

## Grand Canonical Monte Carlo Simulations on Aqueous Solutions of NaCl and NaDNA: Excess Chemical Potentials and Sources of Nonideality in Electrolyte and Polyelectrolyte Solutions

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(Received: March 30, 1990)

Grand canonical Monte Carlo computer simulations on  $[\text{NaCl}]_{\text{aq}}$  and  $[\text{NaDNA}]_{\text{aq}}$  in the presence of added salt are reported. The results for the simple electrolyte indicate that a (12,6,1) potential function for the ions in a solvent treated as a dielectric continuum supplemented with a Gurney correction term for desolvation describes the behavior of activity coefficients as a function of concentration quite well over a concentration range of 5–500 mM. The structure of the ion atmosphere is examined and found to provide new insight into structural effects at the onset of the breakdown in Debye–Hückel theory. The results on the NaDNA system in the presence of added simple electrolyte provide an account of the contravariant behavior of nonideality of mobile ions in polyelectrolyte versus simple electrolyte solutions.

### I. Introduction

Nonideality in simple electrolyte solutions in general increases with increasing added salt in the regime of low ionic strength.<sup>1–7</sup> Nonideality of simple electrolyte ions in polyelectrolyte solutions is known to decrease with increasing added simple electrolyte salt.<sup>8–10</sup> The molecular origins of these contrasting behaviors of simple and polyelectrolyte solutions have been the subject of numerous investigations<sup>8–19</sup> in recent years. Despite a wealth of information, both experimental and theoretical, a consistent molecular picture that qualitatively as well as quantitatively ac-

counts for the observed properties of simple electrolytes and polyelectrolyte solutions in the presence of simple electrolytes is still emerging. A theoretical and computational model for electrolytes and polyelectrolytes is a necessary prerequisite to a proper treatment and understanding of the behavior of charged biomolecules such as DNA at physiological ionic strengths, for which the structures and interactions are highly sensitive to salt effects.

The most rigorous computational approach to electrolyte solutions is via molecular simulation (the Born–Oppenheimer (BO) level in the notation of Friedman<sup>20</sup>). The explicit treatment of DNA, water, and counterions together in molecular simulations has just become feasible on present generation supercomputers.<sup>21</sup> Molecular simulations via Monte Carlo methods configured in the grand canonical ensemble provide direct access to chemical potentials and hence to activity coefficients as a function of concentration. Unfortunately, such calculations at concentrations of simple salt, water, and DNA of biophysical interest and experimental accessibility are still quite out of reach. Furthermore, grand canonical Monte Carlo methods with ions, water, and solute considered explicitly suffer from severe convergence problems at densities in the range of interest due to low acceptance rates encountered for particle insertions.<sup>22,23</sup>

The problems confronting molecular simulations of aqueous solutions of electrolyte systems have led to extensive consideration of the so-called “primitive model” and variations thereof, where the ions or polyions are treated explicitly and the solvent water is represented as some kind of dielectric continuum (McMillan–Mayer (MM) level models<sup>20</sup>). Obviously, “neglecting” explicit water places serious limitations on the purview of computations based on this approximation. One advantage of the continuum solvent approach is that the effective particle density of the system is quite low and simulations in grand canonical Monte Carlo

(1) Robinson, R. A.; Stokes, R. H. *Electrolyte Solutions*, 2nd ed.; Butterworths Scientific Publications: London, 1959; Chapter 9.

(2) Lewis, G. N.; Randall, M. *Thermodynamics*; McGraw-Hill: New York, 1961; Chapters 22 and 23; revised by S. Pitzer and L. Brewer.

(3) Bockris, J. O'M.; Reddy, A. K. N. *Modern Electrochemistry*; Plenum Press: New York, 1970; Vol. I.

(4) Atkins, P. W. *Physical Chemistry*; W. H. Freeman: New York, 1986.

(5) Barrow, G. M. *Physical Chemistry*; McGraw-Hill: New York, 1966; Chapter 22.

(6) Pitzer, K. S. *Acc. Chem. Res.* **1977**, *10*, 371–377.

(7) Friedman, H. L. *Annu. Rev. Phys. Chem.* **1981**, *32*, 179.

(8) Alexandrowicz, Z. *J. Polym. Sci.* **1960**, *43*, 337.

(9) Katchalsky, A. *Rev. Pure Appl. Chem.* **1971**, *26*, 327 and references therein.

(10) Record, Jr., M. T.; Richey, B. A. *Sourcebook for Physical Chemistry Teachers*; Society Committee on Education, American Chemical Society: Washington, DC, 1988; Chapter 9.

(11) Katchalsky, A.; Alexandrowicz, Z.; Kedem, O. In *Chemical Physics of Ionic Solutions*; Conway, B. E., Barradas, R. G., Eds.; Wiley: New York, 1966; Chapter 15.

(12) Gross, L. M.; Strauss, U. P. In *Chemical Physics of Ionic Solutions*; Conway, B. E., Barradas, R. G., Eds.; Wiley: New York, 1966; Chapter 17.

(13) Rice, S. A.; Nagasawa, M. *Polyelectrolyte Solutions*; Academic Press: New York, 1961.

(14) Oosawa, F. *Polyelectrolytes*; Marcel Dekker: New York, 1971.

(15) Manning, G. S. *Annu. Rev. Phys. Chem.* **1972**, *23*, 117–140.

(16) Mills, P.; Anderson, C. F.; Record, Jr., M. T. *J. Phys. Chem.* **1986**, *90*, 6541–6548.

(17) Paulsen, M. D.; Richey, B.; Anderson, C. F.; Record, Jr., M. T. *Chem. Phys. Lett.* **1987**, *139*, 448–452; **1988**, *143*, 115–116.

(18) Olmsted, M. C.; Anderson, C. F.; Record, Jr., M. T. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 7766–7770.

(19) Valleau, J. P. *Chem. Phys.* **1989**, *129*, 163–175.

(20) Friedman, H. L. *A Course in Statistical Mechanics*; Prentice-Hall: Englewood Cliffs, NJ, 1985.

(21) Swaminathan, S.; Ravishanker, G.; Beveridge, D. L. *J. Am. Chem. Soc.*, in press.

(22) Valleau, J. P.; Cohen, L. K. *J. Chem. Phys.* **1980**, *72*, 5935–5941.

(23) Mezei, M. *Mol. Phys.* **1980**, *40*, 901–906.

formalism are feasible. Thus, a direct determination of the excess chemical potentials and other thermodynamic properties of this model system can be carried out.

In the following, we report new grand canonical Monte Carlo simulations on  $[\text{NaCl}]_{\text{aq}}$  and  $[\text{NaDNA}]_{\text{aq}}$  in the presence of added  $[\text{NaCl}]_{\text{aq}}$ . We examined different theoretical models for the interparticle interactions and the extent to which they account for the observed thermodynamic properties such as activity coefficients of counterions and co-ions in electrolyte and polyelectrolyte solutions. A good account of the activity coefficient data over a wide range of concentrations has been obtained via certain variations of the primitive model for simple electrolytes. An explanation for the contrasting behaviors of activity coefficients as a function of concentration in simple versus polyelectrolyte solutions has also been obtained.

## II. Background

Theoretical accounts of the thermodynamic properties of simple electrolytes have been the subject of numerous discussions.<sup>1-7</sup> The mean ionic activity coefficients of sodium chloride in aqueous solutions relevant to the present study have been tabulated in ref 1. Activity coefficients of simple electrolytes in general tend to decrease with increasing salt concentration in the low salt regime, which extends up to 1 M for sodium chloride at 25 °C, and increase thereafter.

Debye-Hückel (DH) theory has been successful in accounting for this trend in terms of the long-ranged interionic interactions.<sup>3-7</sup> According to DH theory, interionic interactions lead to the formation of an ion atmosphere of opposite charge around each reference ion. This lowers its chemical potential and results in an activity coefficient that is less than unity. However, the range of applicability of this theory is confined to extreme dilutions ( $\leq 0.01$  M). Deviations from DH theory are observed in various forms, such as (a) electrolytes of the same charge type having very different activity coefficient curves, (b) most of the activity coefficient curves passing through a minimum with increasing salt concentration, and (c) the mean activity coefficients of some electrolytes exceeding unity at high salt concentrations. Thus, the charge of solute and dielectric constant of solvent alone do not constitute an adequate representation of the simple electrolyte system. It is now understood that the deviations from Debye-Hückel theory are a manifestation of the competition between the short- and long-ranged ion-ion interactions and ion-solvent interactions.<sup>1-7</sup>

Parametric extensions of the DH limiting law have been successful in reproducing the observed behavior of some simple electrolyte solutions.<sup>1,6,7</sup> Computer simulations with a continuum solvent and with a restricted primitive model for the ions (i.e., a model in which all ions are treated as hard spheres of equal radii and are allowed to interact via a Coulomb potential in a continuum solvent) have also proved useful in assessing the validity of the DH approach (refs 6 and 7 and references therein). Valleau and Cohen<sup>22</sup> developed the grand canonical Monte Carlo (GCMC) methodology for simple electrolyte solutions and applied it to aqueous electrolyte solutions of different charge types in the primitive model. The results emerging from these simulations were compared with predictions of various existing theories for ionic solutions.<sup>24</sup> The primitive model of electrolyte solutions has also been the focus of attention of a recent study on single ion activity coefficients.<sup>25</sup>

Ramanathan and Friedman<sup>26</sup> on the basis of their hypernetted-chain (HNC) calculations observed that a desolvation (Gurney) term added to a continuous potential between the interacting ions within the framework of a continuum description of the solvent was successful in accounting for the observed osmotic coefficients of aqueous solutions of some simple electrolytes. In their refined primitive model for aqueous electrolyte solutions,

a (9,4,1) potential along with a Gurney term was used for evaluating interion interactions. They also concluded that for the purposes of molecular interpretation of the properties of the electrolyte solutions it was very important to represent the repulsive term accurately in MM level models.<sup>26</sup> Such models that replace the hard-core repulsion term of the primitive models by another form have since been designated as "vanilla models".<sup>27</sup> These have been extensively employed by Friedman and co-workers (ref 27 and references therein) to investigate the equilibrium and transport properties of electrolyte solutions.

