THE EFFECTS OF COUNTERCATION SCREENING ON THE ELECTROSTATIC POTENTIAL OF DNA

The rôle of the nucleic acid conformation

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1. Introduction

In [1–8] we have shown the way in which the macromolecular conformation affects the electrostatic potential of the different allomorphic forms of DNA. These results have been used for interpreting and predicting the reactive behavior of the nucleic acids, particularly towards charged electrophilic species [1,8,9]. Most of these results referred to unscreened nucleic acids and thus represent an attempt to understand their intrinsic properties. However, we have also studied the influence of screening the phosphate groups by counterions [10–14]. These studies have now been extended to all the major allomorphic forms of DNA and we would now like to indicate one of the fundamental aspects of the results obtained.

2. Method

The principal contribution to the overall aspect of the distribution of electrostatic potential around DNA comes from the phosphate groups of the nucleic acid backbones [1,8]. The results presented here refer to computations carried out for B-DNA and for A-DNA using:

(1) Solely the anionic phosphate groups of the nucleic acid, placed in the arrangements corresponding to the different conformers studied.

(2) The same ensemble of phosphates screened by Na^+ or Mg^{2+} cations bound the phosphates.

The cations are fixed in a bridged position between the two anionic oxygens of the phosphate and in the plane containing these atoms and the phosphorus atom. The cation–oxygen binding distances are 2.15 Å for Na^+ [15] and 1.95 Å for Mg^{2+} [12,13], corresponding to the optimum binding distances to an isolated phosphate group. Na^+ are bound to each phosphate of the model double-helix studied (one complete turn), but Mg^{2+} are only bound to alternate phosphate groups in each strand [12].

In the case of A-DNA, because of the close approach of the backbones across the major groove, a second possibility for screening by Mg^{2+} was envisaged. This involves ions bound between two different phosphate groups, one of these groups belonging to each strand of the nucleic acid. This positioning results in cation–anionic oxygen distances of 3.6 Å, closer to the values for an interaction intermediated by water [12].

These screening schemes are simple attempts to test, qualitatively, the influence of counterions and should not be considered as attempts to represent exactly counterion distributions. This is particularly true in the case of Na^+, for which recent evidence suggests that they are probably, unlike Mg^{2+}, not site- but territorially-bound to the nucleic acids [16,17]. However, our models permit us to investigate the general features of a saturated screening of the anionic phosphate charges.

The atomic coordinates employed for the DNA allomorphs were taken from [18] and the models of both B- and A-DNA consisted of one full turn of the corresponding double helix.

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3. Results and discussion

Fig.1 illustrates the positioning of a line, denoted mM, which lies in the central plane bisecting our model DNA double helices, perpendicular to their helical axis. It passes symmetrically through their major (M) and minor (m) grooves in this central plane, these grooves being defined by the projection onto the plane of the central phosphorus atom in each backbone of the model (P).

Fig.2 contains three potentials calculated for our B-DNA model along this line:

(i) (——) due solely to the phosphate groups of the model double helix;

(ii) (– – –) due to these groups plus the screening Na^+;

(iii) (. . .) due to the phosphates plus the screening Mg^{2+}.

It may be observed that the phosphate mM line potential is nearly symmetrical with respect to the helical axis, which is central in fig.2. This situation results from the rather similar nature of the two grooves in B-DNA. In fact, the minor groove of this allomorph is actually somewhat narrower than the major groove and thus the phosphate groups approach somewhat closer on this side of the helix. In consequence, the minimum in the phosphate line potential occurs in the former groove. This asymmetry is lessened, however, by the orientation of the phosphates which turn their anionic oxygens more towards the major groove.

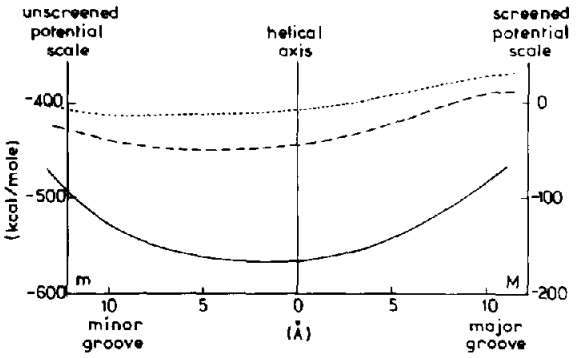

Fig.2. The molecular electrostatic potential along the mM line in B-DNA: (——) potential of the unscreened acid; (– – –) potential of the Na^+-screened acid; (· · ·) potential of the Mg^{2+}-screened acid.

When the influence of Na^+ is included, the potentials are strongly reduced in magnitude, but the form of the mM line potential appears very similar. On closer study it can be seen that their effect has been to slightly deepen the minimum of the minor groove, because the screening cations are brought somewhat closer together on the side of the major groove due to the phosphate orientation. The effect is, however, relatively small.

