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DNA architecture: from G to Z

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Abstract

G-quadruplexes and Z-DNA are two important non-B forms of DNA architecture. Results on novel structural elements, folding and unfolding kinetics, and interactions with small molecules and proteins have been reported recently for these forms. These results will enhance our understanding of the biology of these structures and provide a platform for drug design.

Introduction

Besides the canonical right-handed double helix (B-DNA) first proposed by Watson and Crick, DNA can adopt other biologically relevant structures. Four-stranded structures (G-quadruplexes) and left-handed duplexes (Z-DNA) are two important examples. Although both these structures were first discovered several decades ago [1•,2•], they have recently received particular attention, as their biological relevance has become more clear. Here, we review the latest studies on G-quadruplex and Z-DNA structures published between 2003 and 2005.

G-quadruplex structures

Guanine-rich oligonucleotides can form four-stranded G-quadruplex structures through the stacking of planar G-tetrads [1•]. Cations, such as K^+ or Na^+, stabilize G-quadruplexes by coordinating electronegative carbonyl groups of guanines, which are directed towards the interior of G-tetrads. Because of the size difference, Na^+ ions are positioned mainly in the plane of the G-tetrads, whereas K^+ ions are positioned between G-tetrad planes. G-quadruplex architecture is dependent on the nature of cations and, generally, K^+ stabilizes G-quadruplexes better than Na^+. G-quadruplexes are highly polymorphic, as regards three mutually related factors: the orientation of the strands, the *syn/anti* glycosidic conformation of guanines and the loop connectivities. Oligonucleotides containing one, two or four G-stretches can form tetrameric, dimeric or monomeric G-quadruplexes, respectively [1•,3,4]. In dimeric and monomeric G-quadruplexes, loops connect G-stretches. These loops can be classified into four major families: edgewise loops connecting two adjacent antiparallel strands (Figure 1a), diagonal loops connecting two opposing antiparallel strands (Figure 1b), double-chain-reversal loops connecting adjacent parallel strands (Figure 1c) and V-shaped loops connecting two corners of a G-tetrad core in which one supporting column is lacking (Figure 1d). These various loop motifs, in combination with different strand orientations and

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syn/anti distributions, have been found in many different monomeric (intramolecular) and dimeric G-quadruplexes [1•,3,4].

New topologies

Telomeric DNA has probably attracted the greatest attention of G-quadruplex researchers because of the natural existence of a G-rich single-strand overhang at telomere 3′ ends and its relevance to a potential anticancer strategy. The first solution structure of a four-repeat human telomeric sequence, d[AGGG(TTAGGG)$_3$], was characterized in 1993 by NMR in Na^+ solution [5]. This sequence forms an intramolecular G-quadruplex involving three stacked G-tetrads with *anti*•*anti*•*syn*•*syn* alignments around each tetrad. Three connecting TTA loops adopt successive edgewise, diagonal and edgewise alignments, such that each strand has both parallel and anti-parallel adjacent strands (Figure 2a). A decade later, Parkinson *et al*. [6] reported the crystal structure of a completely different G-quadruplex formed by the same sequence in the presence of K^+. In this structure, known as ‘propeller type’, all four strands are parallel, the connecting TTA loops are double-chain-reversal motifs and all guanines adopt *anti* glycosidic conformations (Figure 2b). This latter structure was very different from all G-quadruplexes reported previously, and could readily facilitate higher order telomere folding and unfolding [6]. However, data on the same human telomeric sequence in K^+ solution, derived using different physical and chemical techniques, and reported in a large number of subsequent papers, indicated the presence of a mixture of several G-quadruplex forms [7••,8–12,13•,14•].

For the two-repeat human telomeric sequence d(TAGGGTTAGGGT), both parallel (Figure 2c) and antiparallel G-quadruplexes (Figure 2d) were found to co-exist and interconvert in K^+ solution [7••]. The parallel-stranded structure is symmetrical and similar to the ‘propeller-type’ G-quadruplex crystal structure [6], with double-chain-reversal loops and all *anti* guanines (Figure 2c). The antiparallel-stranded structure is asymmetrical, with all adjacent strands antiparallel, two edgewise loops and *syn*•*anti*•*syn*•*anti* G-tetrad alignments (Figure 2d).

