sites occupied. Here, K_H and K_{Cl} are the equilibrium constant for binding of H^+ and Cl^-, respectively. f is a scale factor

Fig. 8 *Simulation of I_{ClVol} time course and ion-dependence of I_{ClVol} decay.* **a** Time course of I_{ClVol} between -80 and +120 mV was simulated using the model shown in Fig. 7 and the rate constants listed in Table 2. **b** FIC vs V_m curves as a function of $[Cl^-]_i$ (25, 70, 140 and 200mM) were also simulated. Continuous lines are fits with equation 2 using z=1.43. **c** and **d**: Simulations of FIC vs V_m as a function of pH_e (5.5, 7.3, and 9.0) and $[Cl^-]_i$ (140 mM, c or 25 mM, d). Continuous lines are fits with equation 2 using z=1.53 and 1.44 for 140 and 25 mM $[Cl^-]_i$, respectively

Supplemental Fig. 9 *Hypothetical V_m-dependence of volume-sensitive chloride channels.* **a** Simple barrier model representing the energy landscape along the VRAC pore. This energy profile plus the kinetic model shown in Fig. 7 were used to qualitatively explain the V_m- (panel a) and external Cl^--dependence (panel b) of inactivation. The energy profiles depict the landscape along the pore that the permeant anions (with symmetrical $[Cl^-]_i=[Cl^-]_e=140$ mM) experiment at -100, 0 and +100 mV. At each voltage the pore occupancy changes and thus the probability that the pore is empty (P_U) is greater at positive voltages. Moreover, P_U changes as a function of the Cl^- gradient across the membrane. **b** P_U becomes larger as the Cl^- gradient decreases. P_U was calculated using the V_m-dependent rate constants: $\alpha_V=[Cl^-]_o*k_1+[Cl^-]_i*k_{-2}$ and $\beta_V= k_{-1+}*k_{-2}$ recorded in Table 2

Fig. 9

a

b