Molecular simulations with a fully explicit consideration of the solvent water (i.e., the BO level models) are well-known to give an oscillatory potential of mean force (pmf) between two ions of opposite charge.<sup>28-32</sup> Pettitt and Rossky<sup>29</sup> and Dang and Pettitt<sup>30,31</sup> observed this to be true for two chloride ions as well. Rashin<sup>33</sup> subsequently showed that a dielectric continuum representation of the solvent when desolvation of two proximal ions is considered does reproduce this behavior between ions of opposite charge but not between ions of like charge. More recently, Dang and Pettitt<sup>34</sup> and Jorgensen and Buckner<sup>34</sup> have reported corroborative evidence from molecular simulations for the stability of a contact anion pair in water. This raises a question as to whether a theoretical or computational account of the simple electrolytes based on a simple continuum description of the solvent can ever be successful in accounting for both the experimentally observed thermodynamic properties and structural features of aqueous solutions of simple electrolytes. However, the stability of the anion pair concluded from the BO level simulations has been critically examined and questioned recently by Friedman and co-workers<sup>27,35</sup> in the context of available experimental data. Kusalik and Patey<sup>36</sup> in an interesting comparison of the BO and MM level descriptions of aqueous electrolyte solutions found that the success of the MM theory strongly depended upon the electrolyte solution and in particular upon the cation and anion considered. Nevertheless, a calibration of the MM level simple electrolyte models on the experimental thermodynamic properties appears to be an obvious course to take and forms the basis for our study of the behavior of polyelectrolytes such as DNA in the presence of simple electrolytes.

Some early experimental data on the thermodynamic properties of polyelectrolytes in aqueous solutions<sup>8,37-45</sup> were reviewed by Katchalsky, Alexandrowicz, and Kedem.<sup>11</sup> The colligative properties in the salt-free case are practically independent of molecular weight of the polyelectrolyte and slightly dependent on its concentration (the osmotic and activity coefficients decrease with dilution indicating a stronger binding of the counterions to the polyion upon dilution, contrary to the behavior of simple electrolytes) and are determined by and large by the linear charge density on the chain. In an attempt to understand this unique behavior, Katchalsky and co-workers<sup>9,11</sup> set up a cell model for polyelectrolyte solutions, solved the nonlinear Poisson-Boltzmann (PB) equation, and determined osmotic and activity coefficients.

(27) Friedman, H. L. *Faraday Discuss. Chem. Soc.* **1988**, *85*, 1-11.

(28) Berkowitz, M.; Karim, O. A.; McCammon, J. A.; Rossky, P. J. *Chem. Phys. Lett.* **1984**, *105*, 577-580.

(29) Pettitt, B. M.; Rossky, P. J. *J. Chem. Phys.* **1986**, *84*, 5936-5844.

(30) Dang, L. X.; Pettitt, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5531-5532.

(31) Dang, L. X.; Pettitt, B. M. *J. Chem. Phys.* **1987**, *86*, 6560.

(32) Jorgensen, W. L.; Buckner, J. K.; Houston, S. E.; Rossky, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 1891-1899.

(33) Rashin, A. A. *J. Phys. Chem.* **1989**, *93*, 4664-4669.

(34) Dang, L. X.; Pettitt, B. M. *J. Phys. Chem.* **1990**, *94*, 4303-4308.

(35) Friedman, H. L.; Raineri, F. O.; Xu, H. *Pure Appl. Chem.*, in press. Their private communication prior to publication is gratefully acknowledged.

(36) Kusalik, P. G.; Patey, G. N. *J. Chem. Phys.* **1988**, *89*, 7478-7484.

(37) Kern, W. Z. *Phys. Chem.* **1938**, *A181*, 249; **1939**, *A184*, 197.

(38) Kern, W. *Makromol. Chem.* **1948**, *2*, 279.

(39) Kagawa, I.; Katsuura, K. *J. Polym. Sci.* **1952**, *9*, 405.

(40) Mock, R. A.; Marshall, C. A. *J. Polym. Sci.* **1954**, *13*, 263.

(41) Nagasawa, M.; Kagawa, I. *J. Polym. Sci.* **1957**, *25*, 61.

(42) Nagasawa, M.; Izumi, M.; Kagawa, I. *J. Polym. Sci.* **1959**, *37*, 375.

(43) Nagasawa, M.; Takahashi, A.; Izumi, M.; Kagawa, I. *J. Polym. Sci.* **1959**, *38*, 213.

(44) Alexandrowicz, Z. *J. Polym. Sci.* **1959**, *40*, 91; **1962**, *56*, 97, 115.

(45) Shack, J.; Jenkins, R. J.; Thompson, J. M. *J. Biol. Chem.* **1952**, *198*, 85-92.

(24) Valleau, J. P.; Cohen, L. K.; Card, D. N. *J. Chem. Phys.* **1980**, *72*, 5942-5954.

(25) Sloth, P.; Sorensen, T. S. *J. Phys. Chem.* **1990**, *94*, 2116-2123.

(26) Ramanathan, P. S.; Friedman, H. L. *J. Chem. Phys.* **1971**, *54*, 1086-1098.



The calculated line of the "practical osmotic coefficient" (defined as the ratio of the observed osmotic pressure to the ideal osmotic pressure of the polyelectrolyte solution multiplied by the reciprocal interchange distance versus the latter) lies above the experimental line. However, the shape of the curve is identical, indicating that the ratio between the calculated and the observed osmotic coefficients is constant. Two reasons were given to explain this discrepancy. The value assumed for the axial charge separation is possibly larger than the actual value, or the dielectric constant may be less than that of bulk water within the proximity of the polyion. Hence, real osmotic coefficients would be lower than calculated values. This implies that dielectric saturation within the vicinity of the polyion may have to be taken into account in a theoretical description of the thermodynamic properties of the polyelectrolyte solutions.

Studies on ternary mixtures of polyelectrolyte solutions with added salt such as NaDNA with added NaCl are more relevant to realistic physiological conditions. The mean ionic activity and osmotic coefficients of the added salt and the Donnan salt exclusion factor are indicative of nonideality in these mixtures. Kotin and Nagasawa<sup>46</sup> and Alexandrowicz and Katchalsky<sup>47</sup> accounted for the potentiometric titrations of polycarboxylic acids by obtaining numerical solutions to the nonlinear PB equation, but the axial charge density of the polyion had to be treated as a variable parameter and an unrealistic value had to be assigned to account for the colligative properties. Gross and Strauss<sup>12</sup> investigated the influence of site binding on the observed colligative properties of the ternary mixtures via numerical solutions to the PB equation. In particular, they examined the trends in the Donnan salt exclusion factor when site binding of the counterions is considered. The Donnan salt exclusion factor  $\Gamma$  was calculated as a function of added salt concentration for the NaDNA and NaCl systems by a numerical solution to the PB equation and compared with experiment.<sup>45</sup> The net charge on phosphates,  $\alpha$ , was inferred to be  $\leq 0.5$ . At low electrolyte concentrations and at sufficiently high linear charge densities, the quantity  $2\Gamma$  may be interpreted as an effective thermodynamic degree of dissociation.<sup>46</sup> At low ionic strengths,  $\Gamma$  is independent of the site binding; any change in the site binding produces a compensating change in the territorial binding so as to keep the total effective binding of the counterions to the polyion constant.

Lyons and Kotin<sup>48</sup> determined the activity of sodium ion in pure sodium salts of DNA and mixtures of NaDNA with NaCl by ion-exchange membrane potentials. The concentration dependence of counterion binding in pure polyelectrolyte solutions and the additivity rules for activities of counterions in systems containing polyelectrolyte and added salt were examined. They observed that the additivity rule is not followed closely by the polyelectrolyte-simple electrolyte systems and is not applicable for sodium systems. In the absence of added salt, the counterion activity coefficient decreases with increasing phosphate concentration for native NaDNA. Most sodium polyelectrolytes show a decrease in activity coefficient with dilution. NaDNA shows the opposite trends which is attributed to changes in the secondary structure of DNA caused by dilution, a phenomenon called "dilution denaturation". In the presence of added salt, at any given simple electrolyte salt concentration, the activity coefficient decreases with increasing phosphate concentration in the range 0.165–2.91 mM. At any given phosphate concentration, the activity coefficient increases with increasing salt concentration in the range 0.651–2.58 mM.<sup>48</sup>

Manning<sup>49,50</sup> derived formulas for the various colligative properties of polyelectrolyte solutions based on counterion condensation (CC) theory, which differ from those of Katchalsky, Alexandrowicz, and Kedem.<sup>11</sup> Manning observed that the CC theory predictions of activity coefficients, osmotic coefficients, and Donnan salt exclusion factors are generally in agreement with

experiment. The agreement between the theories of Katchalsky et al.<sup>11</sup> and Gross and Strauss<sup>12</sup> and the CC theory is qualitative but not quantitative. DNA in the CC theory is of course treated as a line of charge. Klein, Anderson, and Record<sup>51</sup> developed expressions for the colligative properties of cylindrical polyions in the presence of excess added salt based on the Poisson-Boltzmann cell model and concluded that they conformed over a wide range of salt concentrations with the limiting laws of the CC theory.

Canonical Monte Carlo simulations on aqueous solutions of DNA in the presence of simple electrolytes and Poisson-Boltzmann studies have been the subject of research interest in diverse laboratories (refs 52–60; also see references in refs 61 and 62) and have been discussed in detail in a recent article.<sup>63</sup> Monte Carlo simulations on aqueous solutions of DNA in the grand canonical ensemble were reported initially by Vlachy and Haymet,<sup>64</sup> more extensively by Anderson, Record, and co-workers,<sup>10,16–18</sup> and recently by Valleau.<sup>19</sup> Vlachy and Haymet employed the GCMC method to obtain structural and thermodynamic data for model polyelectrolyte solutions by treating the polyion as an impenetrable, rigid, infinitely long cylinder, and these were compared with PB and HNC integral equation studies using the mean spherical approximation (MSA). The PB equation was concluded to retain its semiquantitative utility even in the range of moderate to high (1 M) concentrations of added salt. The agreement between GCMC and HNC/MSA was found to be better, but detailed comparison with experimental data was not undertaken in this study.

Mills et al.<sup>16</sup> reported extensive GCMC studies on aqueous solutions of NaDNA in the presence of added simple salt. The simulations were used to calculate mean ionic activity coefficients and "preferential interaction coefficients" (similar to Donnan salt exclusion factor<sup>15</sup> and the Donnan membrane equilibrium parameter<sup>12</sup>) for a cell model representation of NaDNA with added salt. Results emerging from GCMC simulations were compared with PB results, and the influence of small ion correlations on the thermodynamic properties was analyzed and concluded to be small. In a subsequent study by Paulsen et al.,<sup>17</sup> the calculated preferential interaction coefficients were compared with experimental Donnan coefficients<sup>45,65</sup> with good agreement at low added salt concentrations. The DNA was treated as an impenetrable cylinder, with the phosphate charges modeled as a continuous line of charge on the cylindrical axis in these studies. Olmsted et al.<sup>18</sup> characterized the role of end effects on molecular and thermodynamic properties in oligoelectrolyte solutions via the GCMC method. Valleau<sup>19</sup> reported an extension of the GCMC method to flexible polyelectrolyte immersed in primitive model aqueous electrolyte solutions.

