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# Free Energy of an Arbitrary Charge Distribution Imbedded in Coaxial Cylindrical Dielectric Continua: Application to Conformational Preferences of DNA in Aqueous Solutions

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Theoretical expressions for evaluating the electrostatic contribution to the solvation free energy of macromolecules with cylindrical or quasi-cylindrical symmetry are obtained based on a continuum treatment of the environment. These include provision to consider the detailed spatial charge distribution, the influence of the dielectric boundary, the ion atmosphere, and the dielectric saturation. The theory developed is illustrated with an application to the conformational preferences of DNA in aqueous solutions. It is shown with a discrete spatial charge distribution of DNA that the B form of DNA is favored over both A and Z forms in aqueous solutions at low added salt, thus resolving a contradiction with experiment observed in line charge representations of the double helix.

## Introduction

The theoretical treatment of charge distributions with cylindrical symmetry in dielectric media has been the focus of considerable research interest in recent years,<sup>1-23</sup> primarily due to their relevance to biological and synthetic polyelectrolytes and especially to the DNA molecule (Figure 1). The simplest model applicable to DNA is to treat the polyionic double helix as a line of charge or as a uniformly charged cylinder and use the Poisson-Boltzmann (PB) equation to determine the radial distribution of counterions.<sup>18,22</sup> An alternative approach suggested by Manning is "counterion condensation (CC) theory"<sup>24,25</sup> in which a pheno-

menological model of the solvation free energy of line charge representation of DNA is developed.

Both Poisson-Boltzmann theory and counterion condensation theory have recently been applied to the problem of the B to Z transition in DNA<sup>26-28</sup> discovered in vitro by Pohl and Jovin.<sup>29</sup> The Z form of DNA, confirmed by crystallography to correspond to a left-handed zigzag conformation,<sup>30</sup> has been the subject of considerable subsequent interest and investigation for its possible in vivo biological significance.<sup>31</sup> It is, however, generally appreciated that the line charge model of DNA does not account for the B to Z transition in either PB or CC theory and particularly does not explain the preferential stability of B versus Z at low salt concentration.<sup>26-28,32</sup> The average axial distance between anionic phosphate groups is 1.69 Å for B and 1.85 Å for Z (Table 9-2 of ref 33). Thus the linear charge density is lower for Z, leading to the prediction that the Z form would be more stable than B at low salt, contrary to experiment.

The question that originally motivated this work is whether the replacement of the line of charge model of the DNA polyion by a model in which all charges are in their correct geometrical placement as deduced from fiber diffraction data and single-crystal X-ray crystallography on B<sup>34</sup> and Z<sup>30</sup> DNA leads to electrostatic free energies with the proper relative ordering of B and Z structures at low salt. To treat this problem, we derived new theoretical formulas for the electrostatic free energy of an arbitrary charge distribution enclosed in coaxial concentric cylinders containing a representation of solvent and introducing counterions. The relative electrostatic free energies of A, B, and Z forms of DNA are then evaluated as a special case. The possible implementation of this theory for introducing solvent and counterion effects in molecular simulations on DNA is also discussed.

## Background

The evaluation of Helmholtz free energy of polarization of an arbitrary charge distribution imbedded in concentric dielectric

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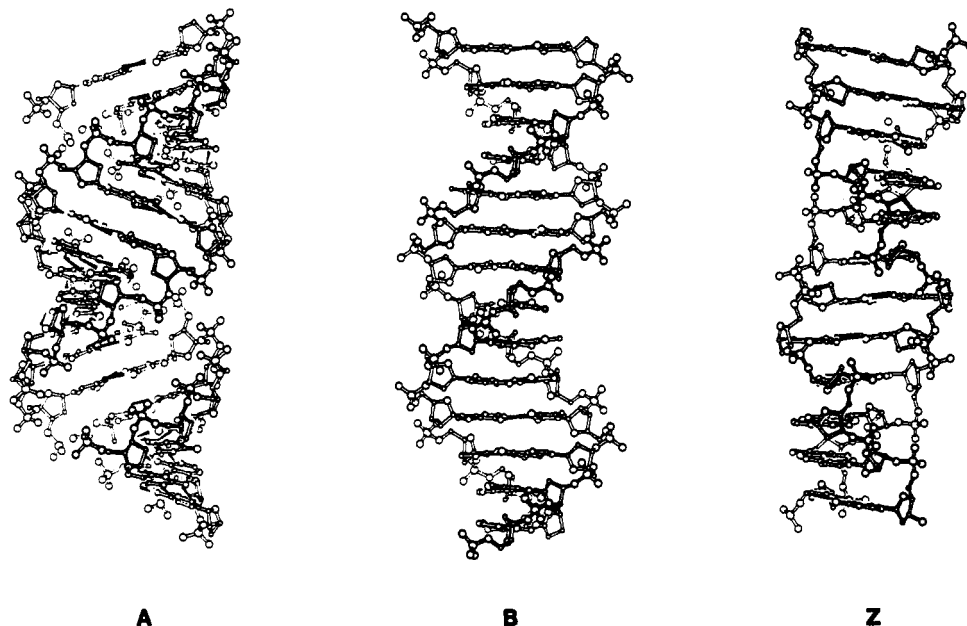


