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Extra-helical guanine interactions in DNA☆

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Abstract

We review the extra-helical guanine interactions present in many oligonucleotide crystals. Very often terminal guanines interact with other guanines in the minor groove of neighboring oligonucleotides through $N_2 \cdot N_3$ hydrogen bonds. In other cases the interaction occurs with the help of Ni^{2+} ions. Guanine/netropsin stacking in the minor groove has also been found. From these studies we conclude that guanine may have multiple extra-helical interactions. In particular it may be considered a very effective minor groove binder, which could be used in the design of sequence selective binding drugs. Interactions through the major groove are seldom encountered, but might be present when DNA is stretched. Such interactions are also analyzed, since they might be important for homologous chromosome pairing during meiosis.

Keywords: Guanine; Netropsin; Nickel; DNA; Oligonucleotides; Genetic recombination

1. Introduction

The study of chromosomal telomeres has shown that they contain unique DNA sequences, repeated many times, which may have peculiar structures, involving G_4 and $(CG)_2$ quadruplex associations. These associations of guanine have been recently reviewed [1]. However, in view of the interest of guanine interactions, it appears to be timely to review other kinds of extrahelical associations of guanine which have been found during the study of oligonucleotide crystals in our laboratory and elsewhere.

Most of the oligonucleotides which have been crystallized have C·G base pairs at both ends, which in many cases show extra helical interactions, often with a disruption of the C·G pair. Such extra helical interactions undoubtedly contribute to stabilize the three-dimensional organization of the crystal.

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On the other hand very few oligonucleotides with terminal A·T base pairs have been crystallized. The fact that adenine has fewer hydrogen bond forming sites than guanine and is much more soluble in water [2] may explain that sequences with terminal AT base pairs might be more difficult to crystallize. In any case it cannot be excluded that adenine might also form extra helical associations, but little information is available on that matter.

As an example of the wide potential of guanine to form hydrogen bonds, the structure of guanine itself is shown in Fig. 1. Each guanine is hydrogen bonded to three other guanines and two water molecules, so that all the hydrogen bonding sites of guanine are involved in the crystal structure. All hydrogen bonded guanines lie in infinite planes which are stacked as in graphite, showing the high tendency of guanines to form continuous stacks.

2. Methods

Coordinates for the structures reported are available either in the Cambridge Structural Database [3] or in the Nucleic Acid Database (NDB) [4]. Drawings have been prepared with the Cerius [5] and SETOR [6] programmes. Optimization of the structure of parallel DNA has been carried out with the XPLOR programme, version 3.851 [7]. For this purpose the coordinates of Yagil and Sussman [8] were taken as the starting model. The DNA sequence was changed and a 12 base pair duplex was sheared in order to diminish to approximately 22° the inclination of the base pairs with respect to the axis of the duplex. The conformation was then optimized with the C1′ atoms fixed, so that a fixed average inclination of the bases was maintained. As a result of this process the base pairs become buckled with a significant propeller twist. The phosphodiester backbone shows an alternating conformation (see Fig. 7a below). It should be noted that the conformation obtained does not correspond to a free energy minimum, since energy contributions due to stretching are not taken into account. The only purpose of these calculations has been to obtain a stereochemically correct model with a limited inclination of the base pairs. The coordinates obtained are given as supplementary material. In vivo, a parallel conformation would be influenced by the stretching forces and proteins present.

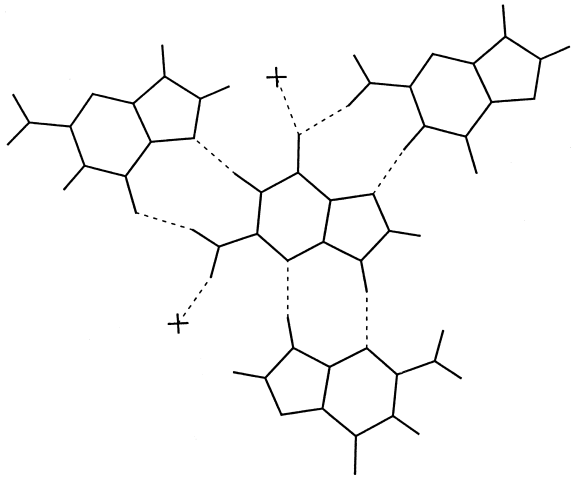

Fig. 1. Hydrogen bonding in guanine crystals [59]. Water molecules are shown by crosses. Each guanine has all its eight hydrogen bonding sites saturated, as indicated for the central guanine. Coordinates have been obtained from the Cambridge Structural Database [3].

