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, $SK_{\text{pred}}$, of the electrostatic binding free energy, $\Delta G_{\text{el}}$, 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 $SK_{\text{pred}}$ 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 $SK_{\text{pred}}$, whereas the nonlinear PBE closely matches the experimental results. The PBE predictions of $SK_{\text{pred}}$ were not correlated with $\Delta G_{\text{el}}$ 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 $\Delta G_{\text{el}}$ 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 $SK_{\text{pred}}$, at least for the charged ligand-nucleic acid complexes studied here, accurate estimates of $\Delta G_{\text{el}}$ 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 $K_{\text{obs}}$ 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($K_{\text{obs}}$) is usually proportional to log($[M^+]$) over a range of moderate salt concentrations (15,16). The slope of a linear log($K_{\text{obs}}$)-log($[M^+]$) plot is called $SK_{\text{obs}}$ in the literature (17) and is negative for cationic drug-DNA complex formation. A constant negative $SK_{\text{obs}}$ 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 $SK_{\text{obs}}$ 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 polyeon (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), but the CCT lacks

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features, like full atomic detail and the dielectric discontinuity between the interior and exterior of the molecule, that are important in some predictions of electrostatic properties, like sequence-dependent features of the electrostatic potential and counterion distributions surrounding nucleic acids (6,7,25). Therefore, the CCT may not reproduce experimental data for systems in which these effects are important (26).

According to the Manning CCT (18),

\[ SK_{\text{obs}} = \frac{d(\ln K_{\text{obs}})}{d(\ln [M^+]^z)} = -z, \]  

(1)

where \( z \) is the charge on the cationic drug. Following similar assumptions, Record et al. (20) predict that \( SK_{\text{obs}} = -z \psi \) where \( \psi \) is the thermodynamic binding fraction, which depends on the charge density of the nucleic acid. Both theories assume that the polyelectrolyte effect is purely entropic and arises when the ligand displaces counterions that were bound to the DNA before association.

Other interpretations of \( SK_{\text{obs}} \) have been discussed in the literature. For instance, Anderson and Record (17) express \( SK_{\text{obs}} \) in terms of preferential interaction coefficients, which take into account changes in the accumulation of cations and the exclusion of anions around the DNA and ligand during binding. If it is assumed that the only salt-dependent terms in the binding free energy are in the electrostatic component of the binding free energy, \( \Delta G_{\text{el}} \), then, following Sharp et al. (27), \( SK_{\text{obs}} \) relates to the change in the osmotic pressure on binding, \( \Delta \Pi \), where \( \Pi \) is the osmotic pressure defined in the Methods section, by:

\[ SK_{\text{obs}} = -\frac{d\Delta G_{\text{el}}}{d \ln [M^+]^z} = \Delta \Pi. \]  

(2)

The Poisson-Boltzmann equation (PBE) (6,28,29) can be solved numerically to find a potential that can be integrated by the methods of Sharp et al. (27) to calculate \( \Delta G_{\text{el}} \). Unlike the CCT, the PBE can make predictions of \( \Delta G_{\text{el}} \) that include the 3D atomic structure of the biomolecules with low CPU cost due to the algorithmic advances made in the past decade. The PBE does not inherently include conformation change effects. The molecules in this study undergo only very small conformation changes on binding, as pointed out by Wilson et al. (4). Therefore, not including these conformational effects is a reasonable approximation, as we show in the Discussion. PBE methods include both the nonlinear PBE and its linear approximation, which is found by taking the first order approximation to the exponential term in the nonlinear PBE. The linear PBE is valid for small electrostatic potentials. The pairwise generalized Born (GB) method approximates the linear PBE by using an empirical Debye-Hückel term (30,31) to account for nonspecific salt effects.