Figure 1. Molecular structure of the A, B, and Z forms of the DNA molecule (after W. Saenger, ref 33).

continua<sup>35,36</sup> and in spheroids<sup>37</sup> generalizing the models of Born for ion solvation, Onsager for dipole solvation, and Debye-Hückel for ion atmosphere effects, within the framework of Kirkwood's<sup>38</sup> reaction potential<sup>39</sup> formalism, has been reported previously from this group. These methods are useful for including effects of dielectric discontinuity and bound-water effects (the influence of dielectric saturation or electrostriction) with a discrete charge distribution of the solute, in a dielectric continuum treatment of the solvent.

Tanford-Kirkwood theory<sup>40</sup> for evaluating the electrostatic interactions in molecules with an overall spherical symmetry has found wide application [see reviews 41-43 and references therein for extensions and applications and ref 44] in the area of structure and conformation of proteins and in particular in understanding the protein titration curves. An application of Tanford-Kirkwood theory to nucleic acids suffers from the inherent drawback of treating nucleic acids as spheres. Thus a Tanford-Kirkwood theory incorporating the cylindrical symmetry appropriate for the DNA double helix is a desirable next step.

The current state of science on hydration and ion atmosphere of DNA has been reviewed in two recent articles from this laboratory.<sup>45,46</sup> Besides the detailed charge distribution of DNA, the influence of dielectric boundary between the macromolecule and solvent and the role of dielectric saturation local to charged species are of current topical interest.<sup>47-58</sup> The B to Z transition<sup>29</sup>

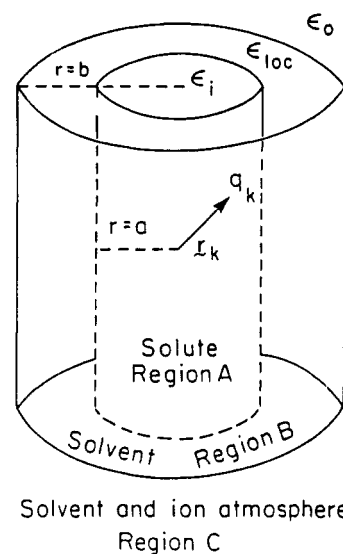


Figure 2. Definition of the parameters for the coaxial cylindrical dielectric continuum problem.

has been the subject of recent theoretical studies from diverse points of view<sup>26,27,32,49,50,54,59</sup> in which electrostatics as well as other contributions have been estimated. In spite of reasonable success in accounting for the transition point, the nature of the transition remains elusive. This leads us to the simpler question of the relative electrostatic stability of DNA at low salt, with a proper discrete charge distribution. A few previous studies dealt with the electrostatic potentials of DNA with a nonlinear PB treatment of the discrete charge distribution of DNA in solution.<sup>50-52,57</sup> Consistency problems in calculating energetics using potentials obtained as solutions to nonlinear PB equation<sup>60</sup> have been pointed out. In particular, the superposition approximation breaks down and the results are sensitive to the charging process.<sup>26,27</sup> Debye-Hückel's linearization of the PB equation circumvents this

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problem. A combination of the counterion condensation postulate and a Debye-Hückel treatment of ion atmosphere as envisaged by Manning<sup>25</sup> extended to a discrete charge distribution holds promise for handling the energetics of DNA in aqueous environment.

The motivation for the present study thus is 2-fold. One is to evaluate the electrostatic contribution to the free energy of polarization of a heterogeneous dielectric by a discrete charge distribution, and the second is to contribute to the understanding of conformational preferences of DNA in aqueous solution. In the course of this we obtain theoretical expressions for the reaction potential which comprises a Tanford-Kirkwood theory that may be used in other theoretical studies on DNA and other macromolecules with cylindrical or quasi-cylindrical symmetry.