3. Results and Discussion

3.1. Extra-helical interactions of terminal guanines in A and B form DNA crystals

Four typical-interactions are shown in Figs. 2 and 3. In the first dodecamer crystallized in the B-form [d(CGCGAATTCGCG)] individual duplexes build infinite columns which are stabilized by a close contact of their minor grooves, which involves $N_2 \cdot N_3$ hydrogen bonding among the guanines in the two terminal base pairs [9]. This type of interactions has been found in many other cases, as reviewed elsewhere [10]. The C·G base pair is usually present, but in some cases [11,12] the terminal cytosine is disordered, which indicates that the essential interaction takes place through the guanine residues.

More recently in a decamer with a related sequence it has been found [13] that terminal guanines may abandon its paired cytosine and

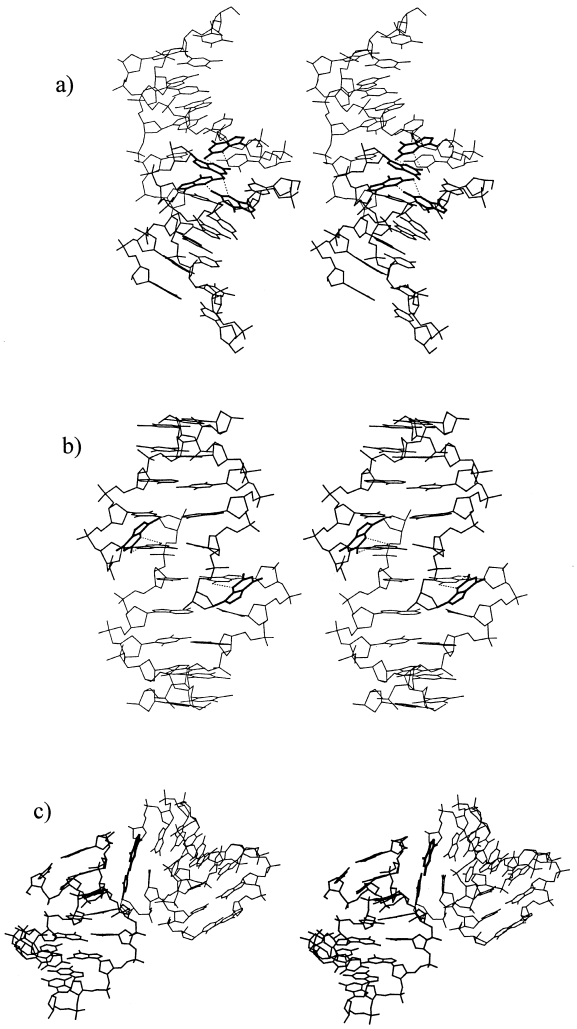

Fig. 2. Stereoviews of extra-helical associations of the terminal guanines in the narrow groove of a neighboring duplex in DNA crystals: (a) pairing of guanines in the two terminal base pairs of d(CGCGAATTCGGG). The data of Shui et al. [60] obtained from the Nucleic Acid Database [4] have been used; (b) interaction of the terminal guanine in d(CGTATATACG) [22]; (c) Van der Waal's interaction of the terminal CG base pairs with the phosphodiester backbone in the A-form [61].

invade the minor groove of a neighboring duplex. Again $N_2 \cdot N_3$ hydrogen bonds are formed with another guanine, as it is shown in Fig. 2b. This type of interaction may occur in crystals of the same dodecamers which show the interaction described in the previous paragraph, although crystallized in a different space group and in the presence of different counterions [14]. In fact the terminal guanine interacts with the second guanine of a neighboring duplex, as in the previous case. However, the relative orientation of the duplexes and of the interacting guanines is quite different in either case, as it is apparent by comparison of Fig. 2a,b.

