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# The molecular electrostatic potential and steric accessibility of poly (dA-dT). poly (dA-dT) in various conformations: B-DNA, D-DNA and 'alternating-B' DNA

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## ABSTRACT

The influence of conformational changes on the molecular electrostatic potential and the steric accessibility of the double stranded polynucleotide poly (dA-dT). poly (dA-dT) are investigated by calculating these properties for three different conformations : B-DNA, D-DNA and alternating-B DNA.

## INTRODUCTION

A number of recent studies have renewed and strengthened interest in the importance of sequence specific conformational variations in the nucleic acids and their possible role in the specificity of the interactions of these macromolecules with external agents, in particular regulatory proteins, but also carcinogens, antibiotics etc. A particularly outstanding example of such a possibility is offered by the discovery of the left-handed double helix, termed Z-DNA, found in the crystal of the self-complementary hexamer CGCGCG (1, 2) and in the high salt solution of poly (dG-dC). poly (dG-dC) (3, 4). Simultaneously, this situation has emphasized the probable heterogeneity of the native B-form of DNA which may be expected to exhibit variations in its configuration and conformation along its length as a result of varying base-pair sequences. This possibility has been strongly substantiated by the recent determination of the X-ray structure of the single crystal of a B-DNA dodecamer with the self-complementary base sequence CGCGAATTCGCG (5, 6).

In a series of papers from our laboratory we have investigated quantum-mechanically two important properties related to the polymorphism and heterogeneity of the nucleic acids, namely, their molecular electrostatic potential (7, 8) and the steric accessibility to their reactive sites (9, 10), which have been shown to play a significant role in their chemical and biochemical reactivities. Particularly we have explored in this way B-DNA, (7, 8, 11, 12), Z-DNA (13, 14), A-DNA (15) and $tRNA^{Phe}$ (16, 17). A similar study was also carried out for Dickerson's dodecamer (18).

In this paper we wish to extend our theoretical investigation to other types of DNA conformers which appear in particular with highly repetitious synthetic polymers having specific base-pair sequences but which may also be of significance in cellular nucleic acids. The subject of the present investigation is the alternating copolymer poly (dA-dT). poly (dA-dT) for which besides the classical B form (19) two other conformations have been proposed :

1) The D form discovered by Davies and Baldwin (20) and refined by Arnott et al. (21), characteristic of low salt, dry fibers of the polynucleotide ; it is an eight-fold variant of the ten-fold B-form whose most striking features are the small molecular diameter, approximately 18 Å, resulting from the closeness of the phosphates to the helix (7.8 Å), the large rotation per residue (45°) and the displacement of the base pairs behind the helix axis.

2) The "alternating B" form proposed by Klug et al. (22), on the basis of an increased affinity of this polynucleotide (with respect to bulk DNA) for the lac repressor, as the most likely conformation for wet fibers or for the molecule in solution ; its main feature is that, while it conserves the average ten-fold B structure, its repetitive unit is a dinucleotide with two different alternating phosphodiester likages, the characteristic torsion angles being $\omega'(O3'-P) = -90°$, $\omega(P-O5') = -60°$ between A and T but $\omega' = -120°$, $\omega = -50°$ between T and A (as against $\omega' = -90°$, $\omega = -60°$ for the phosphodiesters in B-DNA). The rationale for this proposal is the improved stacking of the bases in the alternating form.

The proposal of Klug et al. has recently received confirmation through $^{31}P$ NMR studies of poly (dA-dT). poly (dA-dT) fibers, which exhibit two resonances of nearly equal intensity. This strongly suggests an alternating conformation of the phosphodiester groups (23, 24). CD spectra in low salt solution also suggest a similar conformation (25). Surprisingly enough, in the same low salt conditions, poly (dG-dC). poly (dG-dC) gives only a single $^{31}P$ resonance (24). Whether this sequence is able to form an alternating conformation is a matter of discussion (24, 26).

It may be added that the results for the poly (dA-dT). poly (dA-dT) sequence should be of direct interest for the satellite DNA's found in certain species, whose base sequence approximates that of this alternating copolymer (27).