### Theory

The model considered in the present work, depicted in Figure 2, is so chosen as to be general enough to accommodate many of the existing approaches in the literature cited, besides being per se useful. The coaxial cylindrical system consists of three regions. Region A, the inner region, represents a cylindrical cavity of height  $L$ , radius  $r = a$ , and a dielectric constant of  $\epsilon_i$  wherein the solute charges are located at sites  $\mathbf{r}_k$ . Region B, the local region extending radially from  $r = a$  to  $r = b$ , represents the "first shell" of the solute and contains solvent of dielectric constant  $\epsilon_{loc}$ . Alternatively the region B may be taken to constitute the ion exclusion zone. Region C, the outer region, ranging from  $r = b$  to  $r = \infty$ , contains both solvent of dielectric constant  $\epsilon_o$  and ion atmosphere, i.e., counterions and co-ions. The ion atmosphere enters the theoretical treatment through the Debye inverse length parameter  $\kappa$ , which is proportional to the square root of ionic strength. The problem now is to solve the Laplace equation

$$\Delta\phi = 0 \quad (1)$$

for regions A and B, and the linearized Poisson-Boltzmann equation

$$(\Delta - \kappa^2)\phi = 0 \quad (2)$$

for region C, where  $\phi$  is the electrostatic potential and

$$\Delta = \nabla^2$$

is the Laplacian operator. General solutions for regions A and B are

$$\phi_i \text{ and } \phi_{loc} = \sum_{k=1}^p \frac{B_k}{|\mathbf{r} - \mathbf{r}_k|} \quad (3)$$

and for region C

$$\phi_o = \sum_{k=1}^p \left( \frac{A_k e^{-\kappa|\mathbf{r}-\mathbf{r}_k|}}{|\mathbf{r} - \mathbf{r}_k|} + \frac{B_k e^{\kappa|\mathbf{r}-\mathbf{r}_k|}}{|\mathbf{r} - \mathbf{r}_k|} \right) \quad (4)$$

Here  $\phi_i$  and  $\phi_{loc}$  contain the Coulombic potentials due to the discrete charge distribution,  $\phi_o$  contains the screened Coulombic (Debye) potential, and  $\mathbf{r}_k$  denotes the Cartesian coordinates of the  $k$ th charge. Modifications to the Coulombic potentials due to the presence of dielectric boundaries are introduced via the constants  $A_k$  and  $B_k$  obtained by solving for them with appropriate boundary conditions. These general solutions are to be transformed into a coordinate system appropriate for the symmetry of the problem for the application of boundary conditions. Bessel functions are convenient to work with for cylindrical shapes. A discussion on the Laplace equation in cylindrical coordinates and the form of general solutions is given by Jackson.<sup>61</sup> An overview of the Bessel functions is given by Abramowitz and Stegun,<sup>62</sup> Gray, Mathews, and MacRobert,<sup>63</sup> and Watson.<sup>64</sup> Bailey<sup>47</sup> and

Soumpasis<sup>48</sup> discussed the expansions for the Debye potential in Bessel functions.

The general solutions for the regions A, B, and C in cylindrical coordinates are

$$\phi_i = \epsilon_i^{-1} \sum_{k=1}^p \left[ -\frac{2q_k}{L} \ln \omega_k + B_k + F_k + \sum_{n=1}^{\infty} \left\{ B_{nk} I_0(\lambda\omega_k) + F_{nk} I_0(\lambda\omega_k) + \frac{4q_k}{L} K_0(\lambda\omega_k) \right\} \cos \lambda(z - z_k) \right] \quad (5)$$

$$\phi_{loc} = \epsilon_{loc}^{-1} \sum_{k=1}^p \left[ -G_k \ln \omega_k + F_k + \sum_{n=1}^{\infty} \{ F_{nk} I_0(\lambda\omega_k) + G_{nk} K_0(\lambda\omega_k) \} \cos \lambda(z - z_k) \right] \quad (6)$$

and

$$\phi_o = \epsilon_o^{-1} \sum_{k=1}^p \left[ C_k K_0(\kappa\omega_k) + \sum_{n=1}^{\infty} \{ C_{nk} K_0(\lambda'\omega_k) \} \cos \lambda(z - z_k) \right] \quad (7)$$

In the above equations, the functions  $K_0(s)$  and  $I_0(s)$  are the modified Bessel functions of zero order. The terms in  $B$  originate in the polarization of the local dielectric. Similarly, the terms in  $F$  arise in the polarization of the bulk dielectric continuum. The cylindrical coordinates of the  $k$ th charge are described by  $\rho_k$ ,  $\phi_k$ , and  $z_k$ . The symbols  $\omega_k$ ,  $\lambda$ , and  $\lambda'$  are defined by the following equations.

$$\omega_k = [\rho^2 + \rho_k^2 - 2\rho\rho_k \cos(\phi - \phi_k)]^{1/2} \quad (8)$$

$$\lambda = 2\pi n/L \quad \text{and} \quad \lambda' = (\lambda^2 + \kappa^2)^{1/2} \quad (9)$$

The constants  $B$ ,  $F$ ,  $G$ , and  $C$  are to be evaluated by an application of the boundary conditions. The reaction potential is identifiable with

$$\phi_R = \epsilon_i^{-1} \sum_{k=1}^p \left[ B_k + F_k + \sum_{n=1}^{\infty} \{ (B_{nk} + F_{nk}) I_0(\lambda\omega_k) \} \cos \lambda(z - z_k) \right] \quad (10)$$