The two-repeat *Tetrahymena* telomeric sequence d(TGGGGTTGGGGT), which differs from the human sequence by only one G-for-A replacement in each repeat, interconverts between two asymmetric dimeric G-quadruplex structures in Na^+ solution (Figure 2e,f) [15]. Both structures include a core of four stacked G-tetrads and two edgewise loops. The adjacent strands of the G-tetrad core are alternately parallel and antiparallel. All G-tetrads adopt *syn*•*syn*•*anti*•*anti* alignments, which occur with 5′-*syn*-*anti*-*syn*-*anti*-3′ alternations along G-tracts. In the first structure (head-to-head), two loops are at one end of the G-tetrad core (Figure 2e); in the second structure (head-to-tail), two loops are located on opposite ends of the G-tetrad core (Figure 2f).

The three-repeat human telomeric sequence d(GGGTTAGGGTTAGGGT) forms an asymmetric dimeric quadruplex in Na^+ solution, in which the G-tetrad core involves all three G-tracts of one strand and only the last 3′-end G-tract of the other strand (Figure 3a) [16••]. A three-repeat human telomeric sequence can also associate with a single-repeat human telomeric sequence, forming a structure with the same topology called a (3+1) quadruplex assembly. In this G-quadruplex assembly, there are one *syn*•*syn*•*syn*•*anti* and

two *anti•anti•anti•syn* syn G-tetrads, two edgewise loops, and three G-tracts oriented in one direction and the fourth in the opposite direction. This is the first G-quadruplex structure shown to involve the heterodimeric association of two strands of such different lengths. There is striking similarity between this (3+1) G-tetrad core and the core of both the four-repeat *Tetrahymena* telomeric $d(T_2G_4)_4$ sequence reported in 1994 (Figure 3b) [17] and a variant of the four-G-tract segment of the human *bcl-2* promoter reported in 2006 [18•].

Recently reported G-quadruplex structures formed by non-telomeric G-rich sequences also revealed a number of new structural features. Double-chain-reversal or propeller-type parallel-stranded G-quadruplexes were observed in K^+ solution for G-rich sequences containing four G-tracts from the *c-myc* promoter [19•,20•,21]. Besides loops containing two or six residues, single-residue (A or T) double-chain-reversal loops were observed systematically to bridge three layers of G-tetrads [19•]. This study suggested that a one-residue loop forms the most stable double-chain-reversal loop bridging three G-tetrad layers and a six-residue loop is less stable than a two-residue loop [19•], in agreement with the results of a simulation study [22•]. More recent studies [23••,24••] showed that the structure of single-residue double-chain-reversal loops bridging three G-tetrad layers does not depend much on the nature of the single base, either T or A.

A five-G-tract sequence from the *c-myc* promoter was found to adopt a distinct novel parallel-stranded fold-back G-quadruplex topology in K^+ solution (Figure 4a) [23••]. The study revealed several new structural motifs not observed previously. In particular, a guanine (G24) from the 3′ end is plugged back into the G-tetrad core by participating in G-tetrad formation and displacing another guanine (G10) of a continuous G-tract into a loop. This configuration is stabilized by formation of a diagonal loop, which contains a G•(A-G) triad that stacks on and caps the G-tetrad core. These new folding features are direct consequences of the presence of five G-tracts in the sequence [23••], in contrast to the four G-tracts in the sequences studied previously [19•,20•,21].

The *93del* d(GGGGTGGGAGGAGGGT) oligonucleotide, an inhibitor of HIV-1 integrase, was shown to form a very stable twofold-symmetric dimeric quadruplex in K^+ solution [24] (Figure 4b). Each monomer subunit contains two G•G•G•G tetrads and one A•(G•G•G•G) pentad, in which all the G-stretches are parallel and linked by three single-nucleotide double-chain-reversal loops. Dimer formation is achieved through the mutual pairing of G1 of one monomer with G2, G6 and G13 of the other monomer, to complete G•G•G•G tetrad formation. The compact interlocking of symmetry-related subunits through (3+1) G2•G6•G1•G13 tetrad formation across the dimeric interface (Figure 4b) constitutes an interesting feature of the *93del* architecture and highlights a new principle for robust dimeric quadruplex folding. Another example of the interlocking of two G-quadruplex subunits, in which one G-tetrad at the interface involves two guanines from each subunit, has also been reported [25].