## METHOD

The molecular electrostatic potentials of the different conformations of poly (dA-dT). poly (dA-dT) were calculated by the superposition of the poten-

tials of the subunits of the polynucleotide, bases, sugars and phosphates, using the technique described in our previous publications (7, 8). The potentials of the subunits were evaluated with the use of overlap multipole expansions (28) of the electron density derived from an ab initio wave function for each subunit. These multipolar potentials have been shown to be precise down to 2Å from the constituent atoms of the molecules concerned (29). Below this distance exact electrostatic potentials are evaluated.

The model polynucleotides employed consisted of a complete double helical turn for each of the conformations studied, which thus involve 11 phosphates in each strand for the B and alternating-B forms and 9 phosphates in each strand for the D-form, with, in each case, the corresponding number of sugars and bases. The geometries employed were those of Arnott and Hukins (19) for B-DNA, Arnott et al. (21) for D-DNA and Klug et al. (22) for alternating-B DNA.

The potentials calculated are presented here as : 1) potentials associated with the minima of the reactive atoms of the bases (the results refer to either of the central base pairs of the oligonucleotides studied), 2) the potentials associated with the phosphates of the phosphodiester backbones (the results refer to the central phosphates of the oligonucleotides studied, two different base sequences beginning with A or T at the 3' end of the strands being used to study the two different types of phosphate), 3) surface potentials on an envelope surrounding the nucleic acids, formed by the intersection of spheres centered on each atom with radii proportional to their van der Waals radius (as in our previous studies a proportionality factor of 1.7 was used (12)).

Steric accessibilities are also presented. These were calculated using the technique described previously (9, 10). They quantify the accessible areas on the atoms concerned, within the surface envelope of the nucleic acid, toward a test sphere of radius 1.2 Å, which may be considered to represent a water molecule binding via one of its hydrogen atoms (9, 10).

## RESULTS AND DISCUSSION.

The three conformations of poly (dA-dT). poly (dA-dT) are compared in terms of the potential minima associated with the reactive atoms of the bases, the steric accessibility of these atoms, the potentials and accessibilities of the phosphates, and the surface potentials of the double helices.

### (1) Base potential minima

The potential minima associated with the atoms of adenine and thymine susceptible to electrophilic attack (nucleophilic centers) are given in table

TABLE 1. Potentials (kcal/mole) and accessibilities ($Å^2$) of the bases of poly (dA-dT) . poly (dA-dT) in the different DNA conformations.

| CONFORMATION | PROPERTY | ADENINE SITES | | | | THYMINE SITES | | |
|---|---|---|---|---|---|---|---|---|
| | | N3 | N6 | N7 | C8 | O2 | O4 | C5 |
| B-DNA | POTENTIAL | -676 | -602 | -650 | -601 | -665 | -617 | -583 |
| | ACCESSIBILITY | 0.9 | 0.1 | 2.5 | 0.1 | 1.1 | 2.3 | 0.2 |
| D-DNA | POTENTIAL | -697 | -590 | -639 | -600 | -684 | -595 | -574 |
| | ACCESSIBILITY | 0.3 | 0.1 | 2.6 | 0.3 | 0.3 | 1.9 | 0.0 |
| Alternating-B DNA | POTENTIAL | -653 | -586 | -621 | -579 | -642 | -607 | -554 |
| | ACCESSIBILITY | 1.1 | 0.1 | 2.6 | 0.1 | 1.1 | 1.9 | 0.4 |

1 for each of the three investigated conformations. In order to help comparison between the different conformations these site potentials are visualized graphically in figure 1 on vertical scales, the minima for adenine and thymine being respectively on the left and right of the axis for each conformation.