The electrostatic Helmholtz free energy of the charge distribution is given by

$$A_{el} = \frac{1}{2} \sum_{\nu=1}^p q_{\nu} \phi_R(\mathbf{r}_{\nu}) \quad (11)$$

where  $\phi_R(\mathbf{r}_{\nu})$  is the reaction potential at the charged site  $\mathbf{r}_{\nu}$  of charge  $q_{\nu}$ . The matching conditions for this problem are that the potential and the dielectric displacement across the boundaries be continuous. This imposes on  $\phi_i$ ,  $\phi_{loc}$ , and  $\phi_o$  the following conditions.

$$(\phi_i)_{\rho=a} = (\phi_{loc})_{\rho=a} \quad (12)$$

$$(\phi_{loc})_{\rho=b} = (\phi_o)_{\rho=b} \quad (13)$$

$$\epsilon_i (d\phi_i/d\rho)_{\rho=a} = \epsilon_{loc} (d\phi_{loc}/d\rho)_{\rho=a} \quad (14)$$

and

$$\epsilon_{loc} (d\phi_{loc}/d\rho)_{\rho=b} = \epsilon_o (d\phi_o/d\rho)_{\rho=b} \quad (15)$$

In applying these boundary conditions to (5)–(7), the following expansions are utilized.

$$\ln \left( \frac{1}{\omega_k} \right) = \ln \left( \frac{1}{\rho_{>}} \right) + \sum_{m=1}^{\infty} \frac{1}{m} \left( \frac{\rho_{<}}{\rho_{>}} \right)^m \cos m(\phi - \phi_k) \quad (16)$$

$$K_0(\lambda\omega_k) = I_0(\lambda\rho_{<}) K_0(\lambda\rho_{>}) + 2 \sum_{m=1}^{\infty} \cos m(\phi - \phi_k) I_m(\lambda\rho_{<}) K_m(\lambda\rho_{>}) \quad (17)$$

and

$$I_0(\lambda\omega_k) = I_0(\lambda\rho_{<}) I_0(\lambda\rho_{>}) + 2 \sum_{m=1}^{\infty} (-1)^m \cos m(\phi - \phi_k) I_m(\lambda\rho_{<}) I_m(\lambda\rho_{>}) \quad (18)$$

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With these expansions, the expression for the reaction potential in (10) may be rewritten as

$$\phi_R(\mathbf{r}_k) = \epsilon_i^{-1} \sum_{k=1}^p \left[ B_k + F_k + \sum_{m=1}^{\infty} \cos m(\phi - \phi_k) (B_{nk}^m + F_{nk}^m) \frac{\rho^m}{m} + \sum_{n=1}^{\infty} (B_{nk} + F_{nk}) I_0(\lambda \rho_k) I_0(\lambda \rho) \cos \lambda(z - z_k) + \sum_{m=1}^{\infty} 2 \cos m(\phi - \phi_k) (-1)^m \sum_{n=1}^{\infty} (B_{nk}^m + F_{nk}^m) I_m(\lambda \rho_k) I_m(\lambda \rho) \cos \lambda(z - z_k) \right] \quad (19)$$

By use of (5)–(8), (12)–(18), and some straightforward algebra, the constants in the reaction potential expression, (19), are evaluated. These are

$$B_k = \frac{2q_k}{L\epsilon_b} \frac{(1 - \epsilon_a)}{\epsilon_a} \left\{ \frac{K_0(\kappa b)}{\kappa b K_1(\kappa b)} + \epsilon_b \ln \frac{b}{a} \right\} \quad (20)$$

$$F_k = \frac{2q_k}{L\epsilon_b} \left\{ \frac{K_0(\kappa b)}{\kappa b K_1(\kappa b)} + \epsilon_b \ln b \right\} \quad (21)$$

$$B_k^m = \frac{2q_k}{L} \left( \frac{1 - \epsilon_a}{\epsilon_a} \right) \left( \frac{\rho_k^m}{a^{2m}} \right) \left[ 1 + \left( \frac{a^{2m}}{b^{2m}} \right) \times \left\{ \frac{mK_m(\kappa b) + \epsilon_b(\kappa b) K_m'(\kappa b)}{mK_m(\kappa b) - \epsilon_b(\kappa b) K_m'(\kappa b)} \right\} \right] \quad (22)$$

$$F_k^m = \frac{2q_k}{L} \left( \frac{\rho^m}{b^{2m}} \right) \left[ \frac{mK_m(\kappa b) + \epsilon_b(\kappa b) K_m'(\kappa b)}{mK_m(\kappa b) - \epsilon_b(\kappa b) K_m'(\kappa b)} \right] \quad (23)$$