We have previously reported canonical Monte Carlo simulations on [NaDNA]<sub>aq</sub> in the presence of sodium chloride.<sup>63</sup> The detailed geometry of the charge distribution of DNA and the shape of the major and minor grooves of the double helix were considered in

- (46) Kotin, L.; Nagasawa, M. *J. Chem. Phys.* **1962**, *36*, 873–879.  
 (47) Alexandrowicz, Z.; Katchalsky, A. *J. Polym. Sci.* **1963**, *A1*, 3231–3260.  
 (48) Lyons, J. W.; Kotin, L. *J. Am. Chem. Soc.* **1965**, *87*, 1670–1678.  
 (49) Manning, G. S. *J. Chem. Phys.* **1969**, *51*, 924–933.  
 (50) Manning, G. S. *Q. Rev. Biophys.* **1978**, *11*, 179–246.

- (51) Klein, B. K.; Anderson, C. F.; Record, Jr., M. T. *Biopolymers* **1981**, *20*, 2263–2280.  
 (52) LeBret, M.; Zimm, B. H. *Biopolymers* **1984**, *23*, 271–285.  
 (53) Murthy, C. S.; Bacquet, R. J.; Rossky, P. J. *J. Phys. Chem.* **1985**, *89*, 701–710.  
 (54) Mills, P.; Anderson, C. F.; Record, Jr., M. T. *J. Phys. Chem.* **1985**, *89*, 3984–3994.  
 (55) Conrad, J.; Troll, M.; Zimm, B. H. *Biopolymers* **1988**, *27*, 1711–1732.  
 (56) Anderson, C. F.; Record, Jr., M. T. *Annu. Rev. Phys. Chem.* **1982**, *33*, 191–222.  
 (57) Zimm, B. H.; LeBret, M. *J. Biomol. Struct. Dyn.* **1983**, *1*, 461–471.  
 (58) Klein, B. J.; Pack, G. R. *Biopolymers* **1983**, *22*, 2331–2352.  
 (59) Matthews, J. B.; Richards, F. M. *Biopolymers* **1984**, *23*, 2743–2759.  
 (60) Jayaram, B.; Sharp, K.; Honig, B. *Biopolymers* **1989**, *28*, 975–993.  
 (61) Westhoff, E.; Beveridge, D. L. *The Molecules of Life*. In *Water Science Reviews*; Vol. 5; Franks, F., Ed.; Cambridge University Press: Cambridge, UK, in press.  
 (62) Jayaram, B.; Beveridge, D. L. *J. Phys. Chem.* **1990**, *94*, 4666–4671.  
 (63) Jayaram, B.; Swaminathan, S.; Beveridge, D. L.; Sharp, K.; Honig, B. *Macromolecules* **1990**, *23*, 3156–3165.  
 (64) Vlachy, V.; Haymet, A. D. J. *J. Chem. Phys.* **1986**, *84*, 5874–5880.  
 (65) Strauss, U. P.; Helfgott, C.; Pink, H. *J. Phys. Chem.* **1967**, *71*, 2550–2556.

this study. The mobile ions were treated as soft spheres interacting via continuous potentials in this study, and the influence of dielectric saturation and dielectric discontinuity between the macromolecule and its environment was assessed in a comparison with the simple Coulombic model. It was observed in this study that incorporation of dielectric saturation in the DNA-small ion interactions led to a constancy of the condensed counterion fraction monitored as a function of added salt. This result is consistent with inferences from  $^{23}\text{Na}$  NMR experiments<sup>66,67</sup> and counterion condensation theory.<sup>50</sup> For the purposes of consistency, and in the absence of detailed knowledge on the dielectric properties of water around ions, dielectric saturation was included in the small ion interactions as well in this study.

Grand canonical Monte Carlo (GCMC) simulations offer a computational route to calibrate the primitive model for simple electrolytes against the known thermodynamic properties such as activity coefficients. The GCMC method is particularly adapted for low-density systems,<sup>16,22,68-70</sup> because the probability of insertion and deletion of the particles can be adjusted to a reasonable value. The electrolyte system of ions in a dielectric continuum is thus an ideal case for GCMC study and forms the basis for the studies undertaken in this investigation.

The present research builds on the studies reported above and addressed particularly the following questions: (a) How accurate are the MM level models (ions in a dielectric continuum interacting via solvent-averaged forces) in GCMC simulations on simple electrolyte solutions in comparison with experiment? (b) How can the primitive model be improved to provide optimum agreement with experiment for simple electrolytes as a function of concentration? (c) Can aqueous solutions of DNA be simulated at physiological ionic strengths within a continuum treatment of the solvent without compromising the essential physics and account for experimental data on the known thermodynamic properties of DNA in aqueous solutions as a function of concentration?

### III. Theory and Methodology

The theory and practice of grand canonical Monte Carlo simulations are scattered among several references.<sup>16,22,23,68-70</sup> We feel it is appropriate here to be quite explicit about the protocol we have adopted and the origins and rationale thereof. Adams<sup>68</sup> discussed the theory of  $(T, V, \mu)$  ensemble as applied to hard-sphere fluids. Here  $T$  is absolute temperature,  $V$  is volume, and  $\mu$  is chemical potential. Mills et al.<sup>16</sup> use of  $(T, V, a)$  ensemble, where  $a$  is the mean ionic activity. Valleau and Cohen<sup>22</sup> and Torrie and Valleau<sup>70</sup> use a  $(T, V, B)$  ensemble, where  $B$  is related to the chemical potential. In the following, we briefly review the basic ideas behind GCMC simulations, introducing notational uniformity and emphasizing practical applications to a 1:1 electrolyte system. The theory of canonical Monte Carlo (CMC) simulations as applied to molecular fluids is described earlier in a review article from this laboratory.<sup>71</sup>

In the grand canonical  $(T, V, \mu)$  ensemble,<sup>20</sup> a system with specified  $T$ ,  $V$ , and  $\mu$  is coupled to an external heat bath which is also a large reservoir for the particles comprising the system. The grand canonical partition function is given as

$$\Xi(T, V, \mu) = \sum_N e^{\mu N/kT} Q(T, V, N) \quad (1)$$

where  $Q(T, V, N)$  is the canonical partition function. The canonical partition function in the classical approximation is written as

$$Q(T, V, N) = (V^N / \Lambda^{3N} N!) [Z(T, V, N) / V^N] \quad (2)$$

where  $Z(T, V, N)$  is the configuration integral that describes the nonideality due to all interparticle interactions, and

$$\Lambda = (h^2 / 2\pi m kT)^{1/2} \quad (3)$$

is the thermal de Broglie wavelength. Here  $(V^N / \Lambda^{3N} N!)$  in eq 2 is the partition function of a classical ideal gas made up of  $N$  particles of mass  $m$  in volume  $V$  at a temperature of  $T$ . Combining eq 1-3 results in

$$\Xi(T, V, \mu) = \sum_N \{ [e^{\mu N/kT} / (\Lambda^{3N} N!)] Z(T, V, N) \} \quad (4)$$

The average of a function  $X$  in the  $(T, V, \mu)$  ensemble is then given as

$$\langle X \rangle = (1/\Xi) \sum_N \{ [e^{\mu N/kT} / (\Lambda^{3N} N!)] \int \dots \int X e^{-E/kT} d\mathbf{r}_1 \dots d\mathbf{r}_n \} \quad (5)$$

For a 1:1 electrolyte, the probability of a configuration  $i$  in the  $(T, V, \mu)$  ensemble of unlabeled ions is

$$P_i = (1/\Xi) \{ 1 / (\Lambda^{3N_+} \Lambda^{3N_-}) \} \{ \exp[(\mu_+ N_+ + \mu_- N_- - E_i) / kT] \} \quad (6)$$

and

$$P_j / P_i = \{ [e^{\mu/kT} / (\Lambda^3 \Lambda^3)] e^{-(\Delta E/kT)} \} \quad (7)$$

It is assumed here that  $N_j^+ = N_i^+ + 1$ , for example, as in insertion of a cation. A similar equation for  $N_j^-$  and the identities  $\mu = \mu_+ + \mu_-$  and  $\Delta E = E_j - E_i$  are used.

The transition probabilities  $p_{ij}$ , in addition to the normalization condition, are required to satisfy a condition of microscopic reversibility

$$p_{ij} / p_{ji} = P_j / P_i \quad (8)$$

Let the probability of generation of a trial step be  $q_{ij}$  and the probability of acceptance of the trial step be  $\alpha_{ij}$ . Then  $p_{ij}$ 's may then be written as

$$p_{ij} = q_{ij} \alpha_{ij} \quad (i \neq j) \quad (9)$$

$$p_{ii} = 1 - \sum_{j \neq i} p_{ij} \quad (10)$$

where  $q_{ij} = P/V^2$  for insertion and  $q_{ji} = P/(N^+ N^-)$  for deletion.<sup>22</sup> Here  $P$  is the probability with which insertions and deletions are attempted. Then

$$p_{ij} / p_{ji} = (q_{ij} / q_{ji}) (\alpha_{ij} / \alpha_{ji}) = (N^+ N^- / V^2) (\alpha_{ij} / \alpha_{ji}) = P_j / P_i \quad (11)$$

and

$$\alpha_{ij} / \alpha_{ji} = (V^2 / N^+ N^-) \{ [e^{\mu/kT} / (\Lambda^3 \Lambda^3)] e^{-(\Delta E/kT)} \} \quad (12)$$

GCMC simulations can be performed in a  $(T, V, \mu)$  ensemble with the acceptance probabilities defined as  $\alpha_{ij} = \min \{ 1, \alpha_{ij} / \alpha_{ji} \}$  for addition and  $\alpha_{ji} = \min \{ 1, \alpha_{ji} / \alpha_{ij} \}$  for deletion using the  $\alpha_{ij} / \alpha_{ji}$  in eq 12. Computationally, we find that the  $(T, V, a)$  ensemble, where  $a$  is the activity, is more convenient to work with since the expression  $\{ [e^{\mu/kT} / (\Lambda^3 \Lambda^3)] \}$  in eq 12 takes a much simpler form, and activity as an input parameter for this ensemble is easily interpreted. The acceptance criteria for the  $(T, V, a)$  ensemble can be derived beginning with the chemical potential of an ideal gas

$$\mu_{\text{ideal}} = -kT [\ln(V/N) + (3/2) \ln(2\pi m kT / h^2)] \quad (13)$$

Using the definition of  $\Lambda$ , we may rewrite the above equation as

$$\mu_{\text{ideal}} / kT = \ln(N \Lambda^3 / V) \quad (14)$$

and for a 1:1 electrolyte

$$\begin{aligned} \mu_{\text{ideal}} / kT &= \ln(N^+ \Lambda^3 / V) + \ln(N^- \Lambda^3 / V) \\ &= \ln[\rho^+ \rho^- \Lambda^3 \Lambda^3] \end{aligned} \quad (15)$$

where  $\rho^+$  and  $\rho^-$  are the number densities of the cations and anions in the system. Then

$$\mu / kT = \mu_{\text{ideal}} / kT + \ln f_{\pm}^2 = \ln(a^+ a^- \Lambda^3 \Lambda^3) \quad (16)$$

or

(66) Bleam, M. L.; Anderson, C. F.; Record, Jr., M. T. *Biochemistry* **1983**, *22*, 5418-5425.