The first point to note is the overall range of the potentials. In B-DNA this extends between - 676 kcal/mole for the N3 site of adenine (notation N3(A)) and - 583 kcal/mole for the C5 site of thymine (notation C5(T)). For D-DNA the range is similar but somewhat larger extending from - 697 kcal/mole (N3(A)) to - 574 kcal/mole (C5(T)). This is at first sight suprising because the model polynucleotide representing one turn of the D conformation has only 18 phosphates, 4 less than the model of the B conformation. This would imply that the potentials of the D conformation should be considerably less negative. That this is not the case reflects the closer packing of the anionic phosphate groups in this conformation, both in terms of the smaller rise per base pair (D-DNA : 3.03 Å, B-DNA : 3.38 Å) and of the smaller diameter of the double helix (approximately 18 Å for D-DNA, approximately 20 Å for B-DNA). The increased range of the potentials in the D conformation is associated with the shift of the base pairs towards the major groove of the double helix. Such shifts have been seen in our previous studies to enhance the potential sites in the deepened groove (in this case in the minor groove) and to weaken those in the groove made shallower (13-15).

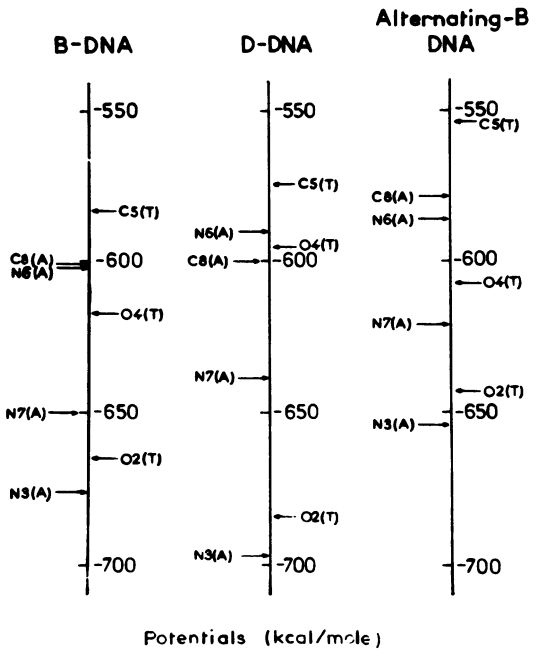



FIGURE 1. Comparison of the site potentials of adenine and thymine of poly (dA-dT) . poly (dA-dT) in the different DNA conformations (kcal/mole).

The range of site potentials in the alternating-B DNA is between - 653 kcal/ mole (N3(A)) and - 554 kcal/mole (C5(T)) and is thus significantly less negative than that of the B conformation, despite the fact that the two model oligonucleotides have the same number of phosphate groups. This finding can be attributed to the slightly lower density of the phosphate groups in the backbone of the alternating-B form, which has the same pitch as B-DNA but whose diameter, approximately 21 Å, is 1 Å larger than that of B-DNA.

If we now consider the order of the site potentials in each of the three conformations (see fig. 1), this may be seen to be largely unchanged. The only exception is C8(A) which is relatively more negative in D-DNA and preceeds both N6(A) and O4(T). The deepest potentials in all cases are associated with the nucleophilic centers located in the minor groove of the helices, N3(A) and O2(T), a result previously demonstrated to be characteristic of A-T segments of B-DNA (7, 8, 30, 31) but not of A-DNA(15). There are, however significant variations in the absolute magnitudes of the potentials. Thus, in D-DNA these two deepest sites, N3(A) and O2(T), become more negative than in B-DNA. This

situation may be attributed, as noted previously, to the shift of the base pairs in the D conformation away from the helical axis toward the major groove, a displacement which deepens the minor groove and enhances the influence of the phosphate potentials on the sites of this groove.

For alternating-B DNA the principal effect, as noted in the range of the calculated site potentials, is a general uniform shift toward less negative values.

(2) Base steric accessibilities

The steric accessibilities have been calculated for the reactive atoms of the bases associated with the potential minima discussed in the preceeding section. The results are given in table 1 and are illustrated graphically in figure 2 in a manner analogous to the presentation of the potentials in figure 1. The principal finding from these results is the stability of the atomic accessibilities with respect to the changes of conformation. In each of the double helices the order and values of the accessibilities are largely maintained, the only important exceptions being the N3(A) and O2(T) sites which