The d(GCGAGAGC) sequence, which does not even contain a GG-tract, nevertheless adopts a novel eight-stranded topology in the crystalline state under low K^+ conditions (Figure 4c), in which G5 participates in G•G•G•G tetrad formation and A4 in A•A•A•A tetrad formation. In this multistranded topology, a given G-tetrad is intercalated between

flanking G- and A-tetrads, as a result of extension at the G4-A5 step [26•]. This intercalation feature has also been observed in the eight-stranded architecture formed by the r(U)d(^{Br}G)r(GUGU) sequence, which forms a mixture of U•U•U•U and G•G•G•G tetrads [27]. Intercalation of guanine residues as part of a G-tetrad by guanine residues of flanking G-tetrads has also been observed for the dimeric G-quadruplex formed by the d(GGGTTTTGGGG) sequence in solution (Figure 4d), whereby G1 is intercalated between an extended G8-G9 step [28•].

Folding and unfolding kinetics

Functions of nucleic acids depend not only on their structure and stability, but also on their dynamics. The folding and unfolding kinetics of G-quadruplexes have been studied for quite some time [29,30], but only recently have more quantitative data been obtained systematically for various sequences using different techniques [7••,8,31–33,34•,35,36]. In order to monitor and measure the unfolding rates of G-quadruplexes, Raghuraman and Cech, in their pioneering work [29], trapped the unfolded strand with the complementary C-rich strand. Adopting the same approach, Balasubramanian and coworkers [8,31] used fluorescence resonance energy transfer (FRET), Halder and Chowdhury [32], and Zhao *et al*. [33] used surface plasmon resonance (SPR), and Phan and Patel [7••] used NMR spectroscopy. The advantage of the last technique is that it enables the monitoring, at high resolution, of the simultaneous unfolding of different G-quadruplexes that coexist in solution, thereby obtaining the unfolding rates by single-exponential fits of signal decays [7••]. The advantages of the two former techniques are simplicity and small sample requirements; furthermore, FRET can allow measurements at single-molecule levels [8]. G-quadruplex unfolding can also be characterized using concentration-jump or temperature-jump approaches [7••].

Because the dissociation of G-quadruplexes is very slow, Mergny *et al*. [34•] used non-equilibrium denaturation curves obtained from UV spectroscopy to systematically determine the dissociation rates of a number of tetrameric G-quadruplexes. The association rates were also systematically measured. A study by Merkina and Fox [35] characterized the dissociation rates of tetrameric G-quadruplexes using fluorescence spectroscopy techniques. Petraccone *et al*. [36] used CD to characterize the association kinetics of quadruplexes formed by PNA/DNA chimeras. Recently, Lee *et al*. [14•] used single-molecule FRET spectroscopy to characterize the structure and dynamics of intramolecular human telomeric G-quadruplexes, and found that a four-repeat human telomeric sequence can exist in short-lived and long-lived states.

The general conclusions of these studies are the very slow folding (association) and unfolding (dissociation) kinetics of G-quadruplexes. The folding and unfolding times of a G-quadruplex depend strongly on the number of G-tetrads in the structure and on the presence of cations. They can range from few seconds to days or years at room temperature.

Interaction with small molecules

Because G-quadruplexes in both telomeres and oncogenic promoters have been established as promising anticancer targets [37,38], development of small molecules that interact with

and stabilize G-quadruplexes remains of great interest to a number of academic laboratories and pharmaceutical companies. Structures of some ligand–quadruplex complexes have recently been reported [23••,39•,40,41••] and should help the structure-based design of new drugs.

Clark *et al*. [39•] reported the crystal structure of a parallel G-quadruplex–daunomycin complex. In this complex, three daunomycin molecules stack on the 5′ end of the G-tetrad core, with daunosamine sugar moieties forming hydrogen-bonding interactions and/or van der Waals contacts with the quadruplex grooves (Figure 5a). Gavathiotis *et al*. [40] reported the NMR solution structure of the parallel G-quadruplex formed by the human telomeric sequence d(TTAGGGT) bound to two molecules of a fluorinated polycyclic methyl-acridinium salt. The structure shows that two ligand molecules stack on the two ends of the G-tetrad core; the partial positive charge of the ligands is positioned above and below the ion channel at the center of the G-tetrad core (Figure 5b).

The structure of a quinobenzoxazine–G-quadruplex complex has been characterized by solid-state NMR [42]. The study showed that the ligand stacks on the 3′ end of the G-tetrad core of the parallel-stranded G-quadruplex formed by the human telomeric sequence d(TAGGGTTA). Cocco *et al*. [43] used solution NMR to show that distamycin, a DNA duplex minor groove ligand, stacks on both ends of the G-quadruplex formed by the same sequence in K^+ solution.