(67) Padmanabhan, S.; Richey, B.; Anderson, C. F.; Record, Jr., M. T. *Biochemistry* **1988**, *27*, 4367-4376.

(68) Adams, D. J. *Mol. Phys.* **1974**, *28*, 1241-1252.

(69) Adams, D. J. *Mol. Phys.* **1975**, *29*, 307-311.

(70) Torrie, G. M.; Valleau, J. P. *J. Chem. Phys.* **1980**, *73*, 5807-5816.

(71) Beveridge, D. L.; et al. In *Molecular-Based Study of Fluids*; Haile, J. M.; Mansoori, G. A., Eds.; Advances in Chemistry Series No. 204; American Chemical Society: Washington, DC, 1983; pp 297-351.



$$\mu/kT = \ln(a_{\pm}^2 \Lambda_+^3 \Lambda_-^3) \quad (17)$$

where  $f_{\pm}$  is the mean ionic activity coefficient,  $a_{\pm} = a$  is the mean ionic activity of the electrolyte solution and  $a^+$  and  $a^-$  are the single ion activities. (The  $f_{\pm}$  symbol refers to the mean ionic activity if the concentrations are expressed in molar units;  $\gamma_{\pm}$  is reserved in some texts to denote molal units.)

Substituting eq 17 in eq 12, we obtain

$$\alpha_{ij}/\alpha_{ji} = (V^2/N^+N^-)[(a_{\pm}^2 \Lambda_+^3 \Lambda_-^3)/(\Lambda_+^3 \Lambda_-^3)]e^{-(\Delta E/kT)} \quad (18)$$

or

$$\alpha_{ij}/\alpha_{ji} = \text{preexp} \cdot e^{-(\Delta E/kT)} \quad (19)$$

with the preexponential factor given as

$$\text{preexp} = a^2 V^2 / N^+ N^- \quad (20)$$

for particle insertions and

$$\text{preexp} = N^+ N^- / a^2 V^2 \quad (21)$$

for deletions.

Equation 19 is for a  $(T, V, a)$  ensemble, and eq 12 is for a  $(T, V, \mu)$  ensemble and both are equivalent. These equations are consistent with the earlier formulations.<sup>16,22,23,68-70</sup> Valleau and co-workers<sup>22,70</sup> introduce a parameter  $B$  by writing  $V^2 a_{\pm}^2$  in eq 18 as  $\exp(B)$ . Here  $N^+$  and  $N^-$  in eq 20 and 21 are to be interpreted as the number of cations and anions, respectively, after insertion for attempted insertions or before deletion for attempted deletions. The methodology of this step is identical with that of Mills et al.<sup>16</sup>

The protocol for a GCMC simulation on electrolyte or polyelectrolyte solutions involves the following steps:

1. Specification of (a) cell dimensions, temperature, and activity (or single ion activities), for simulations performed in a  $(T, V, a)$  ensemble, (b) energy function and parameters for the interacting particles (for example, a (12,6,1) form with 12, 6, and 1 parameter, the dielectric constant, etc.), (c) a trial concentration that fixes the number of particles to start with (it must be established that the results are independent of the starting trial concentrations), and (d) number of particles to be moved in a single canonical Monte Carlo step and the maximum allowed step size.

2. Generation of a random configuration for the particles inside the simulation cell and calculation of the total energy of the starting configuration.

3. Iteration over the GCMC loop, which involves (a) Metropolis MC moves for  $N$ -particles, in which (i) an  $N$ -particle move is attempted and  $\Delta E$  is calculated with appropriate periodic boundary conditions, and (ii) the attempted move is accepted or rejected according to the acceptance probability

$$\alpha_{ij} = \min \{1, e^{(-\Delta E_{ij}/kT)}\} \quad (22)$$

and (b) particle insertion/deletion, which involves (i) a choice between insertion and deletion randomly with equal probability (this step is carried out independent of the outcome of step 3a) and (ii) if insertion is selected, a pair of ions is inserted (a cation and an anion) at random positions inside the cell and  $\Delta E$  is calculated (an ion pair for a 1:1 electrolyte as opposed to a single ion maintains electroneutrality in the simulation cell), or (iii) if deletion is selected, a pair of ions chosen randomly is deleted and  $\Delta E$  is calculated. (iv) In either case the attempted insertion/deletion is accepted or rejected according to the acceptance probability

$$\alpha_{ij} = \min \{1, \text{preexp} \cdot e^{(-\Delta E_{ij}/kT)}\} \quad (23)$$

where

$$\text{preexp} = (a^+ a^- V^2) / (N^+ N^-) \quad (\text{for insertion})$$

Here  $a^+$  and  $a^-$  are the counterion and co-ion activities,  $V$  is the cell volume in which insertion is attempted, and  $N^+$  and  $N^-$  are the number of cations and anions, respectively, after the attempted insertion, and

$$\text{preexp} = (N^+ N^-) / (a^+ a^- V^2) \quad (\text{for deletion})$$

The quantities  $N^+$  and  $N^-$  are the number of cations and anions, respectively, before the attempted deletion. Finally, there is (c) updating the counters for energies, number of particles, acceptance, insertion and deletion ratios, and storage of the coordinates of the entire system at certain specified intervals for subsequent structural analyses.

Steps 3a to 3c are repeated until convergence of the energies, the number of particles in the simulation cell, the acceptance, and insertion and deletion ratios are established. The number of particles to be moved and the step size control the acceptance ratio. These parameters are adjusted to obtain an optimum ratio of 50%. The frequency of insertion/deletion and the number of ion pairs inserted/deleted control their respective ratios. These may be adjusted to obtain a 50% probability that an attempted insertion/deletion is accepted. If this fails, a cavity biased algorithm<sup>23</sup> which changes the available volume for insertion may be explored but is not required here. The insertion ratio must equal the deletion ratio after convergence.

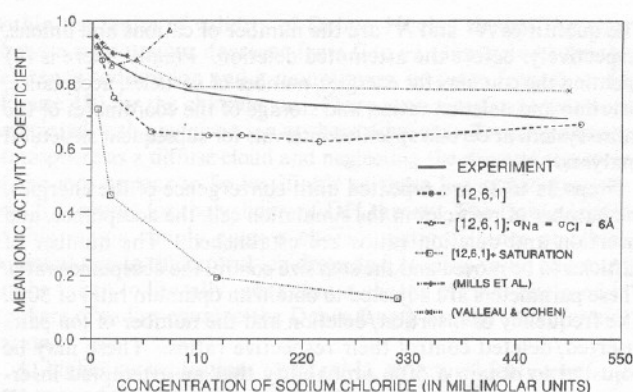
4. Calculation of averages of all quantities in the counters of step 3c. Activity coefficients are calculated from these average concentrations and from input activities. Finally, any desired structural analyses may be performed from the stored coordinates.

#### IV. Calculations and Results on $[\text{NaCl}]_{\text{aq}}$

Grand canonical Monte Carlo computer simulations were performed on aqueous solutions of sodium chloride in the  $[T, V, a]$  ensemble, at a temperature of 298 K. The setup for our calculations hereby closely corresponds to the  $[T, V, N]$  ensemble simulations on NaDNA in the presence of NaCl reported previously.<sup>63</sup> The central cell in the simulations is represented by a cylindrical box of height 67.6 Å and radius 100 Å. The  $N$ -particle configurational energies are calculated by using a (12,6,1) potential, under the assumption of pairwise additivity in interionic interactions. The 12 ( $A_{ij}^2 = 4\epsilon_i \sigma_i^{12}$ ) and 6 ( $B_{ij}^2 = 4\epsilon_i \sigma_i^6$ ) parameters for sodium and chloride ions are taken from GROMOS force field of Berendsen, Van Gunsteren, and co-workers<sup>72</sup> and are reported in Table I of ref 63. These correspond to  $\sigma_{\text{Na}} = 2.575$  Å,  $\epsilon_{\text{Na}} = 0.0148$  kcal for sodium ion and  $\sigma_{\text{Cl}} = 4.448$  Å,  $\epsilon_{\text{Cl}} = 0.1065$  kcal for chloride ion. A dielectric constant of 80 is used in calculating the Coulombic interactions. Periodic boundary conditions in the axial direction and mass-conserving diffusive boundary conditions in the radial direction are imposed on the system. For instance, if a particle moves out of the cylinder radially to  $(r, \phi, z)$ , it is repositioned at  $(r', 180 + \phi, z)$ . Here  $r'$  is given as  $d - r$ , where  $d$  is the diameter of the cylindrical cell. Similarly, in the axial direction, if the particle diffuses out of the cylindrical box to  $(r, \phi, z)$ , it is reset at  $(r, \phi, z-h)$ , where  $h$  is the height of the cylinder. One image of the central box is constructed in each direction in calculating the interaction energies. The rationale for this approach to solutions of polyelectrolytes with cylindrical or quasi-cylindrical symmetry containing simple electrolyte was discussed at length earlier.<sup>63</sup> The strategy of multiparticle moves along with step size adjustment was employed as reported previously<sup>63</sup> to maintain the acceptance ratio for particle moves close to 50%. The minimum typical run length in all cases was the equivalent of 7.5 million single-particle moves. Convergence of the mean energies and co-ion concentrations was monitored during the runs. The insertion and deletion ratios were seen to equal within 0.5 million steps. About 2.5 million moves were treated as equilibration and rejected. Ensemble averages were formed over the last 5 million or more moves.

Results on the mean ionic activity coefficients of NaCl from the GCMC simulations on  $[\text{NaCl}]_{\text{aq}}$  using a (12,6,1) potential with GROMOS Lennard-Jones parameters for the ions in a continuum solvent are shown in Figure 1 (dashed line with circles) as a function of salt concentration along with experimental results (solid line)<sup>1</sup> on this system. It may be noticed that at very low salt concentrations ( $\sim 0.01$  M) the agreement between the cal-

(72) Van Gunsteren, W. F.; Berendsen, H. J. C. *GROMOS88*: Groningen Molecular Simulation System, University of Groningen: The Netherlands, 1988.



