Nonlocal electrostatic calculations of the change in the free energy of transition of ion from aqueous solution to aqueous cavity of the KcsA K⁺ channel in biomembrane

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The problem of overcoming the energy barrier by the K⁺ cation when it enters a spherical water cavity with a diameter of one nanometer of the potassium channel of a biomembrane is important for biological applications [1, 2]. The energy of the image forces U_{im} acting on K⁺ in the center of cavity is calculated by the Eq.(1), in which R_{cav} is the radius of the cavity ($R_{cav} = 5$Å):

$$U_{im} = (e^2/2R_{cav})\{1/\varepsilon_p - 1/\varepsilon_{cav}\}, \quad \text{(in [1] } \varepsilon_{cav} = \varepsilon_S \approx 80; \text{ in [2]: } \varepsilon_{cav} = \varepsilon_2 \approx 5), \tag{1}$$

where ε_p is the dielectric permittivity of the protein environment of the cavity, ε_{cav} is the dielectric permittivity in the cavity, which for water in cavities with a diameter of the order of a nanometer is approximately equal to 5, which was shown in [3] by molecular dynamics methods. In Fig. (b), the energy calculated by Eq.(1) is represented by circles, and the calculation was carried out at $\varepsilon_{cav} = \varepsilon_S \approx 80$, as suggested in the paper [1].

Let us consider the change in $\Delta\mu$ of the standard chemical potential K⁺ during its transition from solution to cavity the channel. The change in $\Delta\mu$ is calculated by Eqs. (2)-(3), in which r_K is the radius of K⁺, (sub index CE is for classical electrostatics, NE is for nonlocal electrostatics):

$$\Delta\mu_{CE} = (e^2/2r_K)[1 - 1/\varepsilon_s] - (e^2/2r_K)[1 - 1/\varepsilon_{cav}], \quad (\varepsilon_{cav} = 5). \tag{2}$$

To derive the Eq. (2), the classical Born's formula is used twice. Then the first term in (2) is the ion solvation energy in a free solution, and the second term is the energy of solvation in the channel cavity. Since the calculation of the ion solvation energy according to the classical Born's formula gives values that are very different from the experimental ones, we calculate W_{NE} the energy in a free solution (the first term in (3)) according to the formulas of nonlocal electrostatics [4]. In this case, the energy of solvation of the cation in the channel cavity (the second term in (3)) is still calculated by the classical Born's formula:

$$\Delta\mu_{NE} = W_{NE} - (e^2/2r_K)[1 - 1/\varepsilon_{cav}], \quad (\varepsilon_{cav} = 5), \tag{3}$$

where W_{NE} is the solvation energy of K⁺ in a free solution, which is calculated by Eqs. (4)-(5) in accordance with paper [4]:

$$W_{NE} = (e^2/\pi) \int [\sin kr_K /kr_K]^2[1 - 1/\varepsilon(k)] \, dk, \quad (0 < k < \infty), \tag{4}$$

$$\varepsilon(k) = \varepsilon_o(k) + \varepsilon_s/[kL_D]^2, \tag{5}$$

where k is wave number, $\varepsilon(k)$ is the Fourier transform of the dielectric function of the solution with the Debye length L_D ($L_D \approx 8$ Å at $c = 0.15$ M), $\varepsilon_s \approx 80$, $\varepsilon_o(k)$ is the dielectric function of water, which for the three-pole model of water [5-8] has the form (6), where the three terms reflect contributions of the electronic, vibrational and (orientational) long-range structure components of the polar solvent, λ_i are the corresponding correlation lengths: $\lambda_1 \cong 0.5$ Å for the electronic mode, $\lambda_2 \cong 1$ Å for the vibrational mode, $\lambda_3 \equiv \Lambda \cong 5$ Å for the orientational mode. Coefficients, C_i, can be expressed via effective dielectric constants of this medium: $C_1 = (1 - 1/\varepsilon_1) = 0.444$, $C_2 = (1/\varepsilon_1 - 1/\varepsilon_2) = 0.352$, $C_3 = 1/\varepsilon_2 - 1/\varepsilon_3 = 0.191$; $\varepsilon_1 = 1.8$, $\varepsilon_2 = 4.9$, $\varepsilon_3 \equiv \varepsilon_S = 78.5$ (ε_S is the static dielectric permittivity of water)

$$[1/\varepsilon_o(k)] = 1 - \{ C_1/[1 + (k\lambda_1)^2] + C_2/[1 + (k\lambda_2)^2] + C_3/[1 + (k\lambda_3)^2]\}. \tag{6}$$