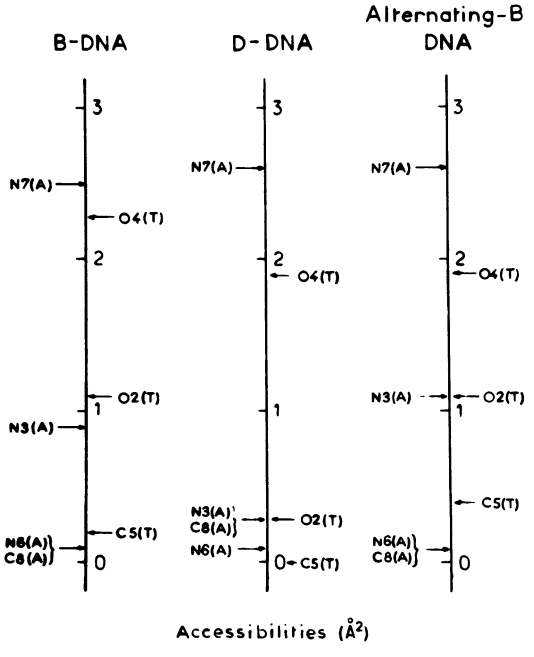



FIGURE 2. Comparison of the atomic accessibilities of adenine and thymine of poly (dA-dT) . poly (dA-dT) in the different DNA conformations (Å2).

are significantly less accessible in D-DNA than in the B conformers. This effect may again be correlated with the deepening and narrowing of the minor groove of D-DNA which, while enhancing the potentials of the nucleophilic sites in this groove, diminishes the access of reactants to these sites.

(3) Phosphate potentials and accessibilities

In order to characterise the potentials associated with the phosphate groups of the different conformations we have calculated the site potential lying in the OL-P-OR plane, 2.15 Å from each of the anionic oxygens OL and OR (using the same notation as Klug et al. (22)). This site, as indicated in our previous studies, corresponds to the optimal binding position of a $Na^+$ ion to an isolated phosphate group (32). The results are contained in table 2.

It may be seen from these results that the potentials of the ApT and TpA phosphates are very similar to one another in each of the three conformations, the TpA phosphate having, a very slightly more negative potential in each case. The potentials are, however, roughly 20 kcal/mole weaker in the D and alternating-B conformations than in B-DNA.

The accessibilities of the phosphate oxygens have also been calculated and are presented in table 2. Two features of these accessibilities are common to the three helical conformations, namely, that OL has a considerably higher

TABLE 2. The bridge site potentials (kcal/mole) and accessibilities associated with the phosphates of poly (dA-dT) . poly (dA-dT) in the different DNA conformations.

| CONFORMATION | PHOSPHATE | BRIDGE SITE POTENTIAL | ACCESSIBILITIES 03' | 05' | OL | OR |
|---|---|---|---|---|---|---|
| B-DNA | ApT (x) | -582 | 1.9 | 0.0 | 9.1 | 6.1 |
| | TpA (xx) | -583 | 1.9 | 0.0 | 9.1 | 7.0 |
| D-DNA | ApT | -555 | 1.7 | 0.0 | 6.1 | 1.0 |
| | TpA | -558 | 1.7 | 0.0 | 6.3 | 2.8 |
| Alternating-B DNA | ApT | -558 | 1.1 | 0.1 | 9.2 | 7.8 |
| | TpA | -560 | 0.2 | 0.7 | 9.7 | 8.0 |

(x) i.e. corresponding to the sequence $_{5'}A_{3'}P_{5'}T_{3'}$
(xx) i.e. corresponding to the sequence $_{5'}T_{3'}P_{5'}A_{3'}$

accessibility than OR and that the accessibilities of both anionic oxygens are greater for the TpA phosphate than for the ApT phosphate, the only exception being for OL in B-DNA which has equal values for TpA and ApT. Comparing the three conformations, the smallest anionic oxygen accessibilities are calculated for the phosphates of D-DNA, for which OR is particularly hindered. The alternating-B conformation has anionic oxygens with the highest accessibility. In this latter conformation the O3' and O5' accessibilities differ, each, for ApT and TpA (unlike those in the B or D helices) ; for its ApT phosphate, O3' is relatively accessible while O5' is inaccessible, while for its TpA phosphate the reverse is observed. (4)

(4) Surface potentials

In order to obtain an overall view of the three double helical conformations we now present the surface potentials associated with each model polynucleotide. In each case we give a molecular diagram of the double helix and a graphic of the surface potentials : figures 3 and 4 for B-DNA, figures 5 and 6 for D-DNA and figure 7 and 8 for alternating-B DNA. Shadings have been used to indicate the values of the surface potentials, darker shadings implying more negative potentials, following the details given in table 3.

