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The Molecular Electrostatic Potential and Steric Accessibility of C-DNA

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The molecular electrostatic potentials and steric accessibilities associated with reactive sites of C-DNA are calculated for the sequences poly($dG \cdot dC$) and poly($dA \cdot dT$). The distribution of potential on the surface envelopes of the double helices are also presented. The results are compared with those obtained for B-DNA.

Key words: C-DNA – Molecular electrostatic potential – Accessibility – Surface envelopes.

1. Introduction

In continuation of our series of researches concerning the properties of the nucleic acids we now present a study of the C allomorph of DNA. We shall compare the results obtained for the molecular electrostatic potential and the accessibility of this conformation with those previously calculated for B-DNA [1–3]. These results should, however, be considered as part of a larger study of the influence of the conformation of DNA on its reactive properties [4, 5], in which we have already dealt specifically with the allomorphs A [6], alternating-B [7], D [7], Z_I [8] and Z_{II} [8, 9].

2. Method

The details of the techniques employed in calculating the molecular electrostatic potentials [1, 3, 4] and accessibilities [2, 8] associated with the nucleic acids have

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been described in detail in previous publications and will not be repeated here. We note simply that in the computations of the surface envelope potentials of C-DNA the atomic spheres forming the envelope were of 1.7× van der Waals radius, this being the usual factor we employ and which enables these potentials to be calculated using multipolar expansions of the electronic densities of the subunits of the nucleic acids [10, 11]. Secondly, the atomic accessible areas quoted are evaluated with respect to a test sphere of radius 1.2 Å, the van der Waals radius of hydrogen. As demonstrated previously these accessibilities may be considered as corresponding to an attack by a water molecule through one of its hydrogen atoms [2] and also as, effectively, the upper limit of the atomic accessibilities, within the nucleic acids, toward molecular species.

The geometry employed for C-DNA is that due to Arnott and Selsing [12] and the model double helix used in all calculations consists of a segment with 11 phosphates in each strand. This represents somewhat more than one full turn of the C-DNA double helix but has the advantage of facilitating comparison with our previous calculations for B-DNA [1–3] where a model with 11 phosphates per strand was also employed.

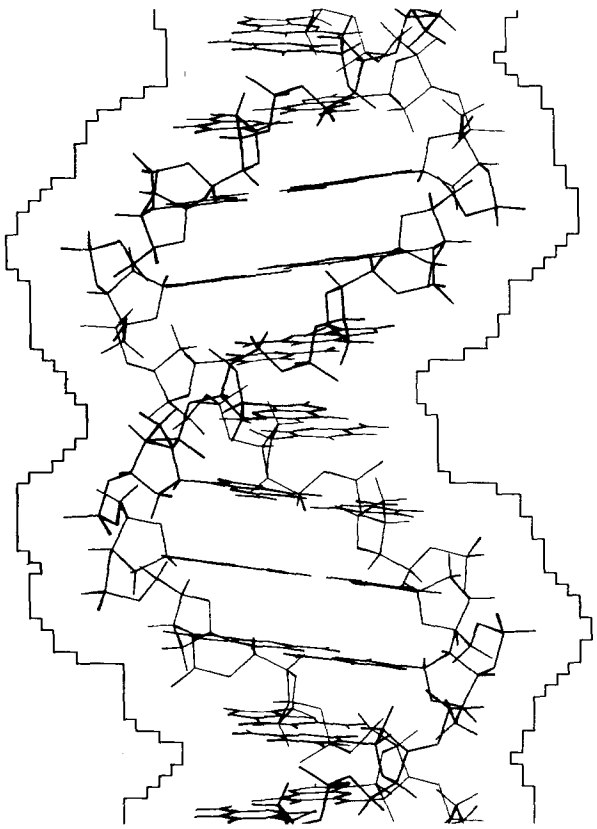

Fig. 1. Molecular diagram of the poly($dG \cdot dC$) model of C-DNA

3. Results and Discussion

We begin by discussing the general distribution of the electrostatic potential around the double helix of C-DNA as obtained with the aid of the surface envelope technique. A molecular diagram of the model segment with the base sequence poly($dG \cdot dC$) is given in Fig. 1. One may note the major groove of the double helix in the lower half of this figure and the minor groove in the upper half. The profile of the surface envelope surrounding the nucleic acid is also indicated by the contours on the left and right hand sides of the graphic. The potentials calculated on this envelope are presented in Fig. 2, where different degrees of shading are used to indicate the values of the potentials, darker shadings indicating more negative potentials. Details of these shadings are given in Table 1 from which it may also be noted that the overall variation of potential on the surface envelope is roughly 170 kcal/mole, from −488 kcal/mole to −657 kcal/mole.