A third type of interaction which also involves the minor groove is found in A-form DNA crystals, as reviewed by Tippin and Sundaralingam [15]. In that case the terminal C·G base pair is apposed onto the minor groove of a neighboring oligonucleotide. The interaction is mainly stabilized by van der Waal's forces with the phosphodiester backbone, since hydrogen bonds are not always present. An example is shown in Fig. 2c.

Triple helix formation by terminal guanines is a fourth case to be considered. It is found when a sequence such as d(GCGAATTCG) is crystallized [16,17]. This nonamer sequence forms a duplex with another nonamer. The duplex formed has the first guanine residues at both ends unpaired. The unpaired guanines form a triple helix with the last CG base pair of a neighboring duplex, as shown in Fig. 3. Such an interaction was first described in a receptor/DNA complex [18]. A similar triple helix has also been found in a longer oligonucleotide [19].

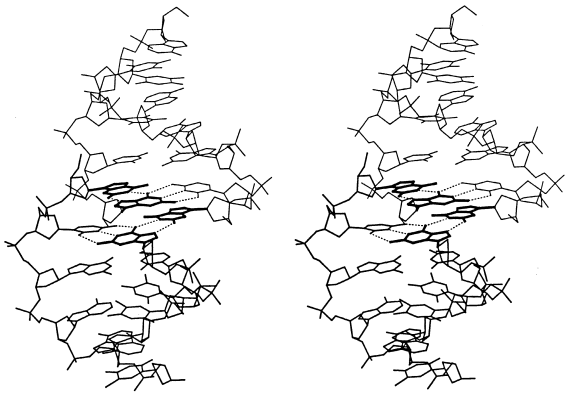

Fig. 3. Stereoview of triple helix formation between neighboring d(GCGAATTCG) duplexes [17].

3.2. The recombination-like structure of CCGCGG

In our laboratory we also found [20] that the oligonucleotide d(CCGCGG) crystallizes with its central tetramer in the Z-form, whereas the terminal bases form Watson–Crick hydrogen bonds with a neighboring molecule in the crystal lattice. The extra-helical C·G base pair is in the B conformation, a feature which suggested that a similar structure could be formed during site-directed recombination. Although this is also an