$$B_{nk}^m = (-1)^m \frac{4q_k}{L} (\epsilon_a' - 1) \frac{K_m'(\lambda a)}{I_m'(\lambda a)} \quad (24)$$

$$F_{nk}^m = (-1)^m \frac{4q_k}{L} \epsilon_a' \Theta \quad (25)$$

$$B_{nk} = B_{nk}^{m=0} \quad \text{and} \quad F_{nk} = F_{nk}^{m=0} \quad (26)$$

$$\Theta = \left[ \frac{\epsilon_b \lambda' K_m'(\lambda' b) K_m(\lambda b) - \lambda K_m(\lambda' b) K_m'(\lambda b)}{-\epsilon_b \lambda' K_m'(\lambda' b) I_m(\lambda b) + \lambda K_m(\lambda' b) I_m'(\lambda b)} \right] \quad (27)$$

$$\epsilon_a' = \left( \frac{\epsilon_a}{\lambda a} \right) \left[ (1 - \epsilon_a) \Theta I_m(\lambda a) I_m'(\lambda a) + K_m(\lambda a) I_m'(\lambda a) - \epsilon_a K_m'(\lambda a) I_m(\lambda a) \right]^{-1} \quad (28)$$

$$\epsilon_a = \frac{\epsilon_{loc}}{\epsilon_i} \quad \text{and} \quad \epsilon_b = \frac{\epsilon_o}{\epsilon_{loc}} \quad (29)$$

On a substitution of the above constants in (19) and (11), the electrostatic free energy is obtained as

$$A_{el} = \sum_{i=1}^p \sum_{k=1}^p \left[ \frac{q_i q_k}{L\epsilon_b \epsilon_i} \left\{ \frac{(1 - \epsilon_a)}{\epsilon_a} \left( \frac{K_0(\kappa b)}{\kappa b K_1(\kappa b)} + \epsilon_b \ln \frac{b}{a} \right) + \left( \frac{K_0(\kappa b)}{\kappa b K_1(\kappa b)} + \epsilon_b \ln b \right) \right\} + \frac{q_i q_k}{L\epsilon_i} \sum_{m=1}^{\infty} \cos m(\phi_i - \phi_k) \left( \frac{1}{m} \right) \left\{ \left( \frac{1 - \epsilon_a}{\epsilon_a} \right) \left( \frac{\rho_i^m \rho_k^m}{a^{2m}} \right) \left( 1 + \left( \frac{a^{2m}}{b^{2m}} \right) \alpha \right) + \left( \frac{\rho_i^m \rho_k^m}{b^{2m}} \right) \alpha \right\} + \frac{2q_i q_k}{L\epsilon_i} \sum_{n=1}^{\infty} \cos \lambda(z_i - z_k) I_0(\lambda \rho_k) I_0(\lambda \rho_i) \times \left\{ (1 - \epsilon_a'') \frac{K_1(\lambda a)}{I_1(\lambda a)} + \epsilon_a'' \Theta_{nk}^{m=0} \right\} + \frac{4q_i q_k}{L\epsilon_i} \sum_{m=1}^{\infty} \cos m(\phi_i - \phi_k) \sum_{n=1}^{\infty} \cos \lambda(z_i - z_k) I_m(\lambda \rho_k) I_m(\lambda \rho_i) \left\{ (\epsilon_a' - 1) \frac{K_m'(\lambda a)}{I_m'(\lambda a)} + \epsilon_a' \Theta \right\} \right] \quad (30)$$

where

$$\Theta_{nk}^{m=0} = \frac{-\epsilon_b \lambda' K_1(\lambda' b) K_0(\lambda b) + \lambda K_0(\lambda' b) K_1(\lambda b)}{\epsilon_b \lambda' K_1(\lambda' b) I_0(\lambda b) + \lambda K_0(\lambda' b) I_1(\lambda b)} \quad (31)$$

$$\epsilon_a'' = \left( \frac{\epsilon_a}{\lambda a} \right) \left[ (1 - \epsilon_a) \Theta_{nk}^{m=0} I_0(\lambda a) I_1(\lambda a) + K_0(\lambda a) I_1(\lambda a) + \epsilon_a K_1(\lambda a) I_1(\lambda a) \right]^{-1} \quad (32)$$

$$\alpha = \frac{mK_m(\kappa b) + \epsilon_b(\kappa b) K_m'(\kappa b)}{mK_m(\kappa b) - \epsilon_b(\kappa b) K_m'(\kappa b)} \quad (33)$$

and  $K_m'(s)$  and  $I_m'(s)$  (Bessel functions with primes) denote derivatives with respect to the argument. These are easily evaluated by the following relations.