**Figure 1.** Results of GCMC simulations on  $[\text{NaCl}]_{\text{aq}}$ . Mean ionic activity coefficients are shown as a function of sodium chloride concentration (in mM units). (a) Experiment from Robinson and Stokes<sup>1</sup> (solid line), (b) simulations with a (12,6,1) potential (dashed line, circles), (c) as in (b) with enlarged van der Waals diameter (6 Å) for both sodium and chloride ions (dotted-dashed line, triangles), (d) as in (b) with dielectric saturation (dotted line, squares), (e) simulations of Mills et al.<sup>16</sup> (dotted-dashed line, filled diamonds), and (f) simulations of Valleau and Cohen<sup>22</sup> (dotted line, crosses).

culated and the observed activity coefficients is good. The calculated trends show disturbing deviations from experiment as the salt concentration increases further. Similar observations were made by Ramanathan and Friedman on osmotic coefficients calculated with the primitive model and with other vanilla models without a solvent term using the HNC formalism.<sup>26</sup>

We then proceeded to use the grand canonical simulation studies on NaCl to calibrate the  $\sigma$  and  $\epsilon$  parameters for NaCl on the experimental activity coefficients, retaining the (12,6,1) functional form for the interaction energies. A systematic variation in the radius of the sodium ion was first carried out with other parameters remaining the same. Preliminary investigations indicated that the results on activity coefficients can be reproduced by changing the radius alone at any one given salt concentration, but the results over the entire range of concentration studied here show that spurious curvature is introduced by a larger radius. This can be corrected for by simultaneously increasing the  $\epsilon_{\text{Na}}$ , but with the elimination of the spurious curvature, the results were not very different from the starting point which is that of the bare ion. Results for a choice of  $\sigma_{\text{Na}} = 6$  Å and  $\sigma_{\text{Cl}} = 6$  Å are shown in Figure 1 (dashed-dotted line with triangles). Changes in the chloride ion parameters, whether carried out in isolation or in conjunction with changes in sodium ion, were seen to have a similar effect. In all these preliminary calibration efforts with increased radii, it was noticed that the deviations from experiment became more significant at higher salt concentrations where the average distance of interionic separation is smaller. These results seem to suggest that it is not profitable to change the ion parameters without changing the functional form for interionic interactions.

We then considered changing the dielectric constant to introduce distance dependence and to account for dielectric saturation. (See ref 63 for details on the functional form and its origins.) Results of representative calculations are shown in Figure 1 (dotted line). In exploratory studies, introduction of saturation in the small ion interactions resulted in an overestimation of the interionic interactions and increased the nonideality of the solution. This led to an even larger discrepancies between the calculated and observed mean ionic activity coefficients. This is consistent with the results of a simulation study on small ion hydration,<sup>73</sup> where it was found that dielectric saturation may be a significant factor for the free energies of hydration of cations only beyond a charge of +1, but not necessarily for monovalent ions studied here. An increase in the dielectric constant of water above 80 did appear to bring the calculated activity coefficients closer to the experiment, but this is nonphysical and was rejected.

The extent of deviation in the calculated and observed activity coefficients is also expected to depend upon details of simulation characteristics and protocol. See Figure 1 for results of some earlier work with the primitive model.<sup>16,22</sup> A simple cubic cell with periodic boundary conditions and minimum image convention as in ref 22 may also be explored for the purposes of calibration of the  $\sigma$  and  $\epsilon$  parameters of the ions and/or the dielectric constant of the solvent, but such studies would not be relevant to the stated objective of developing the best possible MM level model of  $[\text{NaCl}]_{\text{aq}}$  for simulations of aqueous solutions of NaDNA in the presence of added NaCl enclosed in a cylindrical box undertaken here.

Overall, we found that the results shown in Figure 1 (dashed line) cannot be easily improved upon without a further consideration of the solvent in the simulations. A plausible reason for the observed behavior is that the potential of mean force (pmf) between two ions in water shows an oscillatory behavior.<sup>28,32</sup> The (12,6,1) potential or its variations without a solvent term customarily used to treat the small ion interactions in a continuum solvent does not mimic the behavior of the pmf. Two possible directions to follow in this regard are (1) calibrate the interaction energy function to include the pmf obtained from fully explicit BO level molecular simulations or RISM type calculations or (2) use the Gurney parameter approach as suggested by Ramanathan and Friedman<sup>26</sup> to represent solvation effects within a continuum description of the solvent. The concentration dependence of the pmf's makes the former approach computationally overwhelming. We have taken recourse to the Gurney option and modified our potential function for the small ion interactions to include solvation effects.

Thus, in addition to the (12,6,1) terms in calculating the interaction energy between any two given ions, an extra Gurney term of the form  $A_{\text{ion-ion}}(V_{\text{ex}}/V_s)$ , where  $V_{\text{ex}}$  is the excluded volume and  $V_s$  is the volume of a water molecule, is included. This in the following is designated as the "refined primitive model"<sup>26</sup> or simply as the (12,6,1 + Gurney) model. The  $V_{\text{ex}}$  is evaluated via eqs 5 and 6 of ref 26. These are given below for an easy reference:

$$V_{\text{ex}}(r_i + d_w, r_j + d_w, r) = V_{\text{ex}}(a, b, r) \\ = \pi [-(4r)^{-1}(a^2 - b^2)^2 + (2/3)(a^3 + b^3) - (r/2) \times \\ (a^2 + b^2) + (1/12)r^3] \quad (24)$$

Here  $r_i$  and  $r_j$  are the van der Waals radii of ions  $i$  and  $j$ ,  $r$  is the distance between them, and  $d_w$  is the diameter of a water molecule. In this study,  $r_{\text{Na}^+} = \sigma_{\text{Na}}/2$ ,  $r_{\text{Cl}^-} = \sigma_{\text{Cl}}/2$  and a value of 2.76 Å is adopted for  $d_w$ . The Gurney term can be evaluated analytically subject to the specification of  $A_{\text{ion-ion}}$  parameters which are be calibrated on the known activity coefficients. The  $A_{\text{ion-ion}}$  parameters are essentially the molar free energy change of the cosphere solvent returning to its normal state, when the hydration shells of two ions encroach upon each other. Several test GCMC simulations were performed with different  $A_{\text{ion-ion}}$  parameters to obtain good agreement with experimental activity coefficients over a wide range of salt concentrations. As pointed out earlier,<sup>26</sup> there is no unique set for these parameters. The constraint we have employed is that once a set of three parameters have been selected, the same parameters be used at all salt concentrations. In Figure 2, results of the Gurney parameter approach are shown (as dash dots) for a choice of  $A_{\text{Na}^+\text{Na}^+} = -80$  cal,  $A_{\text{Cl}^-\text{Cl}^-} = -80$  cal, and  $A_{\text{Na}^+\text{Cl}^-} = 200$  cal. The agreement between the calculated and experimental activity coefficients is seen to be very good when solvation effects are considered. The (12,6,1 + Gurney) model is seen to give a satisfactory account of the activity coefficients as a function of salt concentration from 5 to 500 mM.

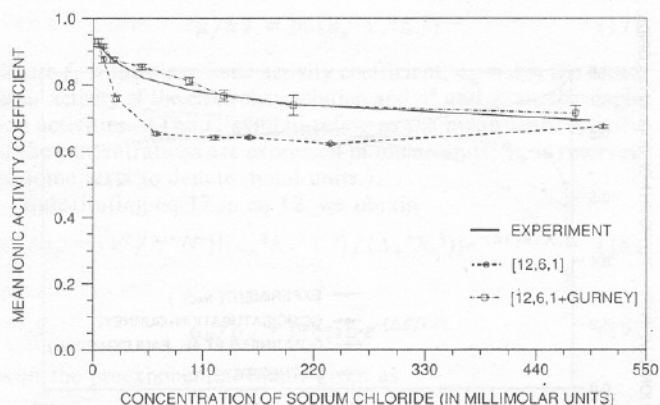
We would like to emphasize here that the Gurney term to account for solvation effects has been widely employed earlier (for example, see refs 26, 27, and 74–76). A similar rationale is

(73) Jayaram, B.; Fine, R.; Sharp, K.; Honig, B. *J. Phys. Chem.* **1989**, *93*, 4320–4327.

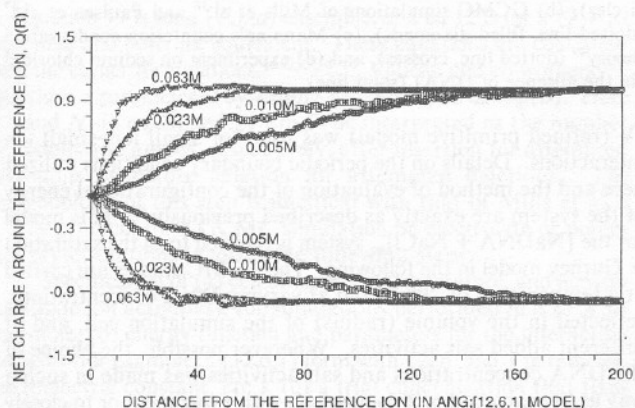
(74) Gurney, R. W. *Ionic Processes in Solution*; McGraw-Hill: New York, 1953.

(75) Friedman, H. L.; Krishnan, C. V. *J. Solution Chem.* **1973**, *2*, 119–138.



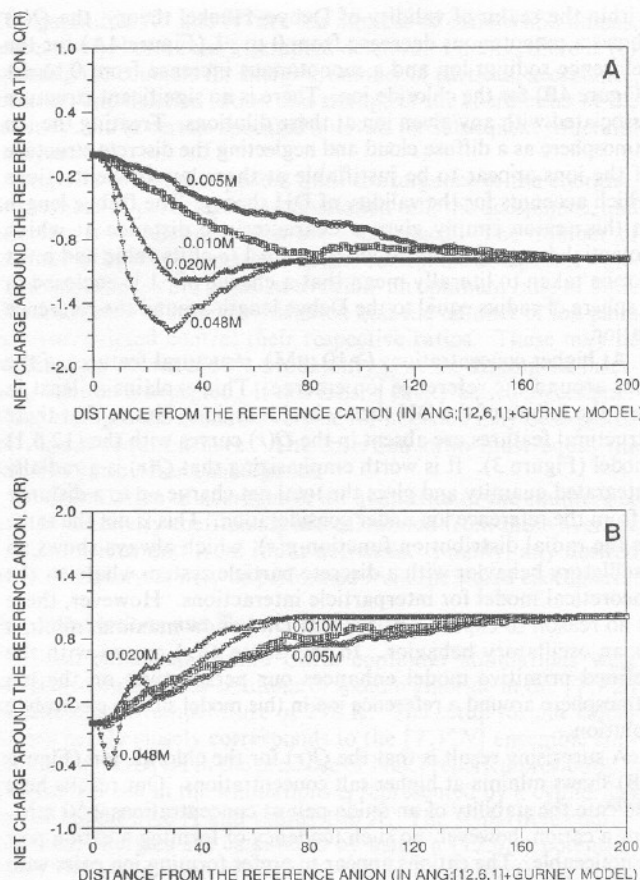


**Figure 2.** Results of GCMC simulations on  $[\text{NaCl}]_{\text{aq}}$ . Mean ionic activity coefficients are shown as a function of sodium chloride concentration (in mM units). (a) Experiment<sup>1</sup> (solid line), (b) simulations with a (12,6,1) potential (dashed line, circles), and (c) as in (b) with a Gurney term for solvation effects (dotted-dashed line, squares).