Some theoretical studies have used the nonlinear PBE to investigate a limited number of drugs binding to nucleic acids (27,28,32–38), whereas several other groups have used either the linear PBE or GB model in lieu of the full nonlinear PBE to study different electrostatic effects in nucleic acids-charged ligand association processes (39–44). Wang and Laughton used molecular dynamics and the molecular mechanics/generalized Born approach to predict the relative affinity of the Hoechst 33258 ligand for different A/T-rich DNA sequences (41). In a newer follow-up study from the same laboratory it was found that predictions of the binding affinity of Hoechst 33258 to different DNA sequences are better when the molecular mechanics/Poisson-Boltzmann surface accessible approach is used as opposed to the molecular mechanics/generalized Born surface accessible approach (45). However, none of these studies have rigorously examined the validity of the linear PBE approximation for a large set of nucleic acid-charged ligand systems. Therefore, one of the main goals in this study is to determine whether the linear PBE provides an adequate approximation to the nonlinear PBE when investigating salt-dependent drug-nucleic acid interactions. Talley et al. (46) did address this question for protein-protein association, but their protein-protein complexes were generally of lower net charge than the complexes examined here. The complexes in this study are therefore expected to exhibit more pronounced nonlinear behavior. To confirm this expectation and to assess the ability of linear and nonlinear PBE analyses to reproduce experimental results, \( SK_{\text{obs}} \) was calculated with the linear and nonlinear PBE for the complexes in this study.

Unfortunately, extracting \( \Delta G_{\text{el}} \) directly from the experimental data of the binding of charged ligands to nucleic acids is not possible. The CCT predicts that \( \Delta G_{\text{el}} \) can be predicted by

\[ \Delta G_{\text{el}} = -kT SK_{\text{obs}} \ln [M^+] + C, \]  

(3)

where \( C \) is a term that does not depend on the salt concentration. This equation is model-independent, as it is simply a thermodynamic identity. Manning then goes on to compute \( C \) by making several assumptions, including that the electrostatic potential can be given by the Debye-Hückel equation and that the atomic structure of neither the polyelectrolyte nor the binding ligand is important to \( \Delta G_{\text{el}} \). (18) These assumptions lead to the prediction that \( C \) is independent of the details of the binding partners and solely depend on the charge density of the polyelectrolyte. Because the PBE does consider this information, \( C \) is not necessarily independent of all parameters except the charge density of the polyelectrolyte, and as will be shown here, the PBE predictions of \( \Delta G_{\text{el}} \) do indeed depend on these parameters.

Frequently, experimental groups (47–52) infer \( \Delta G_{\text{el}} \) from the following equation:

\[ \Delta G_{\text{el}} = -kT SK_{\text{obs}} \ln [M^+] \],  

(4)

which is a simplified version of Eq. 3. Once \( \Delta G_{\text{el}} \) is calculated, the nonelectrostatic binding free energy, \( \Delta G_{\text{non-el}} \) follows from:
\[ \Delta G_{\text{obs}} = -kT \ln K_{\text{obs}} = \Delta G_{\text{el}} + \Delta G_{\text{non-el}}. \] (5)

Whether the predictions of Eq. 4 agree with those of the PBE is not clear, however. For instance, from Eq. 4 a larger \( K_{\text{obs}} \) indicates a larger \( \Delta G_{\text{el}} \), but this disagrees with the results of our recent PBE study (53). If Eq. 4 is not valid, then it is not possible to parameterize the PBE directly against the experimental data that has been reported without resolving the term \( C \) in Eq. 3. In this study, we report a detailed investigation of the behavior of \( \Delta G_{\text{el}} \) with respect to \( \ln[\text{M}^+] \) for a large number of DNA-drug complexes.

THEORETICAL METHODS

The DNA-drug complexes in this study are listed in Table S1, and the atomic coordinates of all the complexes are available in the RCSB Protein Data Bank (http://www.rcsb.org). The complexes were prepared as described in the Supporting Material.

The PBE calculations were carried out with an adaptive grid solver that is described elsewhere (A. Boschitsch and M. Fenley, unpublished) at 1:1 salt concentrations of 0.1-0.4 M at a temperature of 298 K. This PBE solver produced results that were comparable to the more commonly used APBS (54) PBE solver. The exterior dielectric constant, \( \epsilon_{\text{ext}} \), was set at 80, and the interior dielectric constant, \( \epsilon_{\text{int}} \), was fixed at 2. We discuss the effect of \( \epsilon_{\text{int}} \) later. The dielectric boundary separating the solute and solvent regions was the solvent excluded, SE, surface. No ion-exclusion region was used because it has a consistent but small effect on our predictions of \( K_{\text{obs}} \) (55). The dimensions of the grid were set to three times the largest dimension of the complex, and the fine grid spacing was 0.3 Å. The reader is referred to the Supporting Material for a more detailed description of the PBE calculations.