Recently, Phan *et al*. [23••] reported the NMR solution structure of the complex between a G-quadruplex formed by a five-G-tract sequence from the *c-myc* promoter and the cationic porphyrin TMPyP4. In this structure, TMPyP4 is well defined and stacked on the top G-tetrad (5′ end of the parallel-stranded core), somewhat shifted towards one corner of this G-tetrad (Figure 5c). The positive charges of the ligand are in close contact with several negatively charged phosphates. The structure of this G-quadruplex–TMPyP4 complex revealed how stacking and electrostatic interactions contribute to the stability of the complex.

Haider *et al*. [41••] reported the crystal structure of the complex between a dimeric antiparallel G-quadruplex formed by the *Oxytricha* telomeric sequence d(GGGGTTTTGGGG) and a di-substituted aminoalkylamido acridine compound (Figure 5d). In this structure, the ligand is bound at one end of the G-tetrad core, within one of the T_4 diagonal loops. It is held in place by a combination of stacking interactions and specific hydrogen bonds with thymine bases.

The emphasis to date has been on aromatic-ring-containing ligands that have the potential to stack over terminal G-tetrads positioned towards either end of the quadruplex. Nevertheless, opportunities exist for targeting the four grooves of the quadruplex, whose width, depth and accessibility depend on strand alignment and connecting loop topologies. Clearly, double-chain-reversal loops occlude access to the grooves, but no such constraints exist for edgewise and diagonal loops. The Watson–Crick and major groove edges of a guanine are involved in G-tetrad formation, leaving the minor groove edge available for further recognition. Indeed, it has been shown that an adenine can align with the minor groove edge

of a G-tetrad guanine, to form a sheared G•A non-canonical pair, resulting in formation of an A•(G•G•G•G) pentad [24••]. The structure-based design of ligands tailor-made to target individual grooves of defined G-quadruplexes represents an ongoing challenge in the field.

Biological existence and functions

In nature, G-rich sequences are found in a number of important DNA regions, such as telomeres and centromeres, immunoglobulin switch regions and mutational hot spots, and act as regulatory elements within oncogenic promoters and as repeat elements implicated in triplet repeat expansion diseases. Recently, the prevalence of putative G-quadruplexes in the human genome has been systematically examined [44,45]. It has been found that as many as 376,000 potential quadruplexes could coexist. The possible existence and roles of G-quadruplexes *in vivo* have been corroborated by the detection of proteins that bind specifically to G-quadruplexes [46,47] and proteins that have biological activities, such as helicases [48] and nucleases [49], and are specific for G-quadruplexes.

Duquette *et al*. [50•] used EM to detect a novel DNA structure called the G-loop, which is formed during transcription when the non-template strand is guanine rich. G-loops contain G-quadruplex structures on one strand and a stable DNA–RNA hybrid on the other.

Among the most convincing evidence for the biological existence of G-quadruplexes is the generation of a G-quadruplex-specific antibody [51]. Using this antibody, Paeschke *et al*. [52••] have demonstrated G-quadruplex formation in the telomeres of nanochromosomes of *Stylonychia*. The authors showed that the telomere-end-binding proteins TEBPα and TEBPβ cooperate to control the formation of G-quadruplex structure in telomeres *in vivo*. Furthermore, such G-quadruplex formation is regulated by the cell-cycle-dependent phosphorylation of TEBPβ.

It has been shown that formation of intramolecular G-quadruplexes by the telomeric G-rich strand inhibits the activity of telomerase [53–55] and that the POT1 (protection of telomere 1) protein, which binds the overhang end single strand, plays a role in disrupting G-quadruplex structures in telomeric DNA, thereby allowing proper elongation by telomerase [54]. Stabilizing intramolecular telomeric G-quadruplexes and the G-quadruplexes formed by sequences in oncogenic promoters is an attractive strategy for the development of anticancer drugs [37,38]. Indeed, some G-quadruplex ligands exhibit anticancer activities [38,56–58].

Future challenges and prospects

The G-rich tracts found in telomeres and oncogenic promoter sequences adopt a diversity of G-quadruplex scaffolds *in vitro* that appear to be dependent on the length of individual G-tracts, loop composition and size, and type of cation. Indeed, the same four-repeat human telomeric sequence adopts distinct folds in Na^+ [5] and K^+ (unpublished) solution, and in K^+-containing crystals [6]. It is likely that some of these G-quadruplex conformations are isoenergetic, enabling interconversion between two or more distinct topologies, as shown for human [7••] and *Tetrahymena* [15] two-repeat telomeric sequences.

