Understanding the physical basis of the salt dependence of the electrostatic binding free energy of mutated charged ligand–nucleic acid complexes

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ABSTRACT

The predictions of the derivative of the electrostatic binding free energy of a biomolecular complex, ΔG_{el}, with respect to the logarithm of the 1:1 salt concentration, $d(\Delta G_{el})/d(\ln[NaCl])$, SK, by the Poisson–Boltzmann equation, PBE, are very similar to those of the simpler Debye–Hückel equation, DHE, because the terms in the PBE's predictions of SK that depend on the details of the dielectric interface are small compared to the contributions from long-range electrostatic interactions. These facts allow one to obtain predictions of SK using a simplified charge model along with the DHE that are highly correlated with both the PBE and experimental binding data. The DHE-based model developed here, which was derived from the generalized Born model, explains the lack of correlation between SK and ΔG_{el} in the presence of a dielectric discontinuity, which conflicts with the popular use of this supposed correlation to parse experimental binding free energies into electrostatic and nonelectrostatic components. Moreover, the DHE model also provides a clear justification for the correlations between SK and various empirical quantities, like the number of ion pairs, the ligand charge on the interface, the Coulomb binding free energy, and the product of the charges on the complex's components, but these correlations are weak, questioning their usefulness.

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1. Introduction

Given the high negative charge density of nucleic acids, that many charged ligands, including metal cations, cationic drugs, peptides, and large proteins, bind to nucleic acids while carrying out essential biological functions is not surprising. Numerous kinetic and thermodynamic studies have demonstrated that nonspecific electrostatic interactions between the phosphate groups of the nucleic acid and the charged groups of its ligand partner usually cause the binding affinity of these complexes to increase strongly with decreasing salt concentration [1–16]. If competing multivalent ions are not present, the total experimental binding free energy, ΔG, has been observed to vary linearly with the 1:1 salt concentration, [NaCl], and $d(\Delta G)/d(\ln[NaCl])$ is a negative constant, referred to in the literature as SK, at least over a moderate range of salt concentrations [17]. Because SK depends primarily on the nonspecific long-range electrostatic interactions in charged ligand–nucleic acid complexes and is accessible to

experimental tests, it has been frequently used to test the predictions of electrostatic theories [18–22].

One of the first methods of successfully predicting SK for a broad range of biopolyelectrolyte complexes was the counterion condensation theory, CCT [17,23]. Its predictions have been confirmed [18,19,24–27] by their agreement with those of the nonlinear Poisson–Boltzmann equation [28,29], NLPBE, which includes features absent in the CCT like a detailed charge distribution and a dielectric discontinuity. However, in our recent study on the binding of small organic drugs to DNA [30], although both the NLPBE and the CCT produce SK predictions that agree with experimental binding data, the NLPBE in the presence of a dielectric discontinuity does not agree with the relation inferred from the CCT, $\Delta G_{el} = -SK\ln[NaCl]$ [31]. This finding is consistent with other PBE studies on RNA-protein systems like TRAP-RNA, tRNA synthetase-tRNA, and aatRNA-elongation factor Tu complex, where small SK did not imply small ΔG_{el} [32–34]. This observation calls into question the common assumption that ΔG_{el} is proportional to SK [31], and indicates that this assumption should not be used to parse experimental binding free energy data into electrostatic and nonelectrostatic components [5,10,15,16,32].

To explain why the predictions of SK by the NLPBE agree with those of the CCT while their predictions of ΔG_{el} disagree in the presence of a dielectric discontinuity, we examined a version of the

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