RESULTS AND DISCUSSION

Electrostatic binding free energy of drug-DNA complexes

In this study, \( SK_{\text{pred}} \) is considered rather than \( \Delta G_{\text{el}} \) because \( \Delta G_{\text{el}} \) is sensitive to the PBE parameters. This is illustrated in Fig. 1, where \( \Delta G_{\text{el}} \) is plotted against \( \ln[\text{NaCl}] \) for several values of \( \epsilon_{\text{int}} \) for propamidine interacting with AT-rich B-DNA (PDB id: 102D). Unlike \( \Delta G_{\text{el}} \), which clearly exhibits significant change, the slope of the \( \Delta G_{\text{el}} \) versus \( \ln[\text{NaCl}] \) curves, which is proportional to \( SK_{\text{pred}} \), is effectively the same for all \( \epsilon_{\text{int}} \). Comparable variations in \( \Delta G_{\text{el}} \) are observed when varying the dielectric interface definitions used in the PBE calculations (data not shown), although, \( SK_{\text{pred}} \) is essentially invariant under such changes. Similar conclusions on different nucleic acid-charged ligand systems have been made in other PBE studies (56,57).

Intuitively, one would expect the desolvation cost to be unfavorable and the Coulombic interactions to be favorable for the association of unlike charges with the net \( \Delta G_{\text{el}} \) remaining small. This expected anticorrelation between the Coulombic term and the reaction field term was observed for the complexes in this study (results not shown), where the Coulombic term is almost equal in magnitude but of opposite sign to the reaction field contribution. This compensation effect between the Coulombic and reaction field energies was first noted by Shaikh et al. (42) and Jayaram et al. (58) in a free energy component analysis of 25 minor groove drug-DNA complexes using a modified GB model (42,58). More recently, a molecular dynamics study of the essential subunit PA-PB1 interaction in the influenza virus RNA polymerase using the molecular mechanics/Poisson-Boltzmann surface accessible and molecular mechanics generalized Born surface accessible protocols also showed this compensation phenomena between the Coulombic and reaction field binding free energies (59). When the drug and the DNA are far apart, there is a net favorable electrostatic binding contribution, originating from the Coulombic term that is only weakly affected by the choice of PBE parameters. As they come in contact however, the unfavorable reaction field term grows and eventually dominates the Coulombic energy contribution. The sensitivity of \( \Delta G_{\text{el}} \) to the parameters is largely attributable to the reaction field contribution. This desolvation energy is also what distinguishes the predictions of the CCT from those of the PBE in a simplistic sense. Because the CCT does not include a dielectric discontinuity, there is no desolvation cost, and therefore the \( C \) in Eq. 3 is not dependent on the details of the molecular surface.

Some attempts have been made to identify what surface definition should be used to construct the solute-solvent dielectric boundary in PBE calculations, but the results obtained by different groups are conflicting. In one study, it was found that the van der Waals surface reproduces the effects of charge mutations on the binding affinity of two different RNA-protein complexes better than the SE surface (56). On the other hand, a more recent PBE study of the association of mRNA cap analogs to the translation initiation factor eIF4E showed that both the van der Waals and
SE models provide similar predictions of the effects of mutations on the binding energetics (57). Based on these and our own PBE studies (53,60), we believe it is clear that one should be cautious when drawing any conclusions about whether electrostatics stabilizes or destabilizes binding because, by simply altering the dielectric boundary definition and the value of the interior dielectric constant, one can change $\Delta G_{el}$ from positive to negative.