**Figure 3.** Results of GCMC (12,6,1 model) simulations on  $[\text{NaCl}]_{\text{aq}}$ . Total net charge  $Q(r)$ , around any given ion in the simulation cell treated as the reference ion, is shown as a function of distance (in Å) from the reference ion and concentration (in M units). The top four curves are for a reference chloride ion, and the bottom four curves are for a reference sodium ion. The salt concentrations for each curve shown are 0.005 M (solid line, circles), 0.010 M (dashed line, squares), 0.023 M (dashed-dotted line, triangles), and 0.063 M (dotted line, inverted triangles).

embodied in the hydration shell model of Scheraga and co-workers<sup>77,78</sup> and Hopfinger.<sup>79,80</sup> The relationship between Gurney model and hydration shell model has been pointed out earlier.<sup>81</sup> Regarding the choice of  $\sigma$  and  $\epsilon$  parameters for sodium and chloride from GROMOS and the (12,6,1) functional form, these have been well characterized via molecular simulations before. These parameters are comparable in magnitude and the functional form similar in different existing force fields (see for instance ref 82). We have retained and employed them here in a continuum solvent context. We do not feel that we can yet make a definitive statement on the validity of different MM level models with or without terms accounting for solvation effects to represent aqueous solutions of simple electrolytes. A reasonable inference to be drawn



**Figure 4.** Results of GCMC (12,6,1 + Gurney model) simulations on  $[\text{NaCl}]_{\text{aq}}$ . (A) Total net charge  $Q(r)$ , around any given sodium ion in the simulation cell treated as the reference ion, is shown as a function of distance (in Å) from the reference ion and concentration (in M units). The salt concentrations for each curve shown are 0.005 M (solid line, circles), 0.010 M (dashed line, squares), 0.020 M (dashed-dotted line, triangles), and 0.048 M (dotted line, inverted triangles). (B) Same as in (A) for a chloride ion.

from the results presented here and from the literature cited in the Background section is that several MM level models may be compatible with the activity coefficient data for a given system. Our work here does bring to light the problems to be expected in reproducing the activity coefficient data in simulations of the nature reported above on  $[\text{NaCl}]_{\text{aq}}$  and a way to solve them.

The GCMC simulations on  $[\text{NaCl}]_{\text{aq}}$  performed also provide valuable structural information on the ion atmosphere around a reference ion. Results on the net charge around any given ion  $Q(r)$ , as a function of radial distance from the reference ion at the lowest four concentrations studied here, are shown for the model with (12,6,1) potentials in Figure 3. (These results correspond to the activity coefficient curves shown as dashed line with circles in Figure 1.) The top four curves in Figure 3 are for a reference anion, and the bottom four curves in Figure 3 are for a reference cation for this model. Corresponding results for the (12,6,1 + Gurney) model are shown in Figure 4. Due to an overlap of the curves with this refined primitive model, results with a reference cation are shown in Figure 4A. Corresponding results for the anion are shown in Figure 4B.

Results shown in Figure 4 correspond to our GCMC simulations with a 12,6,1 potential along with a desolvation term for the interacting ions, which gives the best agreement with the experimental activity coefficient data over the entire concentration range of 5–500 mM. Each curve in Figure 4A,B represents a different concentration of the electrolyte. All these curves shown in Figure 4A,B start at zero at very short distances from the reference ion and go over to  $-1$  at large distances from the cation (Figure 4A) and to  $+1$  far away from the anion (Figure 4B), as required by electroneutrality in the simulation cell. At the two lowest concentrations studied (5 and 10 mM), both of which are

(76) Clark, A. H.; Franks, F.; Pedley, M. D.; Reid, D. S. *J. Chem. Soc., Faraday Trans. 1* 1977, 73, 290–305.

(77) Gibson, K. D.; Scheraga, H. A. *Proc. Natl. Acad. Sci. U.S.A.* 1967, 58, 420–427.

(78) Hodes, Z. I.; Nemethy, G.; Scheraga, H. A. *Biopolymers* 1979, 18, 1565–1610.

(79) Hopfinger, A. J. *Conformational Properties of Macromolecules*; Academic Press: New York, 1973; p 70.

(80) Hopfinger, A. J. *Intermolecular Interactions and Biomolecular Organization*; Wiley-Interscience: New York, 1973; p 324.

(81) Jayaram, B.; Ravishanker, G.; Beveridge, D. L. *J. Chem. Phys.* 1988, 92, 1032–1034.

(82) Chandrasekhar, J.; Spellmeyer, D. C.; Jorgensen, W. L. *J. Am. Chem. Soc.* 1984, 106, 903.

within the realm of validity of Debye-Hückel theory, the  $Q(r)$  shows a monotonous decrease from 0 to -1 (Figure 4A) for the reference sodium ion and a monotonous increase from 0 to +1 (Figure 4B) for the chloride ion. There is no significant structure associated with any given ion at these dilutions. Treating the ion atmosphere as a diffuse cloud and neglecting the discrete structure of the ions appear to be justifiable at these low concentrations which accounts for the validity of DH theory. The Debye length in this region simply gives a characteristic distance at which potential due to the central ion drops to  $1/e$  of its value and must not be taken to literally mean that a charge of -1 is enclosed in a sphere of radius equal to the Debye length around the reference cation.

At higher concentrations ( $>10$  mM), structural features of the ions around the reference ion emerge. This explains at least in part the failure of the DH theory in this region. Notice that these structural features are absent in the  $Q(r)$  curves with the (12,6,1) model (Figure 3). It is worth emphasizing that  $Q(r)$  is a radially integrated quantity and gives the total net charge up to a distance  $r$  from the reference ion under consideration. This is not the same as the radial distribution function  $g(r)$ , which always shows an oscillatory behavior with a discrete particle system whatever the theoretical model for interparticle interactions. However, there is no reason to expect a priori that  $Q(r)$  show maxima/minima or an oscillatory behavior. In this sense  $Q(r)$  curves with the refined primitive model enhances our perspectives on the ion atmosphere around a reference ion in this model simple electrolyte solution.

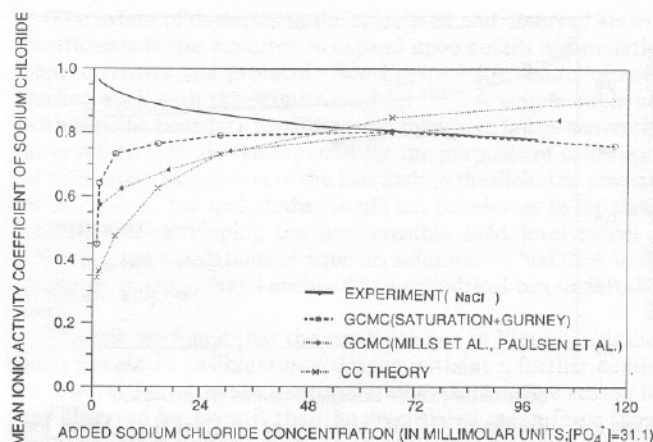
A surprising result is that the  $Q(r)$  for the chloride ion (Figure 4B) shows minima at higher salt concentrations. Our results here indicate the stability of an anion pair at concentrations  $\geq 50$  mM. For a cation, however, no such tendency of forming a cation pair is noticeable. The cations appear to prefer forming ion pairs with anions. These results are reminiscent of the results of chloride-chloride and sodium-chloride potential of mean force calculations with fully explicit solvent molecules.<sup>29-31,34</sup> This does not mean that the same physics is operational in the two models, however.

Thus, the interaction potential for the small ions assumed in this study (the Gurney refined primitive model) not only reproduces well the observed thermodynamic properties as a function of concentration but also appears to give the explicit solvent (BO level) simulation behavior noted in the Background section. Whether or not this constitutes a satisfactory account of the structural features of simple electrolyte solutions is yet to be seen. At this stage these are simply to be taken as consequences of the theoretical model employed here for aqueous sodium chloride solutions.

## V. Calculations and Results on [NaDNA + NaCl]<sub>aq</sub>

The GCMC simulations for [NaDNA]<sub>aq</sub> in the presence of added sodium chloride were set up as an extension of the canonical Monte Carlo calculations described previously.<sup>63</sup> The system in our simulations corresponds to two turns (20 base pairs) of a DNA-shaped molecule with charges on phosphates, discrete sodium, and chloride ions and all interacting with each other in a solvent treated as a dielectric continuum. The number of mobile ions in the simulation cell is dictated by the specified chemical potential/activity.

The choice of the Hamiltonian for the system was based on the strategy of using the potential function for DNA-small ions, which was successful in predicting the constancy of the condensed counterion fraction with added salt concentration<sup>63</sup> as observed experimentally, and using the interaction potential for the small ions which was calibrated as discussed in the previous section on the experimental activity coefficient data of sodium chloride. There is insufficient experimental information to parametrize the desolvation terms (Gurney parameters) for the charges on DNA at the present stage. Thus, a (12,6,1) potential along with a distance-dependent screening function, i.e., a dielectric saturation function reported earlier (DS model of ref 63) modifying the Coulombic part, was used here in computing the DNA-small ion interactions. The (12,6,1 + Gurney) model described in section



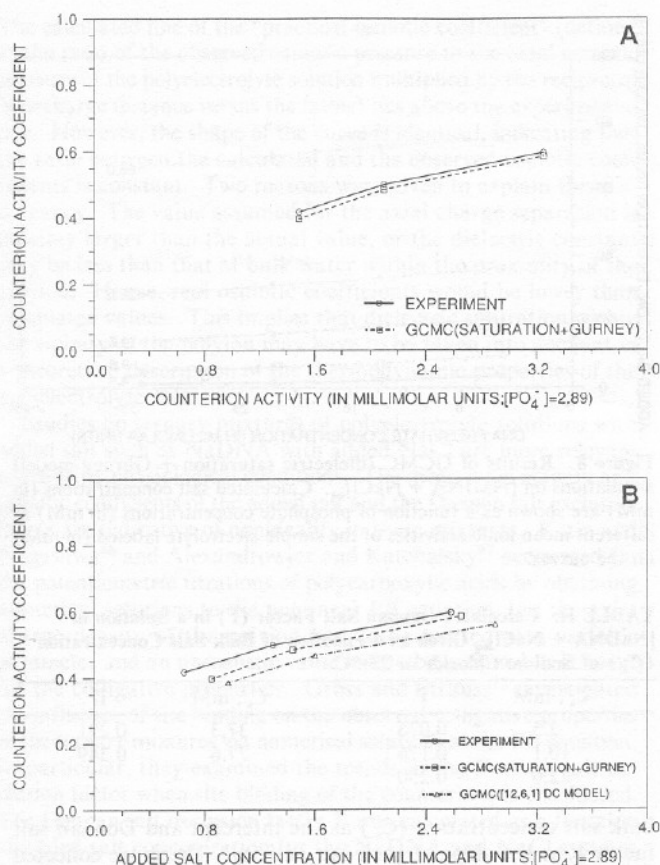
**Figure 5.** Results of GCMC simulations on [NaDNA + NaCl]<sub>aq</sub>. Mean ionic activity coefficient is shown as a function of added salt concentration (in mM units at a DNA phosphate concentration of 31.1 mM). (a) GCMC (dielectric saturation + Gurney model) simulations (dashed line, circles), (b) GCMC simulations of Mills et al.<sup>16</sup> and Paulsen et al.<sup>17</sup> (dotted line, filled diamonds), (c) Manning's counterion condensation theory<sup>49</sup> (dotted line, crosses), and (d) experiment on sodium chloride<sup>1</sup> (in the absence of DNA) (solid line).

