DNA A-tracts bending: Polarization effects on electrostatic interactions across their minor groove

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A B S T R A C T

Bending by the DNA A-tracts constitutes a contentious issue, suggesting deficiencies in the physics employed so far. Here, we inquire as to the importance in this bending of many-body polarization effects on the electrostatic interactions across their narrow minor groove. We have done this on the basis of the findings of Jarque and Buckingham who developed a procedure based on a Monte Carlo simulation for two charges of the same sign embedded in a polarizable medium. Remarkably, the present analysis reveals that for compact DNA conformations, which result from dynamic effects, an overall attractive interaction operates between the phosphate charges; this interaction is especially strong for the narrow minor groove of the A-tracts, suggesting a tendency for DNA to bend toward this groove. This tendency is in agreement with the conclusions of electrophoretic and NMR solution studies. The present analysis is also consistent with the experimental observations that the minor groove is much more easily compressible than the major groove and the bending propensity of the A-tracts is greatly reduced at "premelting" temperatures. By contrast, the dielectric screening model predicts a repulsion between the phosphate charges and is not consistent with the aforementioned bending tendency or experimental observations.

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1. Introduction

The minor and major groove of DNA is an important target for in-depth understanding its structure and function, particularly for its interaction with protein and other molecules (Chou, 2005) as well as from dynamic point of view (Sobell et al., 1983; Zhou, 1989); DNA bending and the wrapping of DNA around the histone octamer in the nucleosome are two cases in which the minor groove of DNA plays an important role and yet the mechanism in each case has not been well established.

DNA bending associated with the A-tracts, runs of four to six consecutive adenine residues in phase with the helical repeat, has generated considerable interest for the past quarter of a century. This interest has been stimulated by their excessive concentration in the promoters of a range of eukaryotic and prokaryotic species (Ross et al., 2001; Shomer and Yagil, 1999; Yagil, 2006) and their participation in the folding of DNA in the nucleosome (Satchwell et al., 1986), as well as by their presence within the replication origins (Bramhill and Kornberg, 1988; Gille and Messer, 1991; Umek and Kowalski, 1988). The anomalous electrophoretic

mobility of the A-tracts (Diekmann, 1987; Koo et al., 1986; Marini et al., 1982; Zinkel and Crothers, 1987) was found to be consistent with bending toward their minor groove (Zinkel and Crothers, 1987). By contrast, X-ray crystallographic measurements (Coll et al., 1987; Dickerson, 1998; DiGabriele et al., 1989; Goodsell et al., 1994; Nelson et al., 1987) found that the A-tracts are straight, with bending occurring at the sequences that flank the A-tracts in an orthogonal direction to that found by the electrophoretic studies. Recent solution NMR studies, which incorporated refinements through the use of residual dipolar couplings, reported bending toward the minor groove of the A-tracts (Barbic et al., 2003; MacDonald and Lu, 2004; Stefl et al., 2004), in agreement with the findings of the electrophoretic studies. Maher and co-workers (Strauss and Maher, 1994; Strauss-Soukup et al., 1997) replaced phosphate groups with neutral methylphosphonate molecules and found DNA bending toward the neutral side, thus providing support for the notion that charge neutralization induces DNA bending. Williams and co-workers (McFail-Isom et al., 1999; Shui et al., 1998) inferred on the basis of crystallographic data the presence of sodium ions in the minor groove of A-tracts, and proposed that bending toward the minor groove is the result of phosphate charge neutralization. This inference was subsequently challenged by Chiu et al. (1999) and Johansson et al. (2000). Moreover, a magnetic relaxation

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dispersion study (Denisov and Halle, 2000) reported that the sodium ion occupancy in the minor groove of the A-tracts is only a few percent. Currently, there is no unanimity in the findings of molecular dynamics simulations as to the extent of ion occupancy in that groove (reviewed by Beveridge et al., 2004).

DNA is also known to undergo major conformational changes as a result of thermal fluctuations which could affect its bending propensity. A molecular dynamics simulation study for the Dickerson dodecamer reported a standard deviation of ~20% for the distance between two neighboring phosphate charges with a range of ~8–15 Å over a 5 ns time period (Young et al., 1997). Also, a time-resolved intrinsic fluorescence anisotropy study (Georghiou et al., 1996) found that DNA undergoes large-amplitude motions that are driven by thermal fluctuations: for a $(dA)_{20} \cdot (dT)_{20}$ 20-mer, the major rotational correlation time was found to be ~130 ps, and the average angle by which the transition dipole moment of an excited base was rotated over a time span of 0.5 ns was ~45°, which is a very large value. Two other fluorescence anisotropy studies, which employed 2-amino-purine as a fluorescent probe, also reported fast large-amplitude motions in a decamer (Nordlund et al., 1989) and in a series of oligomers (Rai et al., 2003). NMR measurements have also detected considerable rotational amplitudes, ~29° for short oligomers (Eimer et al., 1990), and ~23° for a decamer (Kojima et al., 1999). Moreover, we and others reported (Georghiou et al., 1996; Georghiou et al., 1998; Shih and Georghiou, 2006) that environmental impediments to molecular motion, e.g. those imposed by viscous damping by the solvent and/or by molecular constraints (e.g. proteins), can modulate the conformation and dynamics of DNA.