To solve the parameterization problems noted above, one would like to use the reported experimental thermodynamic binding data, but, as mentioned before, the ability of Eq. 4 to predict $\Delta G_{el}$ is questionable. As can be seen in Fig. 2, $\Delta G_{el}$ and $SK_{pred}$ were not correlated for the choice of PBE parameters listed in the Theoretical Methods section. As has been found in other PBE studies (36,38,61), $\Delta G_{el}$ is positive. The problem with Eq. 4 seems to be that it does not account properly for the dielectric discontinuity between the solute and solvent regions. In Fig. 3, $\Delta G_{el}$ was plotted against $SK_{pred}$ where each quantity was calculated with an $\epsilon_{int}$ of 78, so that the dielectric discontinuity was nearly eliminated. This is the limit considered by the CCT, and we would therefore expect Eq. 4 to agree with the predictions of the PBE in this limit. We did not eliminate the dielectric discontinuity completely because this is not possible with our PBE solver, but this should illuminate the behavior in this limit. In this case, $\Delta G_{el}$ was strongly correlated with $SK_{pred}$ with an $R^2 = 0.96$. This indicates that the primary difference between the predictions of $\Delta G_{el}$ by the CCT and those by the PBE arise from the dielectric discontinuity, whereas incorporating a realistic charge distribution is relatively unimportant. However, several studies have indicated that including a dielectric discontinuity is vital for reproducing other physical parameters (8,62,63), and we therefore do not feel that this choice of $\epsilon_{int}$ should be used.

**Effects of the details of the charge distribution on $SK_{pred}$**

$SK_{pred}$ is fairly independent of changes in the 3D charge distribution that preserve the total charge on the complex, as can be seen from Fig. 4, where $SK_{pred}$ calculated with a formal charge distribution is similar to that obtained using an all-atom charge assignment. These observations concur with an earlier study by Sharp et al. (27) that modeled the binding of DAPI to DNA as a cylinder-sphere interaction and compared the results to a classical all-atom DNA-drug model. They found that $SK_{pred}$ predicted by all-atom models differs by <3% from that obtained with the coarse-grained models. Such errors are less than those in experimental estimates of $SK_{obs}$. Therefore consideration of full atomic detail does not appear to be necessary when computing $SK_{pred}$ of charged ligand-nucleic acid complexes. Because the charge distribution does not seem to significantly affect $SK_{pred}$ for the complexes in this study, it seems that the ionizable groups are the major contributors to $SK_{pred}$, with the dipolar groups playing a minor role. A thermodynamic study on the contribution of the closing basepair to the stability of RNA tetraloops supports this observation (64).

**Comparing the predictions of the nonlinear PBE to experimental binding data**

In Table 1, the available thermodynamic salt-dependent binding data for these complexes are compared to our nonlinear PBE predictions, and they are in excellent agreement. This strong correlation between the experimental thermodynamic data obtained from different laboratories and these nonlinear PBE predictions supports the use of the nonlinear PBE in accurately predicting $SK_{obs}$ for these drug-DNA systems. Because the predictions of the linear PBE deviate strongly from the experimental data, the
nonlinear PBE should be used for highly charged complexes like these.

Because predictions from static single-conformation PBE calculations accurately reproduce the experimental data, it appears that conformational flexibility can be neglected for \( SK \) predictions in these systems. The role of conformational dependence is more pronounced and its inclusion becomes necessary for more complicated nucleic acid systems where induced fit effects or intercalation are an integral part of the binding mechanism (65).

The reader is referred to the Supporting Material for a comparison of our PBE predictions of \( SK_{\text{obs}} \) to similar PBE results reported in the literature.

**Linear versus nonlinear PBE predictions of \( SK_{\text{pred}} \)**

\( SK_{\text{pred}} \) obtained with the nonlinear PBE is compared to that obtained with the linear PBE in Fig. 4. For all 33 DNA-drug complexes, the magnitude of \( SK_{\text{pred}} \) obtained from the linear PBE is larger than that obtained from the nonlinear PBE by at least 51%. This overestimation has also been observed in predictions of \( SK_{\text{pred}} \) for charged protein-protein complexes (46) and glutamine synthetase and glutaminyl synthetase bound to their cognate tRNA (66). For the protein-protein complexes considered by Talley et al. (46), the overestimation of the magnitude of \( SK_{\text{obs}} \) using the linear PBE compared with the nonlinear results is much smaller than for the drug-DNA complexes considered here. This is expected, given the larger charge densities of the drug-DNA complexes, and is consistent with the large differences between the linear and nonlinear PBE \( SK \) predictions obtained for the more highly charged tRNA synthetase-tRNA complexes examined by Bredenberg et al. (66). The reason why the linear PBE overestimates the magnitude of \( SK_{\text{obs}} \) is explained using a simple model in the Supporting Material.