When the magnesium screening is considered a very similar situation is found. The form of the mM line potential is very like that for sodium screening, but the shorter binding distance between the cation and

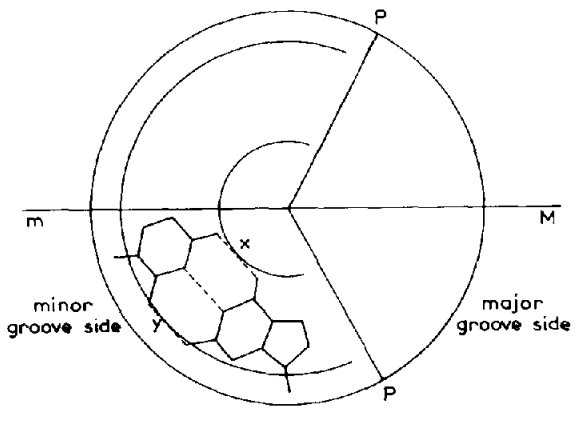

Fig.1. The positioning of the mM line along which the potentials in fig.2 and 3 are computed.

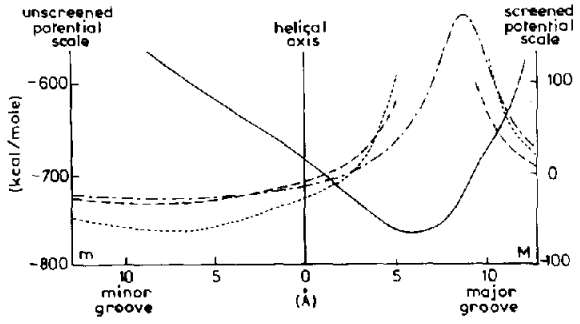

Fig.3. The molecular electrostatic potential along the mM line in A-DNA: (——) potential of the unscreened acid; (– – –) potential of the Na^+-screened acid; (· · ·) potential of the Mg^{2+}-screened acid (ions bound to single phosphates); (–·–) potential of the Mg^{2+}-screened acid (ions bound between two phosphates).

the phosphates has slightly increased their screening effect and the resulting potentials are ~20 kcal/mol more negative than for the sodium screening.

Similar screening of other allomorphs of DNA may lead to very different findings. In fig.3 the potentials along the mM line are shown passing through our A-DNA model. The potentials due to the phosphate groups alone (——) are already very different from those of B-DNA and a clear minimum is visible on the side of the major groove. This asymmetry is due to the very much closer approach of the phosphate groups across the narrow major groove and is accentuated by the orientation of these groups, which are turned so that their anionic oxygens face across the entrance to the groove. This situation means that upon screening this allomorph of DNA, we may expect more important changes in distribution of the potential.

We will now consider the effect of the screening by sodium or magnesium cations, positioned as above. When the potential of these cations is added to that of the phosphate groups the effect is striking (in fig.3 this is shown by the lines, —— for the sodium screening, · · · for magnesium screening, when the cations are bound to single phosphates and —·— for magnesium screening, when the cations are shared between two phosphates across the major groove.) With each of these screening schemes there is an inversion in the form of the mM line potential to yield a strong minimum in the minor groove and a maximum in the major groove. (Two of the screened line potentials are interrupted in the major groove due to the presence of the screening ions which, because the potentials are calculated with multipole expansions, cannot be approached closer than 2 Å [1].) The most effective screening is by Mg^{2+} bound to single phosphate groups, as for B-DNA. The Na^{+} screen slightly less, but the weakest screening is associated with the Mg^{2+} bound between a pair of phosphates. This ordering is understandable in terms of the increasing distances between the anionic phosphates and the countercations in these 3 schemes.

These results are quite unlike those for B-DNA and imply that the potentials and consequently the reactive properties of A-DNA may be dramatically changed by the presence of screening cations.

We have carried out similar investigations (submitted) concerning other allomorphs of DNA and we have been able to conclude that they may be divided into two classes:

(1) The allomorphs for which the two grooves of the double helix are similar in nature (B,C, 'alternating-B') and for which, in consequence, the electrostatic potentials are similar in the two grooves – whether screening cations are present or not.

(2) Those allomorphs in which one groove is very much narrower than the other (A,D,Z) and for which, in consequence, the negative potentials are much stronger in the narrower groove before screening, but, conversely, stronger in the wider groove after screening.

The results of this study are particularly relevant due to the renewed interest in the different structural possibilities of DNA and the recognition that the DNA within the cell is not necessarily the classical double helix of Watson and Crick, but may present regional heterogeneities. Thus the rôle of screening on its various forms may be an important element of distinction for the biological properties of the different allomorphs, either in their interactions with other biomacromolecules or in their susceptibility towards attacking species.

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