Currently, no definitive information has emerged that addresses the critical issue as to which G-quadruplex structure(s) are most relevant *in vivo*. Nevertheless, increasing attention is being paid to the (3+1) G-quadruplex scaffold containing a single double-chain-reversal loop, initially identified in 1994 for the four-repeat *Tetrahymena* telomere sequence [17] and thought to be an outlier at that time. The (3+1) G-quadruplex scaffold has now been observed for a range of sequences including both telomeres [16••,17] and oncogenic promoters [18•] in physiologically relevant K^+ solution. Indeed, the *Tetrahymena* telomere [17] and the human *bcl-2* promoter sequence [18•] adopt the same (3+1) quadruplex scaffold despite different loop compositions and size.

New approaches are needed to clarify the extent and type of G-quadruplex formation *in vivo*. The probes themselves have to avoid induction of quadruplex architecture and/or bias towards certain scaffolds. To date, these probes have been limited to antibodies that recognize quadruplexes in macronuclei [51].

Z-DNA

Z-DNA, the left-handed form of the double helix, can be formed by certain sequences containing alternating purine and pyrimidine bases. The history of more than two decades of Z-DNA research was excellently summarized in a recent review [2•]. The discovery of proteins that bind to Z-DNA with high affinity and specificity [2•] indicated a biological role for this structure and stimulated much research in this area. In the past couple of years, two more families of proteins that specifically recognize Z-DNA have been reported: poxvirus protein E3L [59] and an ortholog of the protein kinase PKR [60]. Furthermore, there are data on the binding activity and the function of the Z-DNA-binding domain of E3L *in vivo* [61].

B-Z junction

One of the most important advances in recent Z-DNA research is the crystal structure of a junction between the right-handed B-DNA and the left-handed Z-DNA forms of the double helix [62••]. Z-DNA is less stable than B-DNA at physiological salt concentrations, but can be stabilized by negative supercoiling or by protein binding [2•]. The structure of the B-Z junction is important because such a junction should be formed each time a double-helical DNA segment turns into Z-DNA. Ha *et al*. [62••] used Z-DNA-binding proteins to keep one end of a DNA duplex fragment in the Z-form, while the other end remained in the B-form (Figure 6a). The handedness of the DNA duplex is completely reversed at the junction by breaking only one base pair and projecting the bases out of the duplex. At the junction, the minor grooves of two adjacent steps are on two opposite sides of the duplex (Figure 6b). Base pairs of the B-DNA and Z-DNA segments are continuously stacked across the junction. Note that, if one considers ‘black’ and ‘white’ faces of the bases (in the nomenclature of Lavery *et al*. [63]), stacking contacts are black-black and white-white across the junction, as opposed to black-white within the B-DNA or Z-DNA segments (Figure 6c). The structure of the B-Z junction maximizes base pairing and stacking, thereby minimizing the energetic cost of the junction and most probably facilitating the use of Z-DNA more widely in nature [62••].

Conclusions

The polymorphism of DNA G-quadruplex structures depends strongly on sequence and experimental conditions. Several new folding topologies and structural elements have been discovered, such as the (3+1) interlocking structure [24••] and fold-back motifs [23••]. Some general rules for G-quadruplex folding have emerged, such as the robustness of the single-residue double-chain-reversal loop in K^+ solution. Methods for studying the folding/unfolding kinetics of G-quadruplexes have been proposed and applied to various structures. More systematic studies are required to understand these important properties. The interaction of some G-quadruplexes with small molecules has been reported, providing a platform for the design of new specific ligands. Reported evidence for the proposed biological existence and function of G-quadruplexes should stimulate more research into this non-canonical DNA architecture. Research on Z-DNA has expanded available insights into its functional role [2•] and the new structure of the B-Z junction [62••] should open fresh avenues of research.

Update

Oleksi *et al*. [64••] have just published a seminal structural paper on a novel supramolecular ligand that targets higher order DNA architecture with high affinity and structural specificity, thus opening new avenues for the development of anti-DNA therapeutic agents. Specifically, a synthetic tetracationic metallosupramolecular helicate, generated from three bis-pyrimidine organic strands wrapped around two Fe^{2+} ions (Figure 7a), was found to match the size and shape of the central trigonal hydrophobic cavity of a three-way DNA junction formed by the palindromic sequence d(CGTACG) (Figure 7b). Molecular recognition within this triangular hydrophobic binding site is associated with a combination of face-to-face π-stacking intercalation and minor groove sandwiching interactions, supplemented by electrostatic and C-H•••X type hydrogen-bonding interactions. The three-way DNA junction observed in this complex adopts the same Y-shaped topology, with stable Watson–Crick-aligned junctional pairs, reported previously for three-way DNA junctions observed in complexes with Cre recombinase [65] and Ku [66]. The design and implementation of ligand-based recognition and stabilization of junctional folds could impact the emerging field of DNA-based nanotechnology research [67]. The research on the metallosupramolecular helicate targeted to a three-way DNA junction [64••] nicely complements earlier research highlighting shape complementarity between a chiral bicyclic Diels–Alder product bound within the central hydrophobic cavity of a three-way RNA helical junction [68].

