LETTERS TO THE EDITOR

The Letters to the Editor section is divided into three categories entitled Notes, Comments, and Errata. Letters to the Editor are limited to one and three-fourths journal pages as described in the Announcement in the 1 January 1999 issue.

NOTES

The role of the molecular shape on the conformational transition from *B*-to *Z*-DNA

José L. F. Abascal[a] and Juan Carlos Gil Montoro
Departamento de Química Física, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, E-28040, Spain

(Received 30 December 1998; accepted 18 March 1999)

[S0021-9606(99)52322-2]

Apart from its possible biological relevance,[1] the conformational equilibrium between the *B* and *Z* forms of DNA[2] has been the topic of several theoretical studies due to the dramatic structural change involved. Among other agents, it is induced by an increase in the salt concentration. The charged phosphates are closer to each other in *Z*-DNA, giving stronger repulsions between them so that *B* is, in principle, more stable. At high salt concentration, the repulsions among the charged phosphates are more effectively screened and the *Z* conformation is stabilized. This must imply significant changes in the structure of the surrounding ions. We have recently shown[3] that the coupling of the DNA shape with its high charge induces important effects in the ionic cloud around the polyion when the salt concentration increases. Therefore, it seems interesting to investigate the role played by the DNA shape in the stabilization of *Z*-DNA at high salt.

To isolate this effect, we will use several models which, for each DNA form, differ only in the degree of definition of the repulsive molecular core. As most of the DNA charge lies at the phosphate groups, unit negative charges are placed at the phosphorus positions. In the ''empty'' model, there is no repulsive core apart from that of the phosphate groups. DNA is, in this case, a double-helical array of charged spheres held fixed in a continuum solvent of relative dielectric constant equal to that of water at 25 °C. Two additional rigid DNA models are considered, the grooved primitive (GP) model, and a discretely charged soft (DS) cylinder. In the latter, the charges are embedded within a cylindrical core whose radius is different for each DNA form. The GP model was obtained by fitting a set of geometrically simple objects to the *B*-[4] and *Z*-DNA shapes. In addition to the phosphates of the empty model, a big sphere mimics the central DNA core while each nucleotide is completed by another uncharged sphere of the same size as the phosphate.

The variation of the relative stability of both DNA forms has been reported by Pohl[5] for $d(C-G)_n \cdot d(C-G)_n$ oligomers in the high monovalent salt region, 2–5 M NaCl. The variation is linear in the logarithm of salt concentration. The transition free energy can be formally split into several contributions[6]

$$\Delta G^{B\to Z} = \Delta G^{B\to Z}_{\text{intro}} + \Delta G^{B\to Z}_{\text{hydr}} + \Delta G^{B\to Z}_{\text{electr}}, \tag{1}$$

where the subscript *intra* represents the intramolecular contributions except the electrostatic ones, which are included in the electrostatic term. $\Delta G^{B\to Z}_{\text{electr}}$ is then independent of the molecular sequence so simple models as those described above are suitable for its calculation. García and Soumpasis[6] have estimated $\Delta G^{B\to Z}_{\text{intra}}$ for the alternating guanine–cytosine hexamer to be about $-0.1\,k_{\text{B}}T$ per phosphate and almost independent of salt concentration.

The hydration term accounts for the possible differences in the *specific* hydration of each conformer. Specific hydration effects are important in DNA (see, for instance, Ref. 7), but their influence on the transition is somewhat controversial.[8,9] Besides, the use of models allowing the calculation of $\Delta G^{B\to Z}_{\text{hydr}}$ by computer simulation would be unaffordable. For these reasons, we neglect the hydration contribution in the present instance.

We have recently proposed[10] a rigorous method especially suited for the calculation of the electrostatic term. The computation for each conformer is split into two steps; the first one consists of the *setup* of the *uncharged* form, while the other one corresponds to the *charging process* of such structure. The application of the procedure to the empty DNA model[11] shows that both the *charging* and the *setup* contributions increase the relative stability of the *Z* form at high salt. From the total change in the electrostatic free-energy difference in going from 0.5 to 4.3 M, the charging term accounts for about 87%. Besides, the *setup* term cannot be easily calculated for the GP model, so we will omit such contribution

$$\Delta G^{B\to Z}_{\text{electr}} \approx \Delta G^{B\to Z}_{\text{charging}}. \tag{2}$$

[a]Electronic mail: jl@juguete.quim.ucm.es

 © 1999 American Institute of Physics

Downloaded 16 Dec 2004 to 147.96.5.17. Redistribution subject to AIP license or copyright, see http://jcp.aip.org/jcp/copyright.jsp

TABLE I. Electrostatic free energies [Eq. (2)] for the DS and GP models in k_BT per phosphate.

DNA model	C^{bulk} (M)	B	Z	$\Delta G^{B\to Z}_{\text{electr}}$
DS	1.0	0.692	1.048	0.356
DS	2.5	0.266	0.598	0.332
DS	4.3	−0.010	0.318	0.328
GP	1.0	−0.070	0.177	0.247
GP	2.6	−0.490	−0.354	0.136
GP	4.5	−0.719	−0.648	0.071
GP	7.8	−0.936	−0.966	−0.030

Our final expression for the transition free energy is then

$$\Delta G^{B\to Z}=\Delta G^{B\to Z}_{\text{intra}}+\Delta G^{B\to Z}_{\text{charging}}. \tag{3}$$

For the calculation of the latter term, we use a charging process; the charging free energy is then given by the usual integral of the electrostatic potentials over the charging parameter λ.[11] For the intramolecular term, the estimation of García and Soumpasis[6] is used. The results for the charging term of the DS and GP models are presented in Table I (for the empty model, see Ref. 11). The estimated error is less than $0.005\,k_BT$ per phosphate. The transition free energies, evaluated from Eq. (3), are displayed in Fig. 1.