$$K_m'(y) = \left( \frac{m}{y} \right) K_m(y) - K_{m+1}(y)$$

$$K_{m+1}(y) = \left( \frac{2m}{y} \right) K_m(y) + K_{m-1}(y)$$

$$I_m'(y) = \left( \frac{m}{y} \right) I_m(y) + I_{m+1}(y)$$

$$I_{m+1}(y) = - \left( \frac{2m}{y} \right) I_m(y) + I_{m-1}(y)$$

*Special Cases.* (a) *Linear Lattice.* A further simplification is achieved by assuming that the magnitude of all charges along the lattice axis is equal. The charges are located along the  $z$  axis spaced at a distance of  $L$  from each other. This implies that  $q_i = q_k = q$  and

$$\sum_{i=1}^p \sum_{k=1}^p \frac{q_i q_k}{L} = \frac{p^2 q^2}{L}$$

Only the  $m = 0$  terms survive in (30).

$$A_{el}' = \frac{p^2 q^2}{L\epsilon_o} \left[ \left\{ \frac{K_0(\kappa b)}{\kappa b K_1(\kappa b)} + \frac{\epsilon_o}{\epsilon_{loc}} \ln \frac{b}{a} + \frac{\epsilon_o}{\epsilon_i} \ln a \right\} + \frac{2\epsilon_o}{\epsilon_i} \sum_{n=1}^{\infty} \left\{ (1 - \epsilon_a'') \frac{K_1(\lambda a)}{I_1(\lambda a)} + \epsilon_a'' \Theta_{nk}^{m=0} \right\} \right] \quad (34)$$

Soumpasis<sup>48</sup> considered this case with a further assumption of  $\epsilon_i = \epsilon_{loc}$  and  $a = b$ . Also  $\rho_k = \rho_l = 0$  and  $\phi_k = \phi_l = 0$ . In this event (34) reduces to

$$A_{el}' = \frac{p^2 q^2}{L\epsilon_o} \left[ \left\{ \frac{K_0(\kappa b)}{\kappa b K_1(\kappa b)} + \frac{\epsilon_o}{\epsilon_i} \ln b \right\} + \frac{2\epsilon_o}{\epsilon_i} \sum_{n=1}^{\infty} \Theta_{nk}^{m=0} \right] \quad (35)$$

This result is identical with that obtained by Soumpasis (eq 21 of ref 48).

(b) *Uniformly Charged Cylinder.* For the case of a uniformly charged cylinder considered by Hill,<sup>3</sup> the series terms in (34) vanish (and  $\epsilon_{loc} = \epsilon_o$ ), giving

$$A_{el}'' = \frac{p^2 q^2}{L\epsilon_o} \left[ \left\{ \frac{K_0(\kappa b)}{\kappa b K_1(\kappa b)} + \ln \frac{b}{a} \right\} + \frac{\epsilon_o}{\epsilon_i} \ln a \right] \quad (36)$$

with  $(p^2 q^2 / L)$  in (36) replaced by a charge density parameter ( $z'^2 \rho^2 L$ ). The first two terms (enclosed in {} in (36)) refer to the work of charging a length ( $l$ ) of a cylinder of charge  $z'e$  per unit length. This compared exactly with the result of Hill (eq 9 of ref 3).

(c)  $\epsilon_{loc} = \epsilon_o$ . Bailey<sup>47</sup> has treated this case with discrete charge distribution, along with certain assumptions about the symmetry of the charge distribution, and arrived at the potential for the inner region that includes reaction potential (eq 29 of ref 47). The result of Bailey<sup>47</sup> is derivable from (37) here given below. The potential in the inner region in our case is given as

$$\phi_i = \sum_{k=1}^p \frac{2q_k}{L\epsilon_i} \left[ \ln \left( \frac{1}{\rho} \right) + \left( \frac{\epsilon_i}{\epsilon_0} \right) \left( \frac{K_0(\kappa b)}{\kappa b K_1(\kappa b)} \right) + \left( \frac{\epsilon_i}{\epsilon_{loc}} \right) \ln \frac{b}{a} + \ln a + \sum_{m=1}^{\infty} \cos m(\phi - \phi_k) \left( \frac{1}{m} \right) \times \left( \frac{\rho_k}{\rho} \right)^m \left\{ 1 + \left( \frac{1 - \epsilon_a}{\epsilon_a} \right) \left( \frac{\rho}{a} \right)^{2m} \left( 1 + \left( \frac{a}{b} \right)^{2m} \alpha \right) + \left( \frac{\rho}{b} \right)^{2m} \alpha \right\} + \sum_{n=1}^{\infty} 2 \cos \lambda(z - z_k) \left\{ I_0(\lambda \rho_k) K_0(\lambda \rho) + \left( (1 - \epsilon_a'') \frac{K_1(\lambda a)}{I_1(\lambda a)} + \epsilon_a'' \theta_{nk}^{m=0} \right) I_0(\lambda \rho_k) I_0(\lambda \rho) \right\} + \sum_{m=1}^{\infty} 4 \cos m(\phi - \phi_k) \sum_{n=1}^{\infty} \cos \lambda(z - z_k) \left\{ I_m(\lambda \rho_k) K_m(\lambda \rho) + \left( (\epsilon_a' - 1) \frac{K_m'(\lambda a)}{I_m'(\lambda a)} + \epsilon_a' \theta \right) I_m(\lambda \rho_k) I_m(\lambda \rho) \right\} \right] \quad (37)$$