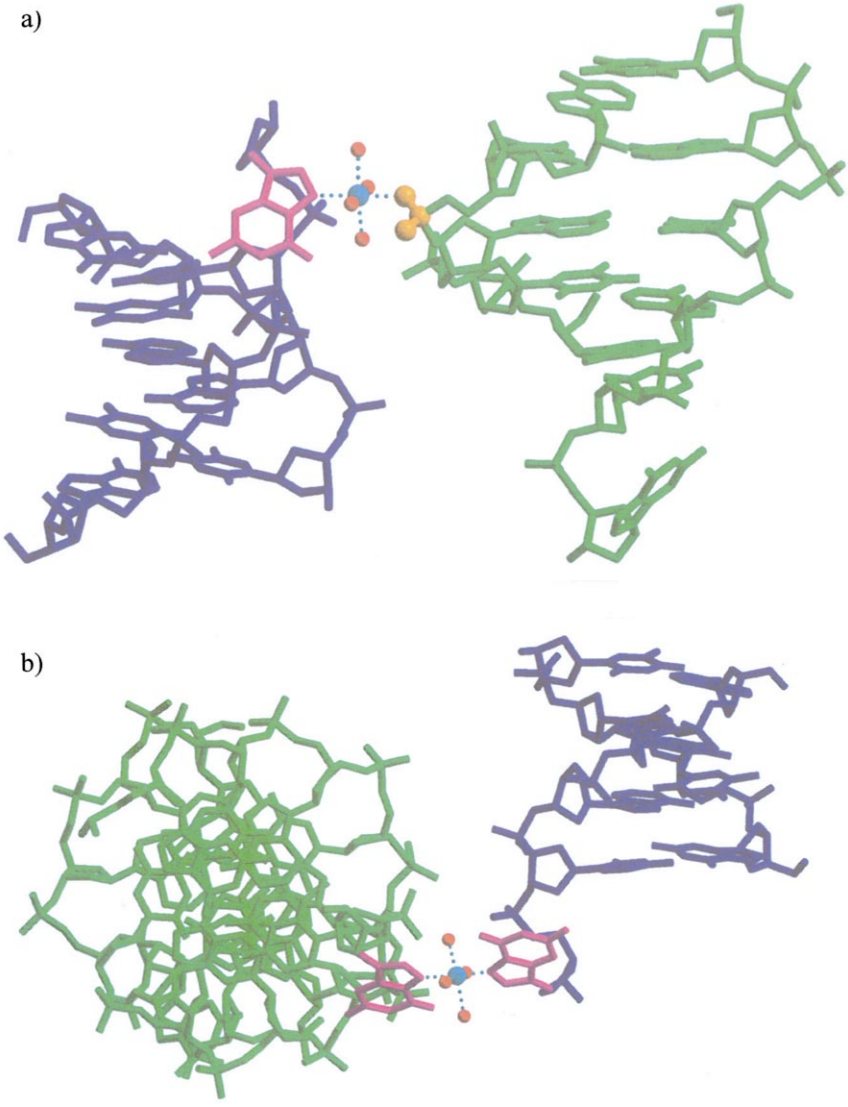

Fig. 4. Ni^{2+} mediated guanine interactions in oligonucleotide crystals: (a) guanine-phosphate interactions in the orthorhombic crystal form of d(CGTATATACG) [22]; (b) guanine–guanine interaction in the tetragonal form of the same duplex [21]. The duplexes are perpendicularly oriented, whereas the guanines that interact lie on the same plane. Water molecules are shown as red spheres, Ni^{2+} ions in light blue and the interacting phosphate group in brown. The guanines that interact through Ni^{2+} are shown in violet.

extra-helical interaction of guanine, only standard Watson–Crick base pairs are formed.

3.3. Interactions of guanine through Ni^{2+} ions

Recently in our laboratory we have crystallized the oligonucleotide d(CGTATATACG) in the presence of Ni^{2+} ions [21,22]. As expected the ions are associated with the N_7 atom of guanines [23]. In some cases solvated Ni^{2+} ions are attached to the oligonucleotide without showing any further interactions. However, in other cases they may interact with neighboring molecules in the crystal lattice, as shown in Fig. 4. The Ni^{2+} ion may form either guanine–guanine or guanine-phosphate bridges between two neighboring duplexes. Such interactions undoubtedly stabilize the crystal matrix and might be related to the toxicity of Ni^{2+} ions [24].

3.4. Guanine–netropsin stacking

In order to improve the quality of our crystal data on d(CGTATATACG) [21], we decided to crystallize it in the presence of netropsin [22]. To our surprise, a different space group was found with a quite different crystal organization. In particular one of the terminal guanines invaded the minor groove of a neighboring oligonucleotide and became stacked on netropsin, as shown in Fig. 5. Such an interaction is reminiscent of the minor groove binding features of some drugs, which may associate in tandem forming a double stack in the minor groove [25].

In this case guanine is stacked between the netropsin drug and the phosphodiester backbone of the duplex. At the same time its N_2 and N_3 atoms form hydrogen bonds with consecutive adenine and thymine bases of an AT step, as shown in Fig. 5.

3.5. Guanine as a minor groove binder

As shown in Fig. 2b and Fig. 5 guanine has several modes of binding inside the narrow groove, either associated with guanine or with adenine–thymine through hydrogen bonding. The interaction is further stabilized by van der Waal's contacts with the phosphodiester backbone and stacking with netropsin in one case. Thus, it appears that guanine might be a useful compound to consider in the design of sequence selective minor groove binding drugs.

An important feature of guanine–guanine interactions is that they are often not coplanar. Interactions at the minor groove (Fig. 2a,b) involve either guanine molecules or G·C base pairs which are not coplanar and, furthermore, the relative orientation of guanine rings is different in each case. These observations indicate that guanine–guanine hydrogen bonds may form in a variety of orientations, a feature which is of inter-