These strongly negative values are largely due to the anionic phosphates in the backbones of the double helix. A cursory inspection of Fig. 2 shows, however, that the most negative potentials on the surface envelope are not in fact associated with the backbones, but are located rather in the grooves of this helix. This, at first sight surprising, result is due to the way in which the potentials of all the units of the nucleic acids sum together and was found to be true for B-DNA and also for other DNA allomorphs studied. The exact partitioning of the potential between the two grooves is, however, variable. In Fig. 2, the local

Table 1. Shadings used for surface envelope potentials

SHADING	POTENTIAL (kcal/mole)
	-488
	-516
	-544
	-572
	-600
	-628
	-657

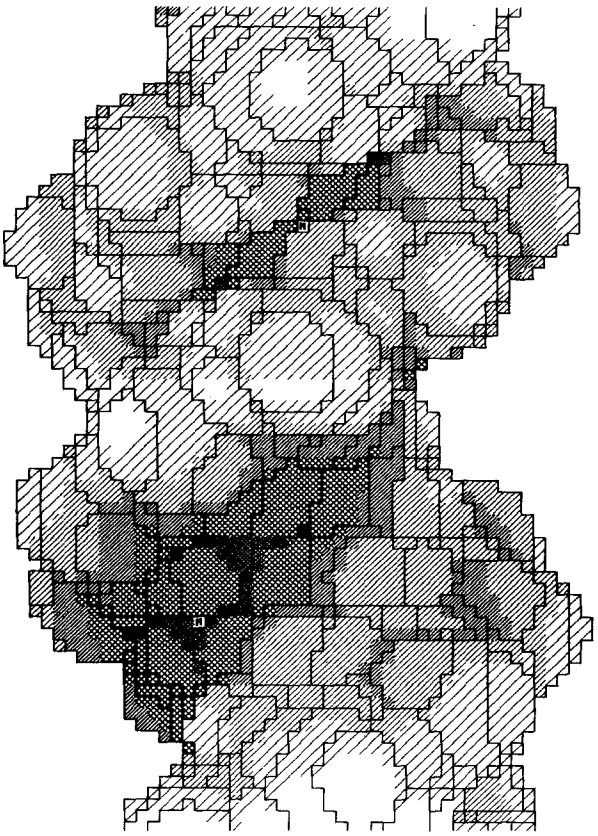

Fig. 2. Surface envelope potentials of the poly($dG \cdot dC$) model of C-DNA

minimum of the potential in each groove has been marked by the letter M, the corresponding values being −632 kcal/mole in the minor groove and −645 kcal/mole in the major groove. A similar preponderance of the major groove for a poly($dG \cdot dC$) sequence was also noted for B-DNA [3]. This result appears to be related to the nature of the *GC* base pair which has intrinsically stronger potentials on the side of its major groove, associated with the sites N7 and O6 of guanine (notation N7(G) and O6(G)), than on the side of its minor groove, where the potentials, associated with N3(G) and O2(C) are screened, to some extent, by the 2-amino protons of guanine. This fundamental trend is thus preserved in *C* and B-DNAs.

We have also studied a poly($dA \cdot dT$) model of C-DNA. The molecular diagram of this double helix is given in Fig. 3 and the corresponding surface potentials in Fig. 4 (the shading is the same as that for the preceding sequence, see Table 1). The results once again show a concentration of negative potential in the grooves of the double helix, but the magnitudes of the local minima in each groove (denoted by *M* in Fig. 4) reveal a change. Whereas for the *GC* com-

