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Revisiting the Association of Cationic Groove-Binding Drugs to DNA using a Poisson-Boltzmann Approach

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ABSTRACT Proper modeling of nonspecific salt-mediated electrostatic interactions is essential to understanding the binding of charged ligands to nucleic acids. Because the linear Poisson-Boltzmann equation (PBE) and the more approximate generalized Born approach are applied routinely to nucleic acids and their interactions with charged ligands, the reliability of these methods is examined vis-à-vis an efficient nonlinear PBE method. For moderate salt concentrations, the negative derivative, SK_{pred}, of the electrostatic binding free energy, ΔG_{el}, with respect to the logarithm of the 1:1 salt concentration, $[M^+]$, for 33 cationic minor groove drugs binding to AT-rich DNA sequences is shown to be consistently negative and virtually constant over the salt range considered (0.1–0.4 M NaCl). The magnitude of SK_{pred} is approximately equal to the charge on the drug, as predicted by counterion condensation theory (CCT) and observed in thermodynamic binding studies. The linear PBE is shown to overestimate the magnitude of SK_{pred}, whereas the nonlinear PBE closely matches the experimental results. The PBE predictions of SK_{pred} were not correlated with ΔG_{el} in the presence of a dielectric discontinuity, as would be expected from the CCT. Because this correlation does not hold, parameterizing the PBE predictions of ΔG_{el} against the reported experimental data is not possible. Moreover, the common practice of extracting the electrostatic and nonelectrostatic contributions to the binding of charged ligands to biopolyelectrolytes based on the simple relation between experimental SK values and the electrostatic binding free energy that is based on CCT is called into question by the results presented here. Although the rigid-docking nonlinear PB calculations provide reliable predictions of SK_{pred}, at least for the charged ligand-nucleic acid complexes studied here, accurate estimates of ΔG_{el} will require further development in theoretical and experimental approaches.

INTRODUCTION

Many important clinical drugs bind noncovalently to the minor groove of B-type DNA duplexes containing three or more consecutive AT basepairs (mG-binders) (1). These small organic drugs are used to treat many conditions, including cancer, genetic disorders, and viral and parasitic diseases. Various structural and biophysical studies have examined the noncovalent interactions that contribute to the binding affinity between the mG-binders and B-DNA (2–4). In particular, the complementarity of both shape and electrostatic potential, as discussed in the Supporting Material, between the drugs and the B-DNA as well as the short-range van der Waals and H-bonding contacts enhance binding affinity and contribute to the base sequence specificity (5–9). These studies, however, do not show the relative importance of these noncovalent interactions in stabilizing drug-DNA complexes (10–12). Understanding how these different interactions contribute to binding at the atomic level is critical to developing novel drugs with enhanced binding affinity, specificity, and biological activity.

Several experimental studies have observed that the binding affinities of mG-binders to B-DNA are very sensitive to small variations in salt concentration. In the literature, this observation has been interpreted to mean that nonspecific electrostatic interactions are important in the formation of these complexes (10,13,14). If K_{obs} is the experimental binding constant, and $[M^+]$ is the concentration of 1:1 salt in the bulk solution, then, in the absence of competing multivalent cations, $\log(K_{obs})$ is usually proportional to $\log[M^+]$ over a range of moderate salt concentrations (15,16). The slope of a linear $\log(K_{obs})$-$\log[M^+]$ plot is called SK_{obs} in the literature (17) and is negative for cationic drug-DNA complex formation. A constant negative SK_{obs} over a moderate salt range has historically been interpreted as a characteristic of the polyelectrolyte effect and originates from the high charge density of the negatively charged phosphate groups on the polyanionic DNA backbone (18–20). Because SK_{obs} is easy to obtain experimentally, predicting it is an ideal test of electrostatic models.

The first theoretical attempt to explain the binding of charged ligands to polyelectrolyte DNA was the counterion condensation theory (CCT) developed by Manning (18). The CCT was originally based on a coarse-grained model where the polyion (the DNA in our case) is treated as an infinite line charge representing the projection of the negatively charged phosphate groups onto the helical axis of the DNA. The ionic solvent is modeled as a uniform high dielectric medium, and the ions as point charges. The CCT was later extended by Fenley et al. (21) to account for the 3D arrangement of the phosphate groups obtained from structural data. More recently, others have considered more detailed nonuniform finite charge distributions within the framework of the CCT (22–24), CCT lacks features, like

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