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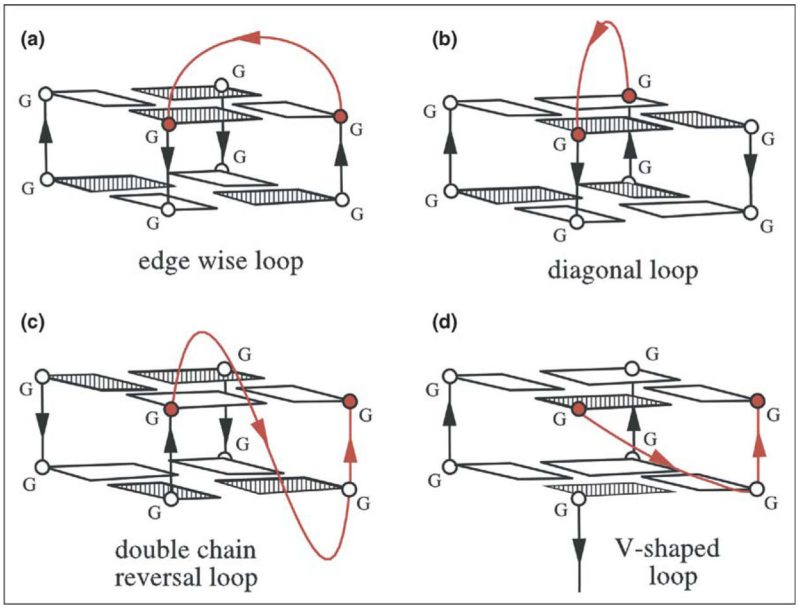

Figure 1.

Polymorphism of the loops connecting individual strands of the G-quadruplex: **(a)** edgewise loop, **(b)** diagonal loop, **(c)** double-chain-reversal loop and **(d)** V-shaped loop. Adapted with permission from [69].