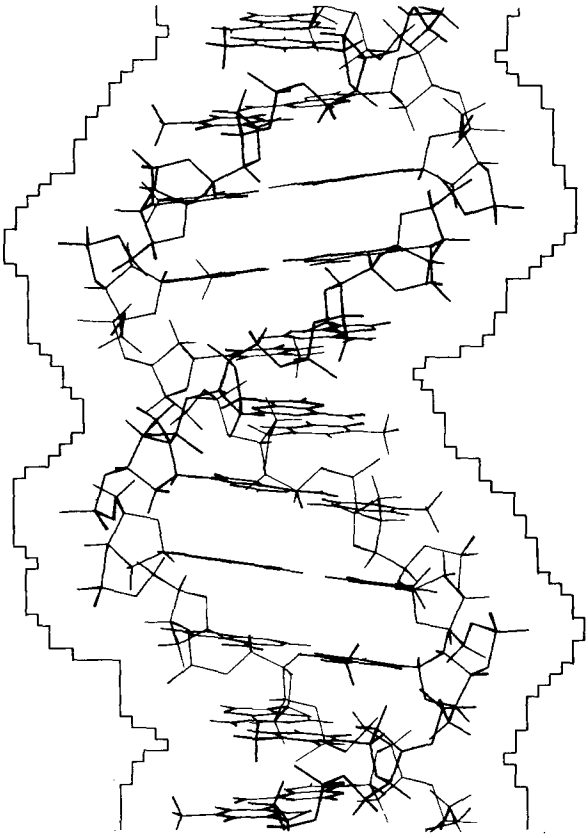

Fig. 3. Molecular diagram of the poly($dA \cdot dT$) model of C-DNA

plementary homopolymer the major groove contained a deeper minimum than the minor groove, the reverse is true for the polymer with the AT sequence, the surface minimum of its minor groove (−656 kcal/mole) being some 40 kcal/mole more negative than that of its major groove (−614 kcal/mole). This situation is also similar to that calculated for B-DNA [3] and, once again, can be related to the nature of the AT base pair for which the minor groove sites, N3(A) and O2(T), produce stronger negative potentials than the major groove sites, N7(A) and O4(T), these latter suffering from the screening effect of the 6-amino group protons of adenine. The less negative potentials associated with the adenine amino groups can indeed by seen in Fig. 4 as the paler zones equally spaced along the center of the major groove in the lower half of the figure.

It is interesting to note a further distinction between B-DNA and C-DNA, related to the surface potential minima. For the sequence poly($dG \cdot dC$) the C conformation yields a difference of −13 kcal/mole between the two groove minima (major-minor); for the B conformation the difference is larger: −29 kcal/mole (−632 kcal/mole in the major groove less −603 kcal/mole in the

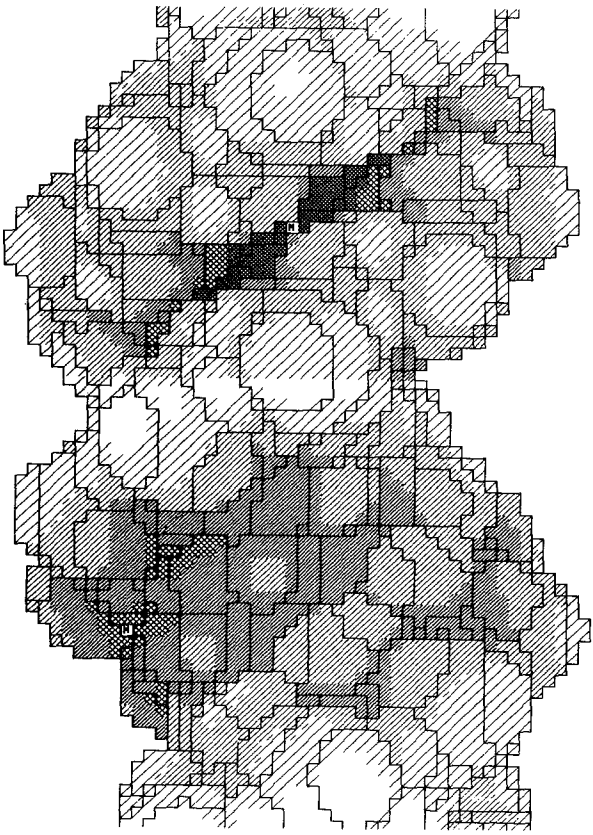

Fig. 4. Surface envelope potentials of the poly($dA \cdot dT$) model of C-DNA

minor groove). For the sequence poly($dA \cdot dT$) the situation is reversed and the difference (major groove minimum-minor groove minimum) for the *C* conformation, +42 kcal/mole, is greater than for the *B* conformation, +27 kcal/mole, (−598 kcal/mole in the major groove less −625 kcal/mole in the minor groove). This reflects a second determining factor for the values of the surface potentials, which overlays the intrinsic potentials of the base pairs, namely, the positioning of the base pairs with respect to the helical axis. We have previously remarked on the importance of this effect for A- and Z-DNAs, where the strong displacement of the base pairs, toward the minor groove for A-DNA or toward the major groove for Z-DNA, leads to an imbalance in the phosphate potentials and renders the deepened groove much more negative. Although the changes are much smaller between the *B* and *C* conformations, nevertheless, whereas for C-DNA the base pairs are situated almost symmetrically about the helical axis, they are somewhat displaced in B-DNA toward the minor groove. This displacement is sufficient to favour slightly less the potentials in the minor groove of B-DNA than in the minor groove C-DNA. Thus in passing from the *C* to the *B* conformation the intrinsic imbalance of the *GC* potential (which favours