Although a very large number of studies have been carried out and a number of models have been proposed [for reviews, see Beveridge et al., 2004; Crothers and Shakked, 1999; MacDonald and Lu, 2004; Stellwagen and Mohanty, 2004], the physical origin of the bending of DNA remains unclear. The controversial nature of the findings suggests that there are deficiencies in our understanding of the underlying physics, e.g. additional interactions may be operating. In particular, electronic polarization effects on the electrostatic interactions across the DNA grooves have not so far been taken into account. Very few studies have included polarization effects in nucleic acids, with a polarizable force field at the production level currently not being available for molecular dynamics simulations (Beveridge et al., 2004). Such simulations, which employed a polarizable force field in conjunction with AMBER 7 (Baucom et al., 2004), or a polarizable force field based on a classical Drude model (Anisimov et al., 2005), were reported. Also, an ab initio quantum mechanical calculation reported that polarization effects are important in the interaction of divalent ions with DNA bases (Sponer et al., 2000).

An approach that would employ polarizable force field for DNA has limitations arising from the complexity of the parametrization process which puts a limit on finding a general protocol able to work for different kinds of molecular systems. Thus, limiting its value for heterogenous systems such as DNA. In addition, the theoretical strength of a force field and its feasability for molecular dynamic simulation are of concern. It should be noted here that promising attempts have been made for small organic molecules and water as well as for model protein systems (see reviews Halgren and Damm, 2001; Ponder and Case, 2003; Rick and Stuart, 2002). The above considerations and the nonfeasibility of an ab initio calculation for a complex and heterogeneous system such as DNA have turned our attention to a different kind of approach. Jarque and Buckingham (1989) recognized that many-body polarization effects in a polarizable system contribute an *attractive* interaction for charges of the same sign, which, for a highly polarizable system, can even exceed the Coulomb repul-

sion. This finding is consistent with the results of other theoretical treatments (Cho et al., 2000; Gao et al., 1991; Williams, 1992) that took into account the contribution of polarization interactions. Furthermore, a study (Gao et al., 1991) that reported from a survey of the Cambridge Structure Database the common occurrence of chloride ion pairs near the contact distance, has provided experimental evidence for the attractive nature of the overall interaction between charges of the same sign in a highly polarizable medium. Jarque and Buckingham (1992) carried out a further study of many-body polarization effects in a system of Xe atoms with two charges of the same sign embedded in it, through a Monte Carlo simulation in conjunction with the Padé Approximant method. This approach has the attractive feature of allowing the calculation, explicitly at the microscopic level, of the polarization energy as a function of the intercharge distance. On the basis of the findings of that study (Jarque and Buckingham, 1992), we have here investigated the effects of many-body electronic polarization interactions on the Coulomb repulsion between the phosphate charges across the DNA grooves. It is found that these effects screen efficiently this repulsion for the minor groove and, for more compact DNA conformations attained dynamically, give rise to an overall *attraction* between the phosphate charges; this attraction is particularly strong for the narrow minor groove of the A-tracts [width ≈ 9.3 Å (Yoon et al., 1988)], suggesting a tendency for DNA to bend toward this groove.

2. Theory

For a homogeneous system of N identical polarizable particles with polarizability α and with two charges q_1 and q_2 embedded in it, the polarization energy u_{pol} is given by (Barker, 1953; Jarque and Buckingham, 1992; Stone, 1996):

$$u_{pol} = -\frac{\alpha}{2} \sum_{j=1}^{N} \mathbf{E}_j^{(o)} \cdot \mathbf{E}_j \qquad (1)$$

Here, $\mathbf{E}_j^{(o)}$ is the electric field at particle j due to the two charges, and $\mathbf{E}_j$ is the total electric field at particle j, which is the sum of the electric field due to the two charges and the induced field $\Delta\mathbf{E}_j$ due to all other particles ($k \neq j$), and is written as:

$$\mathbf{E}_j = \mathbf{E}_j^{(o)} + \Delta\mathbf{E}_j \qquad (2)$$

The electric field due to the charges $\mathbf{E}_j^{(o)}$ is given by:

$$\mathbf{E}_j^{(o)} = \frac{q_1}{4\pi\varepsilon_0} \frac{\mathbf{r}_{1j}}{r_{1j}^3} + \frac{q_2}{4\pi\varepsilon_0} \frac{\mathbf{r}_{2j}}{r_{2j}^3} \qquad (3)$$

Here $\mathbf{r}_{1j}$ and $\mathbf{r}_{2j}$ are the distance vectors from q_1 and q_2 to particle j, respectively, and ε_0 is the permittivity of free space. The induced field $\Delta\mathbf{E}_j$ is given by:

$$\Delta\mathbf{E}_j = \alpha \sum_{k \neq j} \hat{\mathbf{T}}_{jk} \cdot \mathbf{E}_k \qquad (4)$$

Here $\hat{\mathbf{T}}_{jk}$ is the dipole propagator given by:

$$\hat{\mathbf{T}}_{jk} = \frac{1}{4\pi\varepsilon_0} \left(\frac{3\hat{\mathbf{r}}_{jk}\hat{\mathbf{r}}_{jk} - r_{jk}^2 \hat{\mathbf{1}}}{r_{jk}^5} \right) \qquad (5)$$

where $\hat{\mathbf{r}}_{jk}$ is the vector from particle k to particle j. By substituting Eq. (4) into Eq. (2), the total electric field $\mathbf{E}_j$ at particle j is then written as:

$$\mathbf{E}_j = \mathbf{E}_j^{(o)} + \alpha \sum_{k \neq j} \hat{\mathbf{T}}_{jk} \cdot \mathbf{E}_k \qquad (6)$$