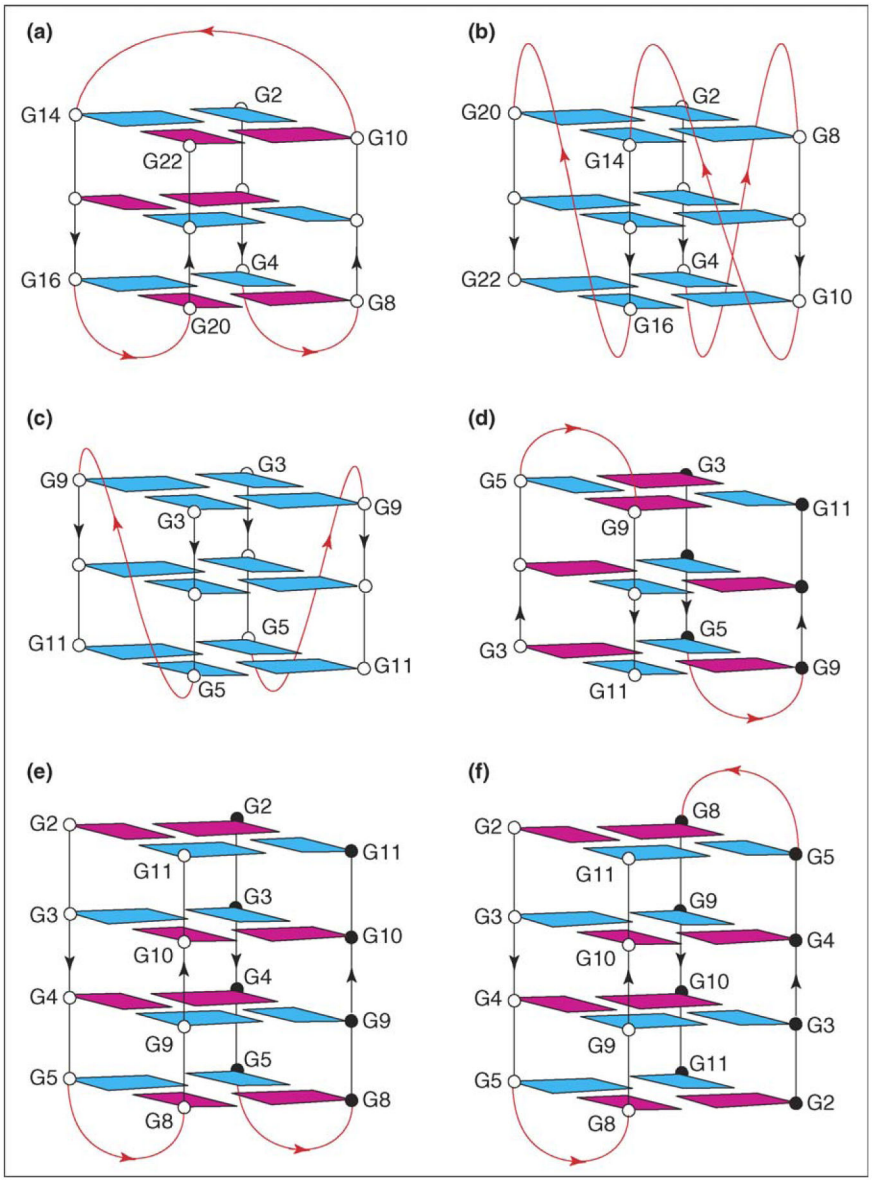

Figure 2.

Telomeric G-quadruplexes. (a,b) Structures formed by the human telomeric sequence d[AGGG(TTAGGG)$_3$] **(a)** in Na^+ solution [5] and **(b)** in K^+ crystal [6]. (c,d) Structures formed by the human telomeric sequence d(TAGGGTTAGGGT) in K^+ solution [7••]: **(c)** parallel form and **(d)** antiparallel form. (e,f) Structures formed by the *Tetrahymena* telomeric sequence d(TGGGGTTGGGGT) in Na^+ solution [15]: **(e)** head-to-head form and **(f)** head-to-tail form. Loops are colored red; *anti* and *syn* guanines are colored cyan and magenta, respectively.

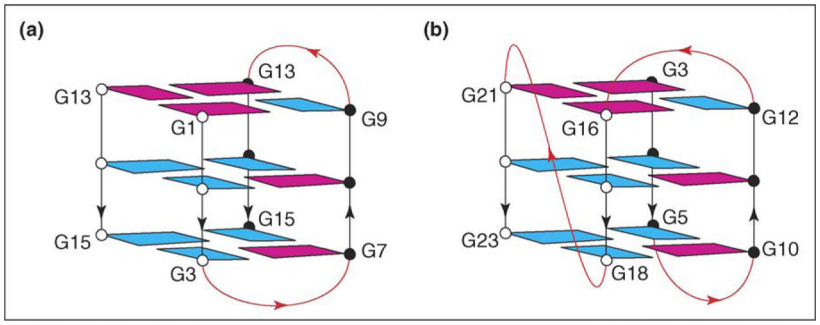

Figure 3.

G-quadruplex topologies containing the (3+1) G-tetrad core. **(a)** (3+1) G-quadruplex formed through dimerization of a three-repeat human telomeric sequence [16••]. **(b)** Intramolecular G-quadruplex formed by the *Tetrahymena* $d(T_2G_4)_4$ sequence [17]. Color coded as in Figure 2.