The change in the free energy ΔG of the transition of the ion from the solution to the channel cavity is calculated by Eqs. (7)-(8), in which U_{im} is the energy of the image forces acting on the cation located in the center of the cavity (U_{im} is calculated by formula (1) with $\varepsilon_{cav} = 5$):

$$\Delta G_{NE} = \Delta\mu_{NE} + U_{im}, \quad \text{(NE – nonlocal electrostatic)} \tag{7}$$

$$\Delta G_{CE} = \Delta\mu_{CE} + U_{im}, \quad \text{(CE – classical electrostatic)} \tag{8}$$

The figure shows the graphs of the dependences of the change in the free energy of the ion, the change in the chemical potential and the energy of the image forces acting on the ion in the center of the water cavity as a function of the dielectric permittivity of the protein environment of the cavity.

(a) NE - nonlocal electrostatic   **(b) CE - classical electrostatic**
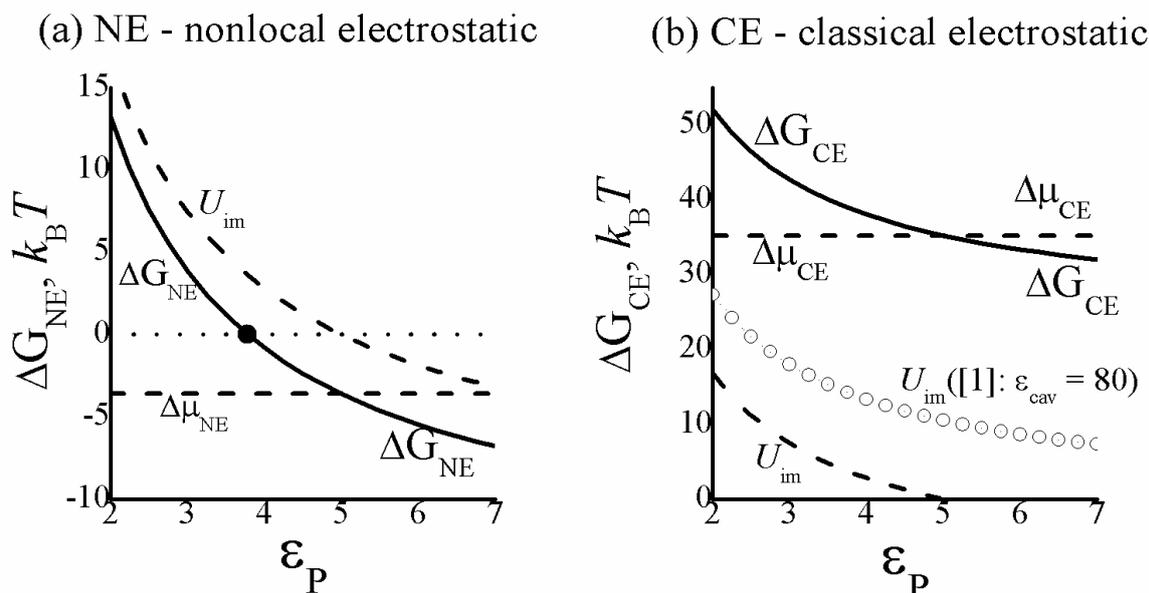
Figure. Dependence of the change in free energy ΔG_{NE} and ΔG_{CE} (Eqs. (7)-(8), solid curves) of the transition of the K^+ cation from a free solution to the center of a spherical water cavity with a radius of 5 Å on the dielectric permittivity ε_p of the medium surrounding the cavity. Also shown are changes in the chemical potential in $\Delta\mu$ of the cation (horizontal dashed lines, calculation by Eqs. (2), (3)), and the energy of the image forces U_{im} (dashed lines, calculation by formula (1) with $\varepsilon_{cav} = 5$). All energies are given in the $k_B T$ units. In Fig. b, circles represent the calculation of the energy of the image forces, under the assumption that the static dielectric constant in the cavity is the same as in free water, as suggested in paper [1].