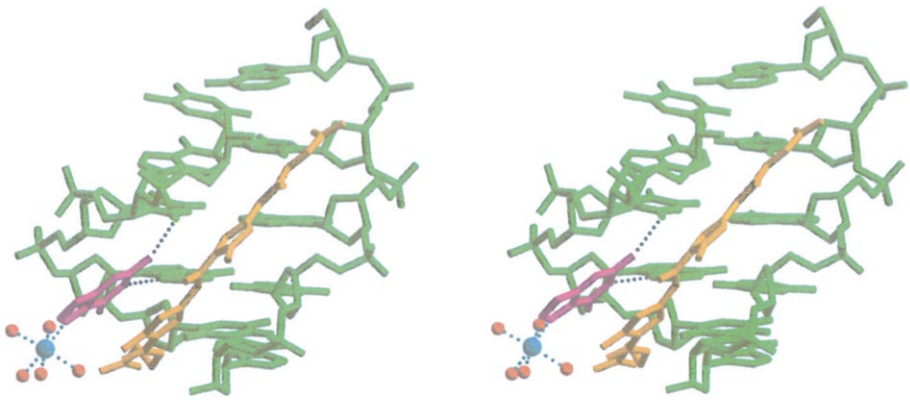

Fig. 5. Stereoview of guanine (violet) stacking on netropsin (brown) in the narrow groove of a d(CGTATATACG) duplex [22]. The guanine forms hydrogen bonds (black dotted lines) with adenine and thymine. A hydrated Ni^{2+} ion associated with guanine is also shown in the figure.

est for the model we will show in the last part of this paper.

3.6. Minor groove vs. major groove interactions of guanine

The interactions we have described always take place on the minor groove side of guanine. Similar minor groove–minor groove interactions of C·G base pairs have also been described in a DNA hairpin [26]. Again in this case the C·G base pairs involved are not coplanar, they form an angle of approximately 40°. On the other hand, interactions involving the major groove of guanine have not been found thus far in oligonucleotide crystals. However, they have been described in a quadruplex structure studied by NMR [27] and in co-crystals of cytosine and guanine derivatives [28,29]. The eventual interaction through the major groove offers great interest, since the pattern of hydrogen bonding might allow a recognition of identical Watson–Crick base pairs as shown in Fig. 6. This type of interaction has been suggested by several authors [30–33] as a possibility for the recognition of identical DNA molecules during genetic recombination in meiosis, a question which we will now review. It should be noted that the four possible quadruplexes are stereochemically equivalent, so that a continuous tetrastranded DNA with any sequence could be built as we will show below.

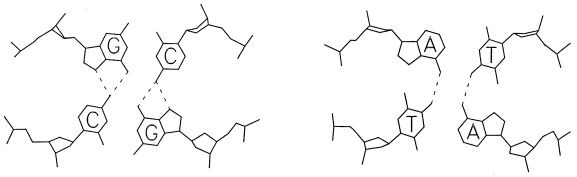

Fig. 6. Quadruplex structures with major–major groove interaction: (a) observed by NMR in a triple repeat quadruplex structure [27], the amino group of cytosine interacts by hydrogen bonding with two acceptor atoms of a neighboring guanine; and (b) a similar interaction which might be present in AT base pairs. Watson–Crick hydrogen bonds between base pairs are not shown. In order to diminish the steric interference of the thymine methyl groups, the base pairs should show either propeller twisting, inclination or both (not shown in the figure).

3.7. Homologous recombination in meiosis

While the molecular structures involved in site-specific recombination are rather clear [34], little is known about the detailed molecular events in homologous meiotic recombination. During meiosis homologous chromosomes are paired, a process which requires that identical sequences of double stranded DNA recognize each other. In a later stage recombination takes place, which occurs at a high level in 'hot spots'. Double strand breaks (DSB) occur in the neighborhood of these hot spots, which appear to have no sequence specificity [35]. The known molecular events associated with these processes have been discussed by different authors [36–39], where reference to previous extensive reviews is also given. In bacteria recombination appears to be facilitated by the RecA protein, as discussed for example by Malkov and Camerini-Otero [40]. In eukaryotes this process appears to be different [38]. Nevertheless many proteins which play a role in strand exchange have been described in different species [41–48], some of which appear to be related to the bacterial RecA protein. On the other hand very little is known about the initial process of homologous chromosome pairing. Several proteins appear to be involved in this process [47,48], but the details of their mode of action are not clear. According to Kleckner [36,49] direct homologous DNA–DNA contacts between intact duplexes are facilitated by proteins, but no known RecA homolog is involved.

