) = \exp\left(\frac{-\Delta H_o + T\Delta S_o}{RT}\right). \qquad \textbf{[S21]}$$

By replacing **[S21]** in **[S20]**,

$$V_{1/2} = \frac{\Delta H - T\Delta S + \Delta H_o - T\Delta S_o + RT\ln[\mathrm{Na}]/C^0}{z\delta F}. \qquad \textbf{[S22]}$$

2. Two-State Model. We consider now only two states S_2 and S_3 (collapsing S_{oc} with S_3) in the steady state:

$$P_3 = \frac{1}{1 + \frac{K}{[\mathrm{Na}]}}, \qquad \textbf{[S23]}$$

$$P_3 = \frac{1}{1 + \frac{C^0\exp(-\Delta G_T/RT)}{[\mathrm{Na}]}}, \qquad \textbf{[S24]}$$

$$P_3 = \frac{1}{1 + \exp\left(\frac{-\Delta G_T - RT\ln([\mathrm{Na}]/C^0)}{RT}\right)} = \frac{1}{1 + \exp\left(\frac{zF\delta V - \Delta H_T + T\Delta S_T - RT\ln([\mathrm{Na}]/C^0)}{RT}\right)}. \qquad \textbf{[S25]}$$

By writing **[S25]** as

$$P_3 = \frac{1}{1 + \exp\left(\frac{zF\delta(V - V_{1/2})}{RT}\right)},$$

$V_{1/2}$ becomes

$$V_{1/2} = \frac{\Delta H_T - T\Delta S_T + RT\ln([\mathrm{Na}]/C^0)}{z\delta F}, \qquad \textbf{[S26]}$$

which corresponds to Eq. **4** in the main text. Comparing this equation with Eq. **S22** we find that $\Delta H_T = AH + \Delta H_0$ and $\Delta S_T = \Delta S + \Delta S_0$.

1. Woo HJ, Roux B (2005) Calculation of absolute protein-ligand binding free energy from computer simulations. *Proc Natl Acad Sci USA* 102:6825–6830.