Table 2. Site potentials (kcal/mole) and steric accessibilities (Å^2) of the bases in C-DNA

Base	Sites				
Guanine	N2	N3	N7	C8	O6
Potential	−651	−702	−696	−632	−666
Accessibility	0.0	0.1	3.8	0.9	2.5
Cytosine	N4	C5	O2		
Potential	−617	−586	−663		
Accessibility	0.2	0.1	0.1		
Adenine	N3	N6	N7	C8	
Potential	−699	−621	−664	−610	
Accessibility	1.0	0.1	2.5	0.8	
Thymine	C5	O2	O4		
Potential	−600	−684	−627		
Accessibility	0.0	1.0	1.6		

the major groove) should be enhanced, while the intrinsic imbalance of the AT potential (which favours the minor groove) should be attenuated. This is indeed seen to be the case from the groove minima presented.

In order to study the potentials associated with the bases of C-DNA in more detail we have also calculated the site potentials associated with atoms susceptible to attack by electrophiles. The numerical results are contained in Table 2 and a graphic comparison with the corresponding results for B-DNA is made in Fig. 5. The values for guanine and cytosine refer to the central base pair of the model poly($dG \cdot dC$) segment and those for adenine and thymine to the central base pair of the model poly($dA \cdot dT$) segment.

If we recall the general remarks made above in relation to the surface envelope potentials, the interpretation of these results is simplified. Firstly, the potentials of the GC base pairs are more negative on the side of the major groove, but the difference with the opposing face is less in C-DNA than in B-DNA. Secondly, the potentials of the AT base pairs are more negative on the side of the minor groove and the difference with the opposing face is greater in C-DNA than in B-DNA. We should note, in addition, that the density of phosphates in C-DNA being slightly greater than in B-DNA, all the potentials associated with the former allomorph are, overall, slightly more negative.

All of these general phenomena are visible in Fig. 5. We may note, for example, much deeper site potentials for the minor groove AT sites, N3(A) and O2(T), than for the major groove AT sites, N7(A) and O4(T), more marked in C-DNA than in B-DNA. The distinction between the major and minor groove sites of GC is, in contrast, less marked in C-DNA and the site with the deepest potential in the minor groove, N3(G), is even slightly more negative than N7(G) in the, otherwise dominant, major groove. The minor groove amino site of guanine

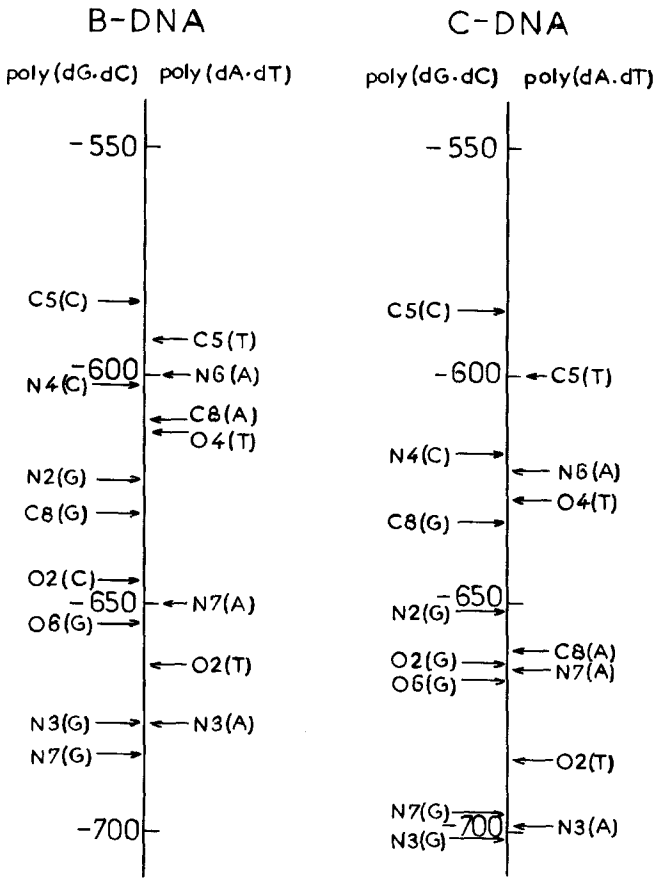

Fig. 5. Comparison of the base site potentials in B-DNA and C-DNA

N2(*G*), is, similarly, considerably more attractive towards electrophiles in C- than in B-DNA. In contrast, two *GC* major groove sites, C5(*C*) and C8(*G*), are hardly more negative in C-DNA despite its greater phosphate density.

