

Importance of hydration and dynamics on the selectivity of the KcsA and NaK channels

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An error was discovered in the computer script used to calculate the relative free energies in the reduced models that were reported in Table II. In some of the calculations, the ion position was not fixed at the origin, and the rigid geometry of the TIP3 water molecules was not constrained. This resulted in free energies that were too favorable for Na⁺ over K⁺ in some of the free energy perturbation molecular dynamics (FEP/MD) calculations. The same results for the reduced models with water and carbonyl had previously appeared in Noskov and Roux (2006. *Biophys. Chem.* 124:279–291). The corrected values are given below in the amended version of the Table II. These corrected values are also reported in Fig. 3 (in corrected figure below, the blue triangles for hydration number of 2, 3, and 4 were changed). Furthermore, the text (p.138, line 4 from bottom) should be revised as: “For both the CHARMM and AMBER force fields, there is a systematic loss of selectivity for each water molecule that replaces a carbonyl group (approximately 0.9 and 0.5 kcal/mol per water using CHARMM and AMBER, respectively).”

The corrected values display the same trend as reported previously, albeit the variations in free energies are smaller. This explains and resolves the apparent discrepancy between different computations carried out on identical reduced models that were previously pointed out (Bostick et al. 2009. *Biophys. J.* 96:3887–3896; Varma et al. 2011. *J. Gen. Physiol.* 137:479–488). The results of Table 2 on the toy models were only included as part of the discussion for illustration purposes, and all the FEP/MD calculations carried out on the all-atom KcsA and NaK channel systems are unaffected. Thus, the general conclusions about the importance of the chemical type of ligands on the ion selectivity remain unchanged.

Table II
The variation of $\Delta\Delta G$ as a function of a toy model ligand composition

No. of carbonyls	No. of water molecules	No. of carboxylates	$\Delta\Delta G$ (kcal/mol)
8	0	0	6.2 (3.9)
7	1	0	4.9 (3.5)
6	2	0	4.0 (3.1)
5	3	0	3.2 (2.6)
4	4	0	2.5 (2.3)
6	0	0	3.6 (1.9)
5	1	0	3.2 (1.7)
4	2	0	2.5 (1.4)
7	0	1	2.1 (−0.5)
6	1	1	1.7 (−0.9)
5	2	1	1.4 (−1.6)
4	2	1	0.3 (−2.0)
3	2	1	−0.6 (−2.3)

The numbers between parentheses are for the AMBER force field. The difference in hydration free energy between Na⁺ and K⁺ is 18.4 kcal/mol for the CHARMM force field and 17.7 kcal/mol for the AMBER force field. The CHARMM force field cation Lennard-Jones parameters E_{min} and $R_{min}/2$ were -0.0469 , 1.40375 , and -0.087 , 1.76375 , for sodium and potassium, respectively; pair-specific Lennard-Jones parameters for the ion–carbonyl interactions used for potassium and sodium were -0.1021763 , 3.64275 , and -0.07502 , 3.2975 , respectively (units are kcal/mol for E_{min} and Å for R_{min}).

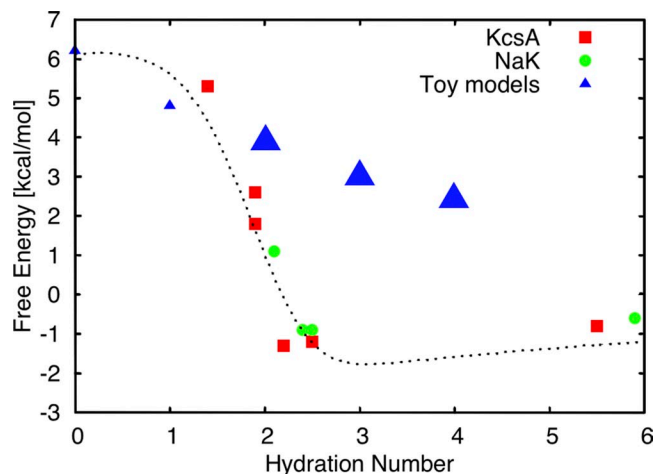


Figure 3. Relative free energy $\Delta\Delta G$ as a function of the average hydration number. The free energy results were taken from Table I for all the binding sites of KcsA and NaK and from Table II for the toy models with eight ligands (eight carbonyls, seven carbonyls and one water, six carbonyls and two water, etc.). The free energies correspond to the computations with the CHARMM force field. The average hydration numbers were taken from Table III in the case of K⁺ occupying the given binding sites. The dotted line is only a visual guide.