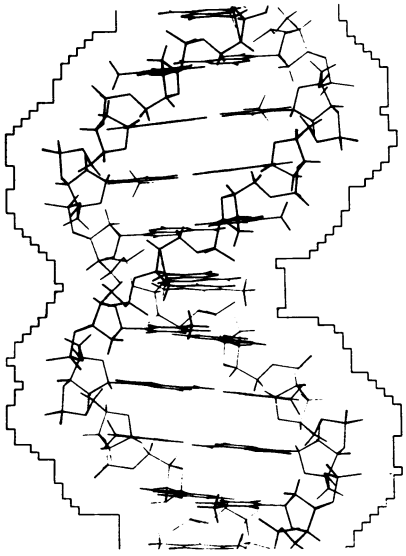


FIGURE 3. Molecular graphic of poly (dA-dT) . poly (dA-dT) in the B-DNA conformation.

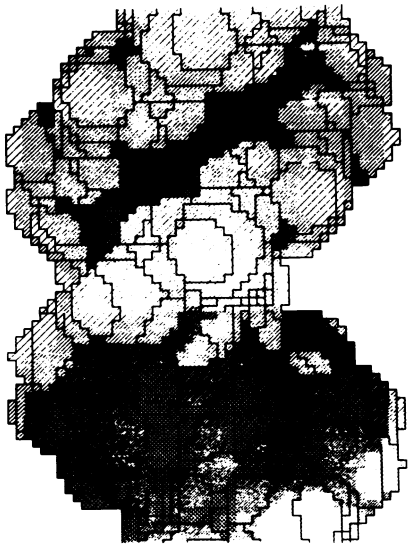


FIGURE 4. Surface potentials of poly (dA-dT) . poly (dA-dT) in the B-DNA conformation (for details of shading see table 3).

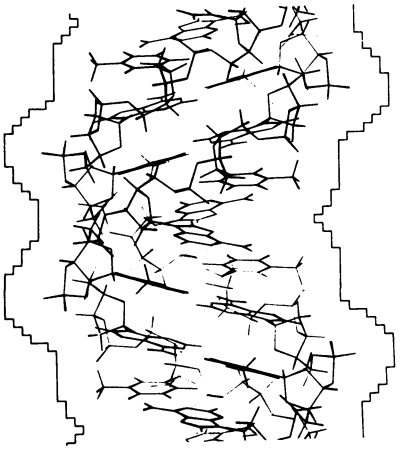


FIGURE 5. Molecular graphic of poly (dA-dT) . poly (dA-dT) in the D-DNA conformation.

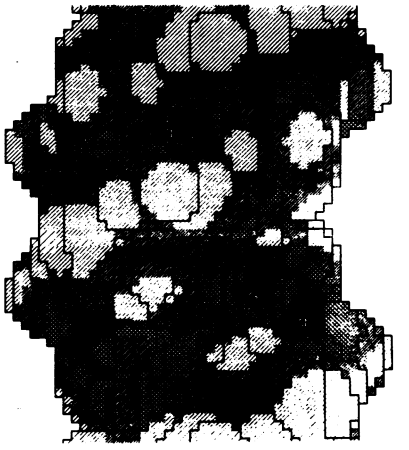


FIGURE 6. Surface potentials of poly (dA-dT) . poly (dA-dT) in the D-DNA conformation (for details of shading see table 3).