Let us try to understand why it was believed in [1] that the static dielectric constant of water in the channel cavity is the same as in a free solution. If we assume that the static value of ε_{cav} in the cavity is 5, then the calculation by Eq. (3) of the change in the chemical potential of the ion during its transition into the cavity gives too large values, as can be seen from Fig. (b). Then the change in free energy, calculated by Eq. (8), will be more than 30, as one can see from Fig. (b). Since exp(-30)<<1, then in this classical model based on Born's formula, it is impossible to explain the overcoming of the energy barrier by the ion when entering the channel cavity. When using the nonlocal electrostatic theory to calculate the energy of solvation of an ion in a solution, the change in the free energy of the ion is greater than zero for $\varepsilon_p < 3.8$ and less than zero for $\varepsilon_p > 3.8$, as can be seen from Fig. (a). Therefore, in the first case, the ion is pushed out of the cavity, and in the second, on the contrary, it is draw into the cavity. Note that the effect of ion pulling is purely nonlocal electrostatic, and it was discussed in [9] for the entry of an ion into cylindrical pores.

From Fig. (a) it follows that for $\varepsilon_p = 3.8$ the change in free energy is zero ($\Delta G_{NE} = 0$, point on the curve $\Delta G_{NE}(\varepsilon_p)$). Therefore, calculations based on nonlocal electrostatics (NE) explain the stabilization of K^+ in a nanometer-sized cavity, in contrast to calculations of ΔG by classical electrostatic (CE) (Fig. (b)) and conclusions made in [1].

[1] B. Roux and R. MacKinnon, The cavity and pore helices in the KcsA K+ Channel: Electrostatic stabilization of monovalent cations, Scence, 285, 100-102, (1999).
[2] A.A. Rubashkin and P. Iserovich, A new approach to the selectivity of ion channels: Nonlocal electrostatic consideration, Dokl. Biochem. Biophys., 417, 302-305, (2007).
[3] L. Zhang, H.T. Davis and D.M. Kroll, Molecular dynamics simulations of water in a spherical cavity, J. Phys. Chem., 99, 2878-2884, (1995).
[4] A.A. Kornyshev, Non-local dielectric response of a polar-solvent and Debye screening in ionic solution, J. Chem. Soc. Faraday Trans.II, 79, 651-661, (1983).
[5] R.R. Dogonadze, A.A. Kornyshev, Polar solvent structure in the theory of ionic solvation, J. Chem. Soc., Faraday Trans.II, 70, 1121–1132, (1974).

[6] A.A. Kornyshev, A.G. Volkov, On the evaluation of standard Gibbs energies of ion transfer between two solvents, J. Electroanal. Chem., 180, 363–381, (1984).

[7] M.A. Vorotyntsev, A.A. Kornyshev, Electrostatics of Media with Spatial Dispersion (in Russian), Nauka, Moscow, 1993 (240 p).

[8] M.A. Vorotyntev, A.A. Rubashkin, Uniformity ansatz for inverse dielectric function of spatially restricted nonlocal polar medium as a novel approach for calculation of electric characteristics of ion–solvent system , Chem. Phys., 521, 14-24, (2019).

[9] A.A. Kornyshev, G.I. Tsitsuashvili, A.E. Yaroschuk, The effect of polar solvent structure in the theory of dielectric exclusion of ions from polymer membrane pores. Calculation of free energy of charge transfer from the solvent into a pore, Sov. Electrochem., 25, 932–938, (1989).