IV (refined primitive model) was used for small ion-small ion interactions. Details on the periodic boundary conditions utilized here and the method of evaluation of the configurational energy of the system are exactly as described previously.<sup>63</sup> This model for the [NaDNA + NaCl]<sub>aq</sub> system is referred to as the saturation + Gurney model in the following. The GCMC studies are carried at a temperature of 298 K and at varying DNA concentrations, reflected in the volume (radius) of the simulation cell, and at different added salt activities. Wherever possible, the choice of the DNA concentrations and salt activities was made in such a way as to enable a direct comparison with experiment or to closely correspond to previous GCMC work of Anderson, Record and co-workers<sup>15,16</sup> on this system.

Results on the mean ionic activity coefficients of the counterions (sodium) and co-ions (chloride) as a function of added salt activity are shown in Figure 5 (dashed line) for a phosphate concentration of 31.1 mM, along with results from some earlier GCMC simulations<sup>16,17</sup> (dotted line with diamonds) and predictions from the counterion condensation theory<sup>49</sup> (dotted line with crosses). The experimental mean activity coefficients of NaCl in water at 25 °C are also shown in Figure 5 (solid line) to underscore the simple electrolyte behavior. Notice that for a simple electrolyte the activity coefficients decrease with added salt, while for polyelectrolyte the activity coefficients increase with added salt. The agreement between the present work and the other two models<sup>16,17,49</sup> is qualitative.

For a quantitative assessment of the model employed in this study, a comparison with the experiments of Lyons and Kotin<sup>48</sup> on the counterionic activity coefficients at a phosphate concentration and added salt activities given in Table IV of ref 48 was carried out. Two issues are of relevance here. Firstly, the counterion activity coefficients were derived by Lyons and Kotin from the measured ratio of single ion activities. Secondly, in a GCMC simulation although any desired single ion activities can be chosen in principle as input parameters (see eq 16) and the simulation conducted with these single ion activities, in practice, however, it is the product of these activities which enters the transition probabilities (see eqs 17 and 18) that dictate the path of the stochastic walk of the system in configuration space. Any partitioning scheme of the activity coefficients is therefore not above the well-known uniqueness problems of separating the mean ionic activity coefficients into its components. The counterion activity coefficients here are calculated as the ratio of the specified input counterion activity to the average concentration of counterions, i.e., the sum of the input phosphate concentration and added salt concentration determined from the GCMC simulations. While this is consistent with eqs 16-18, it is not unique and is





**Figure 6.** Results of GCMC simulations on  $[\text{NaDNA} + \text{NaCl}]_{\text{aq}}$ . (A) Counterion activity coefficients are shown as a function of counterion activity (in mM units). Experimental results of Lyons and Kotin<sup>48</sup> (solid line, circles), GCMC (dielectric saturation + Gurney model) results (dashed line, squares). (B) Counterion activity coefficients are shown as a function of added salt concentration (in mM units). Experimental results of Lyons and Kotin<sup>48</sup> (solid line, circles), GCMC (dielectric saturation + Gurney model) results (dashed line, squares), GCMC (with a 12,6,1 potential, DC model<sup>63</sup>) results (dashed dotted line, triangles).

the equivalent of the approximation  $a^+ = (a_{\pm}^2)^{1/2}$  and  $a^- = (a_{\pm}^2)^{1/2}$  given that  $a_{\pm}^2 = a^+a^-$ , where  $a^+$  and  $a^-$  are the counterion and co-ion activities, respectively, and  $a_{\pm}$  is the mean ionic activity.

Results of these computations (with the saturation + Gurney model) are shown in Figure 6A (dashed line) along with experimental results (solid line). The agreement between the calculated and the observed counterionic activity coefficients is exceptionally good. Considering the approximations involved in both the calculated and experimentally derived counterion activity coefficients, such an agreement is surprising. To understand the influence of the Gurney term and dielectric saturation on the results, we have repeated these simulations with a (12,6,1) potential and without the Gurney term and dielectric saturation. This simple Coulombic model (DC model of ref 63) is closer to that of Anderson, Record, and co-workers<sup>16,17</sup> than the earlier model (saturation + Gurney) which considers the saturation around DNA and has the Gurney term for simple electrolyte to describe solvation effects. Results on counterion activity coefficients as a function of added salt concentration emerging from these calculations are shown in Figure 6B together with the values of Lyons and Kotin and saturation + Gurney model results. A general agreement between the various theoretical approaches and experiment is perceivable. It would have been worthwhile to make a direct comparison with experiments on mean ionic activity coefficients and over a much wider range of added salt concentration. This possibility is being explored. Overall, subject to the stated approximations and qualifications, these results appear to suggest that a dielectric continuum representation of solvent provides with a viable alternative to fully discrete simulations including explicit waters for the purposes of calculating ther-

**TABLE I:** Added Salt Concentrations and Activity Coefficients of Sodium Chloride at 25 °C in a Solution of  $[\text{NaDNA} + \text{NaCl}]_{\text{aq}}$  Calculated from GCMC Simulations<sup>a</sup>

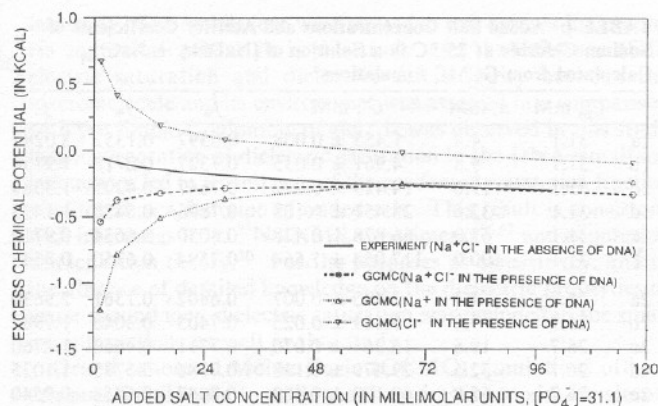
	$C_p$ , mM	$a$ , mM	$C^-$ , mM	$f_{\pm}$	$f_+$	$f_-$
1a	31.1	4.4	$1.453 \pm 0.008$	0.6397	0.1352	3.0282
1b	31.1	9.8	$4.961 \pm 0.035$	0.7327	0.2718	1.9754
1c	31.1	19.6	$14.429 \pm 0.072$	0.7647	0.4305	1.3584
1d	31.1	32.5	$28.451 \pm 0.108$	0.7896	0.5458	1.1423
1e	31.1	65.0	$66.878 \pm 0.428$	0.8030	0.6634	0.9719
1f	31.1	100.0	$117.054 \pm 1.564$	0.7594	0.6750	0.8543
2a	26.7	4.4	$1.485 \pm 0.007$	0.6802	0.1561	2.9630
2b	26.7	9.8	$5.449 \pm 0.025$	0.7405	0.3048	1.7985
2c	26.7	19.6	$15.361 \pm 0.070$	0.7711	0.4660	1.2760
2d	26.7	32.5	$29.479 \pm 0.128$	0.7986	0.5785	1.1025
2e	26.7	65.0	$68.132 \pm 0.462$	0.8087	0.6854	0.9540
2f	26.7	100.0	$119.581 \pm 0.970$	0.7561	0.6836	0.8363
3a	21.6	4.4	$1.602 \pm 0.011$	0.7217	0.1896	2.7466
3b	21.6	9.8	$6.087 \pm 0.030$	0.7549	0.3540	1.6100
3c	21.6	19.6	$16.351 \pm 0.076$	0.7868	0.5165	1.1987
3d	21.6	32.5	$30.972 \pm 0.117$	0.8054	0.6182	1.0493
3e	21.6	65.0	$69.954 \pm 0.454$	0.8122	0.7100	0.9292
3f	21.6	100.0	$122.454 \pm 1.045$	0.7529	0.6942	0.8166
4a	13.8	4.4	$2.072 \pm 0.011$	0.7672	0.2772	2.1236
4b	13.8	9.8	$7.369 \pm 0.049$	0.7846	0.4629	1.3300
4c	13.8	19.6	$18.454 \pm 0.054$	0.8034	0.6077	1.0621
4d	13.8	32.5	$33.172 \pm 0.120$	0.8233	0.6919	0.9797
4e	13.8	65.0	$72.864 \pm 0.469$	0.8180	0.7500	0.8921
5a	5.0	4.4	$3.449 \pm 0.019$	0.8152	0.5208	1.2757
5b	5.0	9.8	$9.584 \pm 0.042$	0.8290	0.6720	1.0225
5c	5.0	19.6	$20.941 \pm 0.058$	0.8409	0.7556	0.9360
5d	5.0	32.5	$36.001 \pm 0.089$	0.8459	0.7927	0.9028

<sup>a</sup>  $C_p$  = phosphate concentration,  $a$  = activity of sodium chloride,  $C^-$  = co-ion concentration,  $f_{\pm}$  = mean ionic activity coefficient of sodium chloride, and  $f_+$  and  $f_-$  are counterion and co-ion activity coefficients.

modynamic properties of polyelectrolyte solutions.