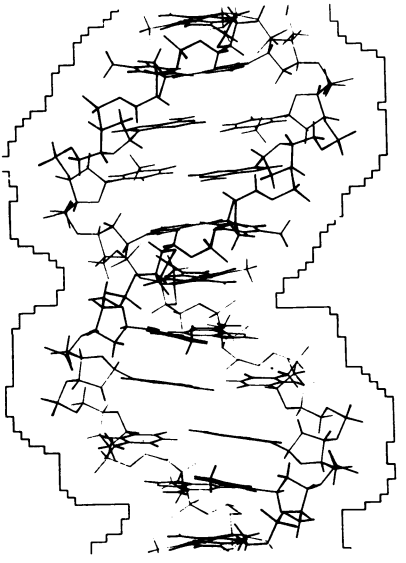
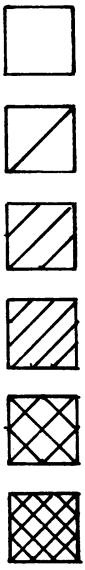


FIGURE 7. Molecular graphic of poly (dA-dT) . poly (dA-dT) in the alternating-B DNA conformation.

FIGURE 8. Surface potentials of poly (dA-dT) . poly (dA-dT) in the alternating-B DNA conformation (for details of shading see table 3).

TABLE 3. Shadings used for the surface potential graphics of the different DNA conformations (values in kcal/mole).

| SHADING | B-DNA | D-DNA | Alternating-B DNA |
|---|---|---|---|
|  | -483 | -430 | -446 |
| | -507 | -456 | -472 |
| | -532 | -482 | -499 |
| | -557 | -508 | -525 |
| | -582 | -534 | -552 |
| | -607 | -560 | -579 |
| | -632 | -587 | -606 |

The results for B-DNA show a concentration of negative potentials in the grooves of the double helix with the deepest potentials occuring in the minor groove (in the upper half of figure 4), as has already been noted for this conformation in our previous publications (7, 8, 12). This result is substantiated by the minima of the surface potentials in each groove, indicated in table 4, which show a 32 kcal/mole difference in favour of the minor groove. D-DNA also exhibits the greatest concentrations of potential in the grooves, but, as figure 6 shows, the more negative potentials appear in the major groove. This is confirmed by the surface minima in table 4 where one may note a 25 kcal/mole difference in favour of this groove for this conformation. This result may seem to be in conflict with the one for the site potentials of the bases where N3(A) and O2(T), both in the minor groove, were associated with the deepest potentials for this form. The explanation can be deduced from the mole-

TABLE 4. Surface potential minima for the different DNA conformations of poly $\overline{(dA-dT)}$ . poly (dA-dT).

| CONFORMATION | MINOR GROOVE MINIMUM (kcal/mole) | MAJOR GROOVE MINIMUM (kcal/mole) |
|---|---|---|
| B-DNA | -631 | -599 |
| D-DNA | -561 | -586 |
| Alternating-B DNA | -605 | -572 |

cular graphic of D-DNA in figure 5, where the narrowness of the minor groove, in the upper half of the figure, is evident. The bases in this groove are almost entirely hidden by the extremely close sugar-phosphate backbones and consequently the stronger potentials associated with the sites N3(A) and O2(T) are occluded from the surface envelope. This result correlates with the very low calculated accessibilities of these sites or the relatively weak surface minima calculated for D-DNA which do not reflect its rather strong site potentials.

The surface potentials for the alternating-B DNA in figure 8 are much closer to those of B-DNA. The associated surface minima in table 4 show the more negative potentials to be located in the minor groove with a difference of 33 kcal/mole with respect to the major groove, almost exactly that calculated for B-DNA. The surface potentials are, however, altogether roughly 30 kcal/mole weaker in alternating B-DNA than in B-DNA. This situation parallels the weaker site potentials calculated for alternating-B DNA with respect to B-DNA.

## CONCLUSIONS

The potentials and accessibilities associated with the bases and phosphates of poly (dA-dT). poly (dA-dT) have been presented for three conformations envisaged for this double helix. The question which may now be considered is whether these results may contribute to the identification of the biologically significant conformer and to the elucidation of the particularities of its behavior.