3.8. Stretched DNA

Stretching the DNA molecule may facilitate its interaction with homologous sequences. Stretched DNA has been recently studied by different authors [50,51] who have demonstrated that individual DNA molecules can be stretched in a reversible manner without breaking with a maximum increase in length of approximately 70%. If the force is increased, very little further stretching is achieved. The change in length observed corresponds to an increase in the rise per base pair from 3.4 to 5.8 Å. Since stretched DNA appears to have both strands parallel and the

bases exposed, it is of interest to determine whether such stretched DNA might be able to associate with an homologous molecule and form a tetrastranded DNA molecule with the four DNA strands organized in a parallel fashion.

DNA stretching has been modelled by different authors. Lebrun and Lavery [52] find that upon stretching the Watson–Crick base pairs are disrupted and individual bases form hydrogen bonds with non-complementary bases. These authors have carried out a very detailed analysis, allowing different degrees of stretching (up to 90%) by pulling DNA both at the 3′–3′ and 5′–5′ ends. Different sequences of DNA have also been studied. Konrad and Bolonick [53] have modelled the distortion of DNA under the influence of a force and find a considerable distortion of the DNA, with an increase in length of over 100%. The Watson–Crick base pairs are partially preserved. From these model studies it is not clear up to what extent Watson–Crick base pairing is maintained upon stretching DNA.

A related model was presented several years ago by Yagil and Sussman [8], who aimed to obtain a model for non-helical DNA. However, their model can be considered as an alternative for stretched DNA. A similar model was already considered by Watson and Crick [54] as an eventual solution to the replication problem of the double helix.

These various models can be used to interpret the fiber diffraction diagrams of stretched DNA obtained by Wilkins (reported by Arnott, [55]) and Fornells et al. [56]. The experimental diagrams are rather poor. They show a single layer line at a spacing of approximately 6 ± 0.6 Å with a single off-meridional spot. A sharp equatorial spot at 13.3 ± 0.9 Å is also present. These features are consistent with the various models which have been proposed and which have been discussed in the previous paragraphs. The presence of a single layer line at approximately 6 Å with an off-meridional maximum indicates that the bases are parallel and inclined, with a displacement along the molecular axis of 6 Å.

A conspicuous feature of the experimental fiber diagrams is the very well defined equatorial spot mentioned above, with a spacing much smaller than the 20 Å found in helical DNA. This feature in itself is a strong argument in favour of a parallel arrangement of the DNA strands, since the projection of DNA has a much smaller cross-section.

3.9. A tetrastranded from of DNA may appear during meiosis

The parallel, stretched DNA molecules may associate through their major grooves in a specific manner, using the hydrogen-bonding schemes shown in Fig. 6. A possible model is presented in Fig. 7. It should be noted that in such models only a moderate inclination of the bases is allowed, further inclination will interfere with specific hydrogen bond formation. So the DNA molecules cannot be fully stretched. Thus, quadruplex formation appears to be optimal with partially stretched molecules, far from the 70% maximum value experimentally observed as described in the previous section.

In the model shown in Fig. 7, the interaction between homologous base pairs is not coplanar, whereas in the triple repeat quadruplex structure [27], shown in Fig. 6, the bases are coplanar. However, as we have discussed in the first part of this paper, quadruplexes are not always coplanar, as it is evident in Fig. 2a, and it has been found in a hairpin [26] and in a related cyclic oligonucleotide [57].

The evidence reviewed shows that pairing between homologous DNA sequences might be possible through the major groove if moderately stretched DNA molecules are involved. In fact there is some evidence that DNA is stretched in the synaptonemal complex [39,49]. Such tetrastranded pairing scheme will allow pairing of homologous DNA duplexes of any sequence which are locally stretched. Since pairing requires untwisting of the double helix, only short DNA sequences should be expected to participate in quadruplex formation. The process would be facilitated by a break in one of the DNA strands involved. Such quadruplex regions would be expected to be widely spaced along the chromosome. In fact Kleckner [49] has estimated that interstitial interactions occur once every 65 kb on