where  $\phi_i$  is expressed as

$$\phi_i = \sum_{k=1}^p \phi_i^k$$

The results of Skolnick and Fixman<sup>53</sup> and Troll et al.<sup>56</sup> for the influence of the dielectric boundary on the angle dependence of the interactions between a single source charge on the surface of the cylinder and a test charge placed at any angle on the surface of the cylinder are derivable from (37) here. With  $\phi_i^k$  in hand, the electrostatic contribution to the total interaction energy for any given structure of DNA can be evaluated as

$$U^e = \sum_{i=1}^p U_i^e = \frac{1}{2} \sum_{i=1}^p q_i \phi_i^k \neq i = \frac{1}{2} \sum_{i=1}^p \sum_{k=1}^p q_i q_k \phi_i^k \quad (38)$$

It may, however, be expedient from a computational standpoint to retain the Coulombic term of the form  $(q_i q_k / \epsilon_i r_{ik})$  as in many of the force fields for evaluating the electrostatic contribution to the intramolecular interaction energy and supplement this with (30) for including the solvent and ion atmosphere effects.

Finally, the electrostatic part of Manning's limiting laws<sup>25,65</sup> follow from the above equations. In the limit of DNA treated as a continuous line of charge, all the series terms in (30) vanish as in (36). Only the first term in (36) depends on salt concentration. At low added salt the denominator in the first term of (36) tends to unity and the Bessel function in the numerator of the first term  $K_0(\kappa b)$  is approximated by its asymptotic form  $-\log(\kappa b)$ . Thus the electrostatic free energy varies logarithmically with the Debye length (also see eq 17 of ref 65 and eqs 22-42 of ref 66). A consequence of this is that melting temperatures vary linearly with the logarithm of the added salt concentration as observed experimentally.<sup>66</sup>

The principal results of the theory developed above are summed up by (30) for the electrostatic free energy and by (37) for the potential at any charge site on DNA. These include the effects of detailed charge distribution, the influence of the dielectric boundary, the effects of ion atmosphere, and the option to incorporate dielectric saturation or bound-water effects.

### Calculations

The theory of coaxial cylindrical dielectric continua developed above is illustrated by performing calculations on the relative stabilities of A, B, and Z forms of DNA in aqueous solutions under the condition of zero added salt (i.e., number of counterions in the system equals number of phosphates on DNA) at a temperature of 298 K. As pointed out in the Introduction, it was observed

**TABLE I: Calculated Transfer Free Energies of A, B, and Z Forms of DNA and Calculated Total Electrostatic Energies of A, B, and Z Forms of DNA Relative to B Form [in kcal/(mol Phosphate)]**

DNA	linear lattice	discrete charge distribn
Transfer Free Energies		
A	-24.36	-20.71
B	-32.72	-38.23
Z	-35.21	-34.74
Total Electrostatic Energies		
A	5.76	14.14
B	0.00	0.00
Z	-1.17	5.32

earlier<sup>28,32</sup> that condensation theory does not account for the stability of the B form of DNA in aqueous solutions relative to the Z form at low salt. It is therefore interesting to see what a detailed charge distribution of DNA would do to this trend. The coordinates of B-DNA are generated from the local coordinates of Arnott and Hukins<sup>34</sup> with one turn of DNA represented in our calculations, those of Z form (ZI) from crystal coordinates<sup>30</sup> and those of A form from ref 67. For simplicity we used only the phosphate coordinates. Sequence-dependent effects can be easily considered in the above theory but are not included here. A charge of  $(-1/\xi)|e|$  is placed on each phosphate group at the site of the phosphorus atom, which is closest to the charge center. Extension of this charge model to a delocalized charge distribution of the phosphodiester group is straightforward. The value of  $\xi$  is taken from condensation theory<sup>25</sup> which is  $\xi = 7.1/d$ , where  $d$  is the distance of average axial charge separation. The effective charges on the phosphates in A, B, and Z forms thus are -0.180, -0.238, and -0.261 (in atomic units), respectively. The radius of the inner cylinder  $r = a$  is taken as 10 Å. The ion exclusion radius  $r = b$  is taken as 12 Å. The dielectric constant inside the inner cylinder is taken as  $\epsilon_i = 2$  and for the bulk a value of  $\epsilon_0 = 80$  is assigned. Two choices for the local dielectric constant  $\epsilon_{loc} = 20$  and 80 are considered. The free energies of transfer from vacuum to water are calculated by defining a reference state of  $\{\epsilon_i = 2, \epsilon_{loc} = 1, \text{ and } \epsilon_0 = 1\}$  with the final state as  $\{\epsilon_i = 2, \epsilon_{loc} = 80, \text{ and } \epsilon_0 = 80\}$  unless mentioned otherwise. This procedure is the equivalent of a charging process.<sup>68</sup> A final state with  $\epsilon_{loc}$  different from both  $\epsilon_i$  and  $\epsilon_0$  can also be examined. The Bessel functions in (30) are evaluated by polynomial approximations given by Abramowitz and Stegun<sup>62</sup> with errors of the order of  $10^{-7}$ , which is satisfactory for the present calculations. Convergence of the series terms in (30) is seen to be satisfactory for  $n = 25$  and  $m = 7$ , for the charge distributions considered here. The intramolecular contribution to the total electrostatic energy is estimated with the function  $(q_i^{\text{eff}} q_k^{\text{eff}} / \epsilon_i r_{ik})$ , where  $q_i^{\text{eff}}$  and  $q_k^{\text{eff}}$  are the effective phosphate charges and  $r_{ik}$  is the distance between them.