The results of the GCMC simulations on  $[\text{NaDNA} + \text{NaCl}]_{\text{aq}}$  obtained here can be used to further analyze the trends in single ion activity coefficients and chemical potentials and to focus on the sources of nonideality. An analysis of the calculated mean ionic activity coefficients in terms of the single ion activity coefficients, with the approximation discussed above in obtaining these quantities and on the basis of the agreement between the simulation and experiment in Figure 6 above, is given in Table I. The counterion activity coefficients increase with added salt concentration at all phosphate concentrations, while the co-ion activity coefficients decrease as with simple electrolyte solutions. The overall behavior of the mean ionic activity coefficients of sodium chloride in the presence of DNA is dominated by the trends in the counterion activity coefficients.

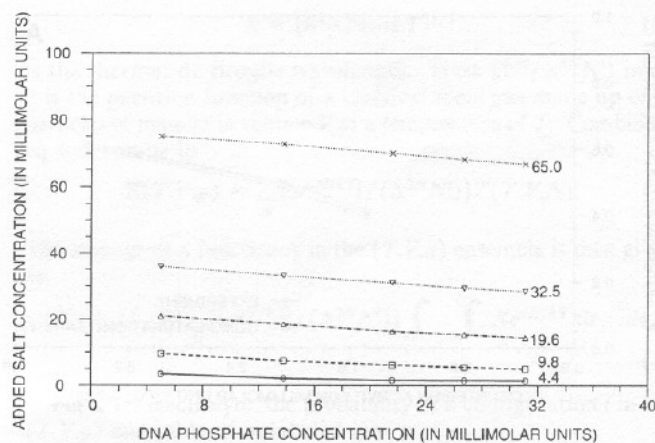
A corresponding analysis of the excess chemical potentials as a function of added salt concentration is given in Figure 7. An explanation based on stoichiometric considerations in the GCMC simulations for the trends seen in Table I and Figures 5–7 for nonidealities in polyelectrolyte solutions goes as follows: Mean activity is the product of concentration and mean ionic activity coefficient. Mean activity is related to the total chemical potential, and mean activity coefficients are related to excess chemical potentials. In a GCMC simulation one fixes the activity or the total chemical potential. At a given counterion chemical potential or counterion activity, the counterion concentration is larger in the presence of NaDNA (DNA contributes its complement of counterions to the solution), relative to a simple electrolyte solution. For the product of the concentration times the activity coefficient to remain constant to maintain the constancy of the activity, the counterion activity coefficients have to be much less than they are in the case of a simple electrolyte. By a similar argument the co-ion activity coefficients are much larger than in the case of simple electrolytes. As the added salt concentration increases, the effect of the extra counterions due to DNA diminishes, and the behavior of the activity coefficients approaches that of a simple electrolyte.



**Figure 7.** Results of GCMC (dielectric saturation + Gurney model) simulations on [NaDNA + NaCl]<sub>aq</sub>. Excess chemical potentials (in kcal) are shown as a function of salt concentration (in mM units) for the simple electrolyte [NaCl]<sub>aq</sub> (solid line) and for the ternary mixture [NaDNA + NaCl]<sub>aq</sub> (dashed line, circles) at a DNA phosphate concentration of 31.1 mM. Results shown in dashed lines are further split into counterion (Na<sup>+</sup>; dotted line, triangles) and co-ion (Cl<sup>-</sup>; dotted line, inverted triangles) contributions.

The results shown in Figure 7 suggest that, in the case of simple electrolytes (sodium chloride in water), the interionic interactions become stronger with increasing salt concentrations with the consequence that the excess chemical potentials become more negative and the activity coefficients much less than unity. In the case of a mixture of simple and polyelectrolyte solution (sodium chloride and sodium salt of DNA in water), at low salt, most of the free sodium ions are still in favorable interactions with the negative charges of the phosphates on the polyelectrolyte, while the repulsive interactions between chloride-chloride and chloride-phosphate make the excess chemical potential of the co-ions (chloride ions) positive. The co-ion activity coefficients exceed unity at low salt. The excess chemical potential of the co-ions becomes more negative with added salt, since more counterions (sodium ions) become available for favorable interionic interactions. The opposite trends hold true for counterion excess chemical potentials, with the latter dominating the total excess chemical potential. (Trends in total chemical potentials parallel the trends in excess chemical potentials here.) Counterions interact more strongly with DNA at low salt than at high salt. It is thus easier to remove or displace counterions from DNA at higher salt concentrations. This observation is also consistent with our earlier free energy calculations (Figure 1 of ref 83). Thus, nonideality in sodium salts of DNA in water in the presence of added sodium chloride salt increases with dilution and decreases with added salt. These observations are consistent with the conclusions of Record and co-workers (ref 10 and references therein) drawn from their PB and GCMC studies on the preferential interaction coefficient discussed below. Record and Richey<sup>10</sup> have attributed this at a molecular level to an increase in nonuniform distribution of ions around the polyanion as the salt concentration is reduced.

The Donnan equilibrium parameter, also called the preferential interaction coefficient,<sup>16</sup> has been studied extensively both experimentally<sup>45,65</sup> and theoretically<sup>10,12,16,17,49</sup> as a measure of nonideality in polyelectrolyte solutions. It is defined as  $\Gamma = \lim_{C_p \rightarrow 0} \{(C_s' - C_s)/C_p\}$ , where  $C_p$  is the DNA phosphate concentration,  $C_s$  is the salt concentration inside the polyelectrolyte compartment, and  $C_s'$  is the salt concentration outside the semipermeable membrane. An equivalent definition is  $\Gamma = \lim_{C_p \rightarrow 0} (\partial C_s / \partial C_p)_{\mu, T}$ . An interesting analogy between the GCMC simulations and Donnan experiments is given in ref 10. The procedure for the evaluation of  $\Gamma$  here is identical with that of Mills et al.<sup>16</sup> Using the simulation data given in Table I, we plotted the calculated salt concentrations as a function of phosphate concentration at each fixed salt activity and temperature. All these curves (shown in Figure 8) are seen to be representable by straight lines with



**Figure 8.** Results of GCMC (dielectric saturation + Gurney model) simulations on [NaDNA + NaCl]<sub>aq</sub>. Calculated salt concentrations (in mM) are shown as a function of phosphate concentrations (in mM) at different mean ionic activities of the simple electrolyte labeled (in mM) on the curves.

**TABLE II: Calculated Donnan Salt Factor ( $\Gamma$ ) in a Solution of [NaDNA + NaCl]<sub>aq</sub> Given as a Function of Bulk Salt Concentration ( $C_s'$ ) of Sodium Chloride at 25 °C**

$C_s'$ , mM	$\Gamma$	$C_s'$ , mM	$\Gamma$
3.5	0.075	37.3	0.291
10.1	0.176	77.6	0.349
22.0	0.250		

bulk salt concentration ( $C_s'$ ) as the intercept and Donnan salt factor  $\Gamma$  as the slope at each salt activity. These are collected in Table II. Although the experimental<sup>65</sup> and the calculated values here are not strictly comparable since bromide is used as the co-ion in experiments (the significance of this difference is not known), some general trends may be seen. The experimental values of  $\Gamma$  at NaBr concentrations of 9.5 and 88.9 mM are 0.122 and 0.204, respectively. The calculated  $\Gamma$  (Table II) increases as a function of salt concentration as found experimentally. Paulsen et al.<sup>17</sup> in their calculations of  $\Gamma$  report a much better agreement with experiment. The calculated values of  $\Gamma$  here are slightly higher than the experimental values. The experimental value of 0.122 at 9.5 mM, however, is seen to be bracketed by the calculated  $\Gamma$  of 0.075 at 3.5 mM and 0.176 at 10.1 mM (first two rows in Table II). The limiting value of 0.06 from counterion condensation theory<sup>49</sup> is seen to be very close to our lowest salt concentration value of 0.075.  $\Gamma_{\text{ideal}}$  according to the condensation theory is 0.5. The trends in Table II indicate that  $\Gamma$  approaches this limit as the salt concentration increases. Results in Table II in general confirm the earlier analysis based on excess chemical potentials here and previous PB and GCMC studies<sup>10</sup> that nonideality of simple electrolyte in the presence of a polyelectrolyte decreases with added salt.

## VI. Conclusions

The results of our grand canonical Monte Carlo simulations on aqueous solutions of sodium chloride in the absence and presence of sodium salt of DNA may be summarized as follows. A variation of the primitive model for the simple electrolyte solutions, with desolvation of two encroaching ions considered via a Gurney factor, reproduces the experimentally observed behavior in the mean ionic activity coefficients of sodium chloride in water in the concentration range 5–500 mM studied here. In addition, this refined primitive model also predicts the stability of sodium and chloride ion pairs as well as chloride and chloride anion pairs at concentrations  $\geq 50$  mM. The novel stability of anion pairs in aqueous solutions, reported previously from detailed molecular simulations, is reflected in calculations based on the refined primitive model with a continuum solvent.

Structural analysis of the ion atmosphere based on the results of our simulations with the refined primitive model leads us to conclude that the success of Debye-Hückel theory for simple



electrolyte solutions at concentrations  $\leq 10$  mM is attributable to a lack of structure in the ion atmosphere around the reference ion and its failure above 10 mM to the onset of structural features in the ion atmosphere.

The GCMC simulations carried out here appear to indicate that a dielectric continuum representation of solvent provides with a viable alternative to fully discrete simulations including explicit waters for the purposes of calculating thermodynamic properties of polyelectrolyte solutions.

The calculated excess chemical potentials suggest that in the case of simple electrolytes ( $[\text{NaCl}]_{\text{aq}}$ ) the interionic interactions become stronger with increasing salt concentrations, resulting in more negative excess chemical potentials and activity coefficients much less than unity. In the case of a mixture of simple and polyelectrolyte solution ( $[\text{NaCl} + \text{NaDNA}]_{\text{aq}}$ ), at low salt, the stronger attractive interactions between the counterions ( $\text{Na}^+$ ) and the polyanion (DNA) and the repulsive interactions between co-ions with themselves and with the polyanion lead to positive co-ion ( $\text{Cl}^-$ ) excess chemical potentials. The co-ion excess chemical

potentials become more negative with added salt, since more counterions become available for favorable interionic interactions. The opposite trends hold true for counterion excess chemical potentials, with the latter dominating the total excess chemical potential. Thus, nonideality in a polyelectrolyte and simple electrolyte mixture increases with dilution contrary to the behavior in simple electrolyte solutions.

*Acknowledgment.* This research is supported by grants from the NIH (GM-37909), from the Office of Naval Research (N-0014-87-K-0312), and via the Bristol Myers Corp. and State of Connecticut High Technology Research and Development Award. Supercomputer time was provided on the Cray Y-MP by the Pittsburgh Supercomputing Center. The authors are thankful to Dr. S. Swaminathan, Dr. K. Sharp, and Prof. B. Honig for useful discussions on this project. The authors also express their gratitude to Prof. H. L. Friedman and Prof. M. T. Record, Jr., for their extremely valuable comments on the manuscript.

**Registry No.** NaCl, 7647-14-5.