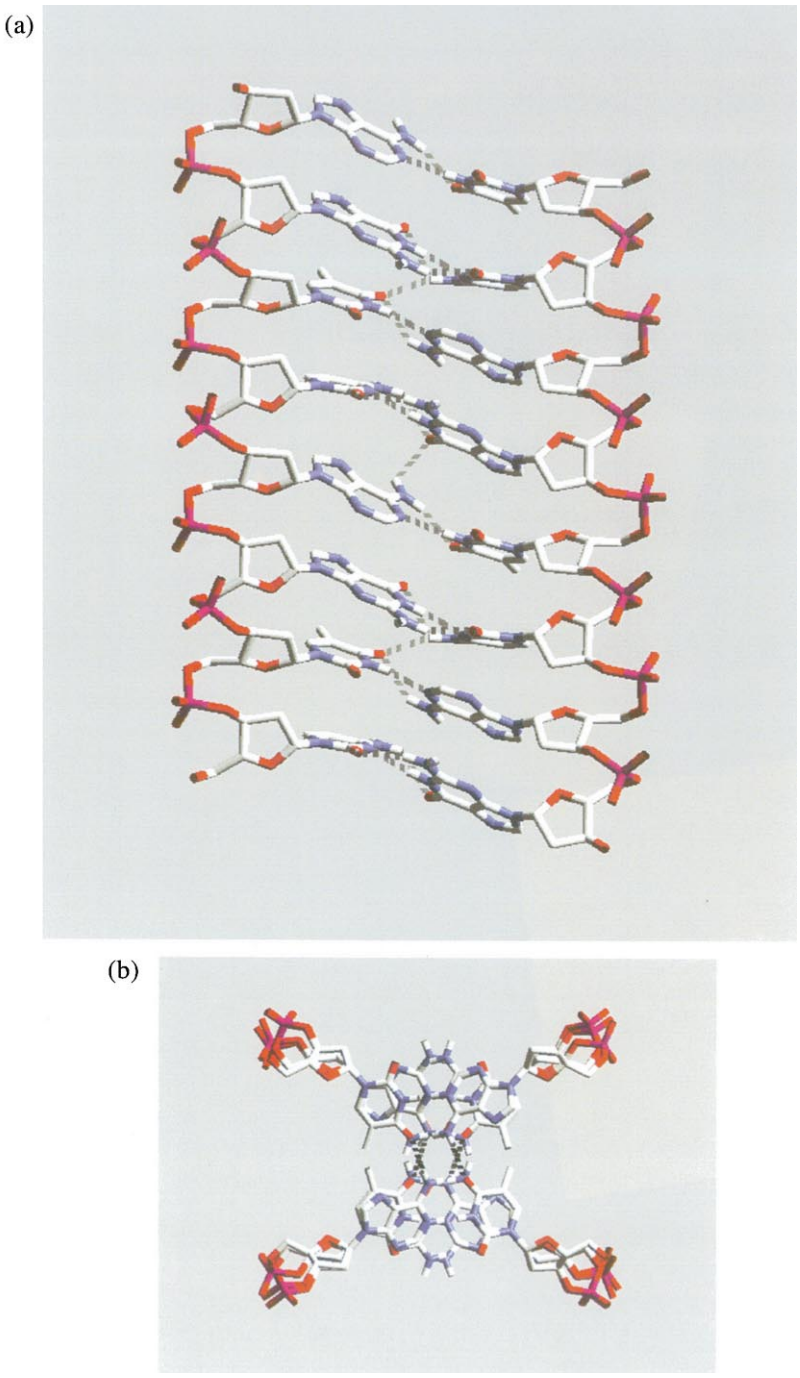

Fig. 7. (a) Parallel conformation of a DNA duplex with the sequence d(TCAGTCAG). Watson–Crick hydrogen bonds are indicated as dashed lines, some additional bifurcated hydrogen bonds are also present. (b) Tetrastranded model formed by two such duplexes viewed in projection. Only hydrogen bonds formed between the two duplexes are shown in this case. The quadruplexes in this model are not planar, but show a significant inclination, similar to that found in a cyclic oligonucleotide [57].

the average. In *Drosophila* it has also been found [58] that chromosome pairing proceeds through multiple independent initiations at random points. Nevertheless, further evidence is required in order to determine if tetrastranded DNA molecules are actually formed during meiosis.

Alternatively specific sequence dependent local conformations may be involved, as the bi-loop [57], local Z-DNA formation [20] or other peculiar DNA associations. Whatever the mechanism used for specific DNA recognition in meiosis, it is likely that the process will be facilitated by proteins whose mode of action remains to be discovered.

Acknowledgements

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