$\Delta G^{B\to Z}$ for the DS model scarcely depends on salt concentration. It is evident that a repulsive cylinder is inappropriate for the thermodynamic description of the transition. It could be surprising that the rough empty model is in much better agreement with experiment. In fact, the results for the empty and GP models are not too different. This is in accordance with the similarities observed in their ionic patterns around *B*-[3] and *Z*-DNA. These consist of the accommodation of counterions—and also coions at high salt for *B*-DNA!—in specific positions inside the polyion, due to the cooperative effect of the closest-charged phosphate groups and the groove's shape. The patterns for the DS model are completely different[3] because the cylindrical core prevents the counterions from entering the grooves. Thus, despite its simplicity, the empty model retains what seems an *essential* feature for the transition to occur: it allows the mobile ions to *penetrate* inside DNA. A simplified explanation is that, due to the particular shape of the conformers, ions entering within the grooves are (in average) closer to the phosphates in *Z*-DNA than in *B*-DNA, and thus the penetration of ions favors the stabilization of the *Z* form.

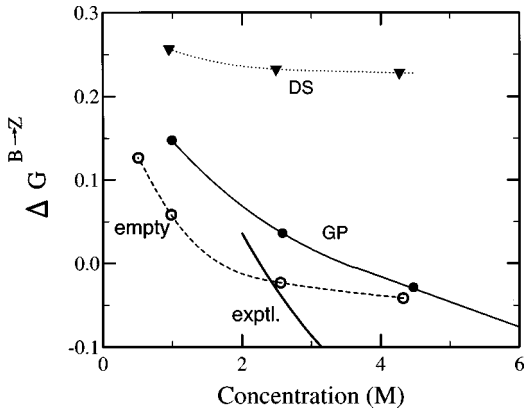

FIG. 1. Transition free energies [Eq. (3)] in k_BT/P. Lines are to guide the eye, except the experimental curve, which is the Pohl's fit.[5]

At relatively low salt concentration, the slope of the curve for the empty model is similar to the experimental one, but at high salt the curve flattens out. This suggests that the counterions accumulate easily inside DNA—and thus *Z*-DNA stabilizes—due to the absence of an internal repulsive core. As the salt concentration increases, the region eventually reaches the quasisaturation and cannot easily accommodate more ions, so the free-energy difference is almost constant. On the other hand, the variation of $\Delta G^{B\to Z}$ for the GP model is smoother; in fact, it is linear with the logarithm of salt concentration, in agreement with the experimental findings. This may be explained by the steric hindrance due to the molecular core which restricts the access to the mobile ions. When the salt concentration increases, the counterions are ''pushed'' from outside DNA toward the grooves. Hence, the stabilization of *Z*-DNA continues at high salt. In summary, the penetration of ions into the grooves—determined by the molecular shape—plays a decisive role in the transition. On the other hand, the presence of ions in the grooves has been proven in a high-resolution refinement of a *B*-DNA dodecamer crystal structure.[12]

In our calculations, the slope of the GP curve is lower than the experimental one. This cannot be ascribed to the small computational error. Besides, the intramolecular term is essentially salt concentration independent. Assuming that the setup term for this model behaves similarly as in the empty model, its inclusion would improve the slope of the curve a little. It is also possible that the use of models with refined DNA geometries improves the results to some extent, but not substantially. It seems that the mentioned refinements would account for only a part of the departures in the slope, so the remaining deviation would be due to the neglected hydration contribution.

This work was supported in part by the SEUI (Spain), Grant Nos. PB96-0588 and PB97-0258-C02-01.

[1] R. R. Sinden, *DNA Structure and Function* (Academic, London, 1994).
[2] F. M. Pohl and T. M. Jovin, J. Mol. Biol. **67**, 375 (1972).
[3] J. C. Gil Montoro and J. L. F. Abascal, J. Chem. Phys. **109**, 6200 (1998).
[4] J. C. Gil Montoro and J. L. F. Abascal, Mol. Simul. **14**, 313 (1995).
[5] F. M. Pohl, Cold Spring Harbor Symp. Quant. Biol. **47**, 113 (1983).
[6] A. E. García and D. M. Soumpasis, Proc. Natl. Acad. Sci. USA **86**, 3160 (1989).
[7] M. A. Young, B. Jayaram, and D. L. Beveridge, J. Am. Chem. Soc. **119**, 59 (1997).
[8] W. Saenger, W. N. Hunter, and O. Kennard, Nature (London) **324**, 385 (1986).
[9] E. Westhof, Annu. Rev. Biophys. Biophys. Chem. **17**, 125 (1988); R. V. Gessner, G. J. Quigley, and M. Egli, J. Mol. Biol. **236**, 1154 (1994).
[10] J. C. Gil Montoro and J. L. F. Abascal, Europhys. Lett. **34**, 471 (1996).
[11] J. C. Gil Montoro and J. L. F. Abascal, J. Chem. Phys. **106**, 8239 (1997).
[12] X. Shui, L. McFail-Isom, G. G. Hu, and L. D. Williams, Biochemistry **37**, 8341 (1998).

Downloaded 16 Dec 2004 to 147.96.5.17. Redistribution subject to AIP license or copyright, see http://jcp.aip.org/jcp/copyright.jsp