To determine whether the difference between the linear and nonlinear PBE, \( SK_{\text{pred}} \) is predictable, the difference, \( \Delta SK = SK_{\text{pred}}(\text{nonlinear PBE}) - SK_{\text{pred}}(\text{linear PBE}) \), was calculated as a function of ligand charge. The result, shown in Fig. 5, suggests that \( \Delta SK \) is proportional to the charge on the ligand. If this pattern holds for other complexes, then the predictions of the linear PBE could be corrected to agree more closely with those of the nonlinear PBE.

**Comparing the nonlinear PBE predictions of \( SK_{\text{pred}} \) to those of the CCT**

In Fig. 6, the values of \( SK_{\text{pred}} \) are plotted against the net charge of the cationic drug, and the magnitude of \( SK_{\text{pred}} \) is generally very close to the net charge on the drug, irrespective of the specific charge distribution and geometry of either the drug or the DNA. This result is in good agreement with the CCT and with the PBE analysis carried out by Rouzina and Bloomfield (67) that uses a coarse-grained DNA model. It is indeed striking to see the extent of agreement between the current and previous 3D PBE analyses and CCT predictions given that the 3D PBE and the CCT are based on very different physical models.
CONCLUSIONS

The binding of mG-binders was studied using the nonlinear PBE, and these results were used to assess the suitability of using the simpler linear PBE for modeling such systems. We believe the results show clearly that the linear PBE substantially overestimates the magnitude of $SK_{\text{pred}}$ with large deviations from the experimental $SK_{\text{obs}}$. On the other hand, the nonlinear PBE provides $SK_{\text{pred}}$ results that agree closely with experimental data as well as the predictions of the CCT. Hence, the linear PBE does not provide an adequate description of the electrostatic properties of these complexes.

The nonlinear PBE predictions of $SK_{\text{pred}}$ closely matched those of the CCT, whereas the PBE predictions of $\Delta G_{el}$ did not agree with those of the CCT. As indicated by our PBE results in the limit of no dielectric discontinuity, this is probably due to the lack of consideration of a low dielectric region in the CCT. The inclusion of a realistic charge distribution had a much smaller effect than the inclusion of a dielectric discontinuity.

This PBE analysis questions the popular method of extracting $\Delta G_{el}$ from experimental thermodynamic binding data of charged ligand-nucleic acid complexes, polysaccharides-proteins, and other charged biomolecular complexes (51,68,69). Because the PBE predictions do not agree with Eq. 4, extracting $\Delta G_{el}$ directly from thermodynamic binding data is not possible, even though Eq. 4 is used widely (51,69–71) to do this. The common practice of inferring that electrostatic interactions are more important when the magnitude of $SK_{\text{obs}}$ is large (72), as implied by Eq. 4, is also questioned by these results, and these concerns should be reexamined by further experimental and theoretical investigations. Also, this work questions the value of obtaining $SK_{\text{obs}}$. Traditionally, it has been valued because of its presumed use to compute $\Delta G_{el}$. If this is not possible, as indicated by these results, then the usefulness of determining $SK_{\text{obs}}$ is debatable. The question as to whether electrostatic interactions favor or disfavor the binding of charged ligands to nucleic acids remains unanswered in light of the sensitivity of PBE predictions of $\Delta G_{el}$ to various input parameters. Proper parameterization of the PBE together with improved solvent descriptions must be developed and validated against reliable experimental data or all-atom molecular dynamics before these important questions can be answered.

In summary, the nonlinear PBE implementations to treat electrostatic interactions in DNA and DNA-ligand systems have evolved to a stage where reliable predictions of $SK_{\text{pred}}$ can be made. However, further advances in a molecular level understanding of binding and, in particular, the effects of solvation (73) seem to be necessary before $\Delta G_{el}$ can be reliably computed for biomolecular complexes.

SUPPORTING MATERIAL

Two tables, two figures, and additional references are available at http://www.biophysj.org/biophysj/supplemental/S0006-3495(10)00601-6.

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