In connection with this situation we may recall first that among the reasons which incited Klug et al. (22) to suggest the alternating-B form for poly

(dA-dT) . poly (dA-dT) was the increased affinity of this polynucleotide, with respect to bulk DNA, for the lac repressor. Our results do not enable a definite identification of the structural factors which could be responsible for this phenomenon although they do eliminate some potential candidates. Thus, the lac repressor has been shown to bind to the minor groove of the double helix (33). Under these conditions, one can consider a priori as possible factors involved in the increased recognition of poly (dA-dT) . poly (dA-dT), either the properties of the surfaces of the bases in this groove or the properties of its deoxyribose-phosphodiester backbone. The examination of our results concerning the values of the minima at the surface potentials of the three forms (table 4), of the potential minima at their N3(A) and O2(T) sites or of their accessibilities to these sites (table 1) do not lead us to expect an increased reactivity for the alternating-B form. Neither does the examination of the bridge site potentials of the phosphates (table 2). On the other hand, the study of the accessibilities to the phosphates indicates that the O5', OL and OR sites are more accessible in alternating B-DNA that in the other two forms considered here (table 2). The computations also show that alternating-B DNA, unlike either of the other two conformations, exhibits different accessibilities for the esteric oxygens of the ApT and TpA phosphates. Whether these factors play a role in the increased recognition of the lac oppressor by poly (dA-dT) . poly (dA-dT) sequences remains an open question.

On the other hand, a much more significant and clear-cut result may be established in connection with another problem, namely, the binding of the antibiotics netropsin and distamycin A to double stranded DNAs. These molecules are found to bind non-intercalatively on the surface of B-DNA and show a marked preference for the minor groove of A-T rich base pair sequences (34-37). In the proposed representation of the binding, hydrogen bonds are considered to be formed between the NH groups of the peptide links of the antibiotics and O2 of thymines and N3 of adenines and also between the positively charged propionamidine group(s) of the antibiotics and the phosphate oxygens of the double helix.

Through a theoretical investigation of the factors responsible for the variation of the affinity of these antibiotics for different types of synthetic polynucleotides we have been able to show (38-39) that the existence and the extent of this affinity may be correlated with the existence and the value of a deep electrostatic potential in the minor groove of these double helices and the accessibility to the "anchoring" sites of this preferred groove, N3 of the purines and O2 of the pyrimidines.

The present computations on poly (dA-dT). poly (dA-dT) enable the exten-

sion of the correlation to this polymer and the identification of the form involved. The basis for this extension is the experimental result indicating that the binding of the antibiotics is stronger to poly (dA) . poly (dT) than to poly (dA-dT) . poly (dA-dT) (35). We recall (12) just that in the synthetic complementary homopolymer, considered to be in the B-DNA form, the deepest surface potential is in the minor groove and has the value of - 625 kcal/mole. It is obvious from the comparison of that value with those of table 4 that the reduced affinity of the antibiotics for the alternating copolymer can be accounted for if the copolymer is assumed to be in the alternating-B form, in which the potential minimum in the minor groove amounts only to - 605 kcal/mole. Should the copolymer be in the B-form its affinity toward the antibiotics would have been greater than that of poly (dA) . poly (dT). The D form is ruled out as a possible receptor form because it has its main surface minimum in its major groove, a situation shown to be incompatible with reactivity toward these antibiotics (38, 39). This result simultaneously supports our theory on the importance of the potential in the minor groove of the double helices for their affinity for netropsin and distamycin A and the proposal that poly (dA-dT) . poly (dA-dT) exists preferentially in the alternating-B form.

The consideration of the potentials at the "anchoring" sites, N3(A) and O2(T), in the different forms lends further support to the above proposal. Their values are - 669 and - 663 kcal/mole, respectively, in poly (d A) . poly (d T), and - 653 and -642 kcal/mole, respectively, in the alternating-B form of poly (dA-dT) . poly (dA-dT) (while their values in the B-form of poly (dA-dT) poly (dA-dT) are - 676 and - 665 kcal/mole, respectively). The accessibilities to N3(A) and O2(T) are satisfactory in all these helices and altogether slightly greater for the alternating-B form of poly (dA-dT) . poly (dA-dT) than for poly (dA) . poly (dT). Obviously, as indicated previously (38) the accessibility, provided it is sufficiently great, plays a secondary role in determining the order of affinities.

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