In completing the study of C-DNA we present, in Table 2, the accessible areas of the atoms whose potentials have been just discussed. Comparison of these results with those for B-DNA, which is made graphically in Fig. 6, shows only slight changes. C-DNA, like B-DNA, yields the highest accessibilities for the ring nitrogens N7(*G*) and N7(*A*) and the carbonyls O6(*G*) and O4(*T*), all in the major groove. Similarly, the minor groove carbonyl O2(*T*), the nitrogen N3(*A*) and the major groove C8 atoms have moderate accessibilities in both conformers. The lowest accessibilities are associated with the O2(*C*), C5(*C*), C5(*T*) and the amino nitrogens. The only distinction between the B and C conformers seems to be the slightly reduced accessibilities of C-DNA in the major groove, most notably of N7(*G*) and O4(*T*). This may be connected with the geometry of the major groove in C-DNA (measured as the closest approach of two phosphorus atoms across the groove) which is somewhat narrower (16.3 Å)

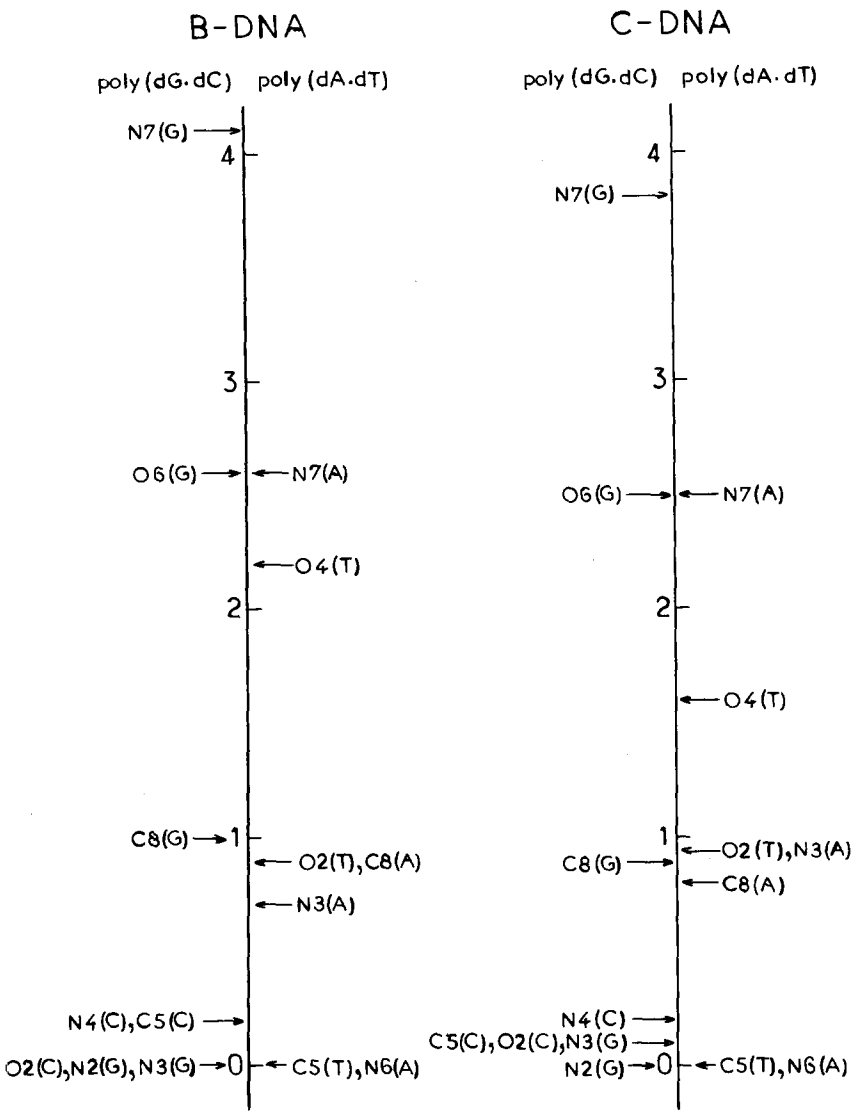

Fig. 6. Comparison of the base atom accessibilities in B-DNA and C-DNA

than in B-DNA (17.0 Å). General trends in accessibilities are, however, much more difficult to discern than trends in potential due to the marked dependence of the former property on the detailed local conformation.

4. Conclusions

C-DNA has been shown to be closely related to B-DNA both in terms of its electrostatic potentials and its atomic accessibilities. Differences have nevertheless been pointed out and related to the geometrical differences between these

two allomorphs. Such differences may conceivably be of significance for the understanding of the detailed reactive properties of DNA in different conformations.

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