### Results and Discussion

The transfer free energies of A, B, and Z forms of DNA (in kcal/mol phosphates) are collected in Table I. Alongside are shown the results from a linear lattice model. The total electrostatic energies, which include both the intramolecular phosphate-phosphate repulsions and the transfer free energies, are shown in the last three rows of Table I. It is evident from Table I that the linear-lattice model predicts that solvation preferentially stabilizes the Z form followed by the B and A forms in that order, noted previously to be contrary to experimental observations.<sup>33</sup> The discrete charge model, however, indicates that solvation favors B form over both A and Z forms, more in line with experiment under conditions of low salt and high water activity. In (30) for the electrostatic free energy, the series terms in  $n$  represent the effects of discreteness of the charge distribution along the axial direction and those in  $m$  describe the effects due to discreteness in the radial direction perpendicular to the helix axis. These series terms are important for an appropriate evaluation of relative conformational stabilities and line of charge or rodlike models

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are inadequate. The above results suggest that continuum electrostatics can be employed to understand the relative stabilities of DNA at low salt.

We also must emphasize that the same conformational stability trends are maintained (results not shown) whatever the salt concentration, suggesting that a continuum treatment of ion atmosphere electrostatics does not produce salt-induced conformational transitions over its range of applicability. The critical NaCl transition concentration for B to Z transition was observed to be 2.3 M,<sup>69</sup> which is beyond the purview of continuum theories. This has been noted earlier<sup>32</sup> as well. Both  $\epsilon_i$  and  $\epsilon_{loc}$  have a larger influence on the conformational differences in the calculated transfer free energies than do changes in the salt concentration.

At this stage of the theory, due to insufficient information on the internal and local dielectric constants,  $\epsilon_i$  and  $\epsilon_{loc}$ , and the radii  $a$  and  $b$  of cylinders defining these regions, these quantities are to be regarded as parameters. Molecular simulations with fully explicit treatment of the solvent, counterions, and co-ions may help define these parameters more precisely. Simulations of this type are in progress in this laboratory.<sup>70</sup> The results as expected are sensitive to the choice of these parameters. Alternatively, within the context of the current model one can reasonably conclude from the data in Table I that a dielectric constant much lower than the bulk value of 80 up to a distance of 10 Å (say  $\epsilon_i = 2$  and  $a = 10$  Å) from the helical axis of DNA stabilizes the B form.

Finally, the electrostatic terms in the potential energy function for atom-atom interactions are given by (37 and 38). Note that

(37) includes both the direct interaction terms (Coulomb potential) as well as the reaction potential. These can be integrated into molecular dynamics simulations of nucleic acids under vacuum to incorporate solvent, dielectric boundary, and ion atmosphere at a continuum level.

### Summary and Conclusions

The major point of this study is a demonstration that a consideration of the proper geometrical distribution of DNA charges in continuum electrostatics resolves a contradiction with experiment at low salt observed in line charge representations of the double helix. We demonstrate here with a detailed charge distribution of DNA that the B form of DNA is favored over both A and Z forms in aqueous solutions at low added salt. This indicates that counterion condensation postulate along with a Debye-Hückel treatment of ion atmosphere extended to discrete charge distributions of DNA may be used to probe conformational energetics at a continuum level effectively. Additional terms, such as entropy of mixing in CC theory beyond continuum electrostatics, will be required for a full theoretical account of the conformational transitions. Current work in this direction has been reported in preliminary form by Fenley et al.<sup>71</sup>

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