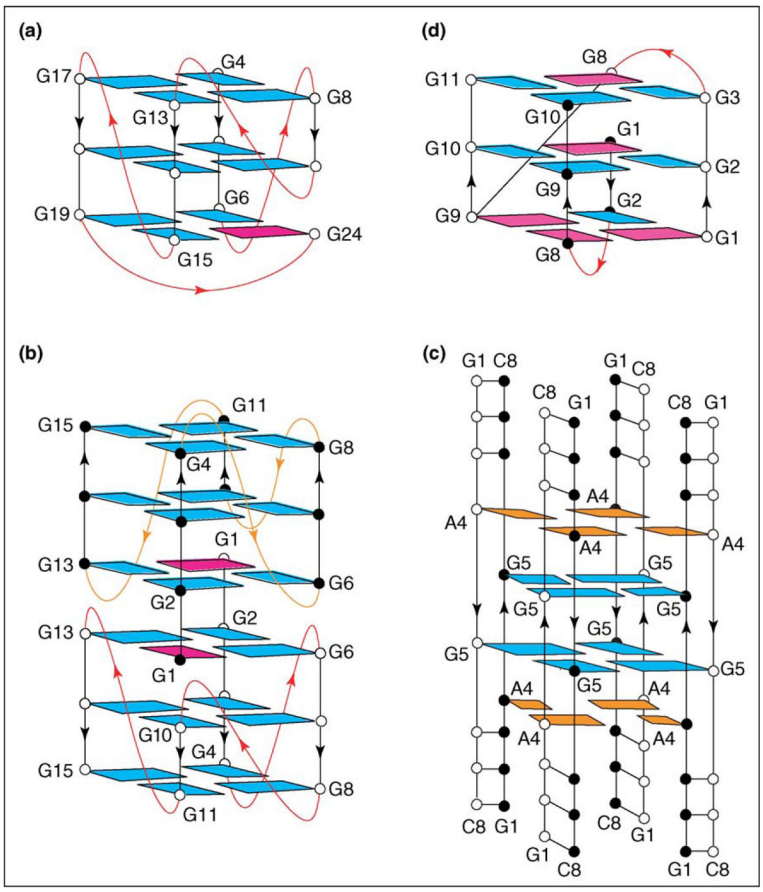

Figure 4.

Novel structural elements in G-quadruplexes. **(a)** Fold-back G-quadruplex of the five-G-tract *c-myc* promoter sequence [23••], **(b)** interlocked dimeric G-quadruplex of *93del* [24••], **(c)** i-motif of G-quartets [27] and **(d)** dimeric G-quadruplex of d(GGGTTTTGGGG) [28•]. Color coded as in Figure 2.

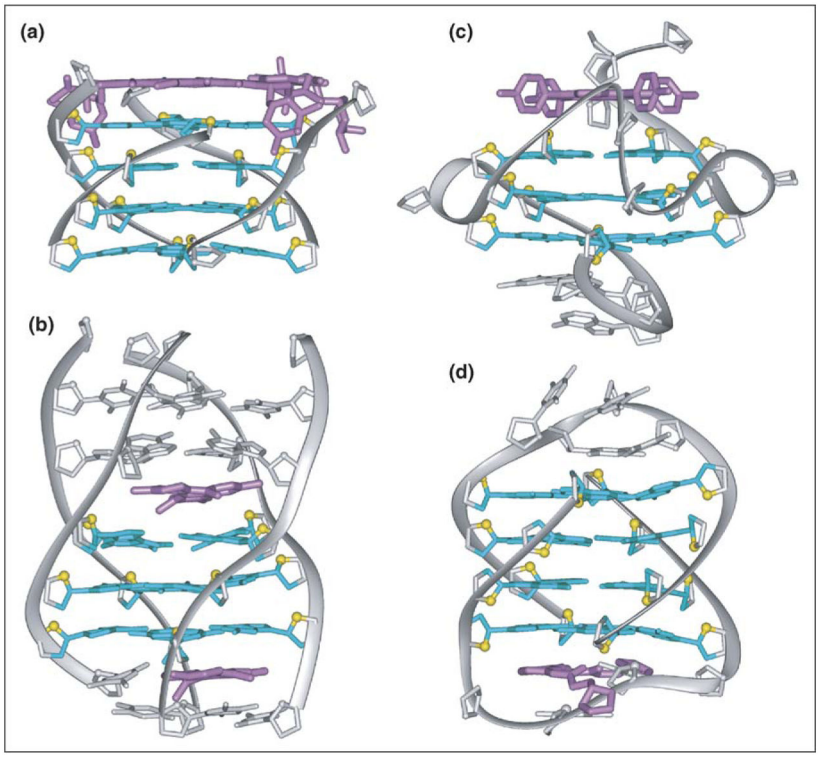

Figure 5.

Interaction of G-quadruplexes with small molecules, as reported by **(a)** Clark *et al*. [39•] for the parallel quadruplex–daunomycin complex, **(b)** Gavathiotis *et al*. [40] for the parallel G-quadruplex bound to two molecules of a fluorinated polycyclic methyl-acridinium salt, **(c)** Phan *et al*. [23••] for the G-quadruplex–TMPyP4 complex and **(d)** Haider *et al*. [41••] for the complex between an antiparallel G-quadruplex and a disubstituted aminoalkylamido acridine. Guanine bases are colored cyan, O4′ are colored yellow and ligands are colored magenta.

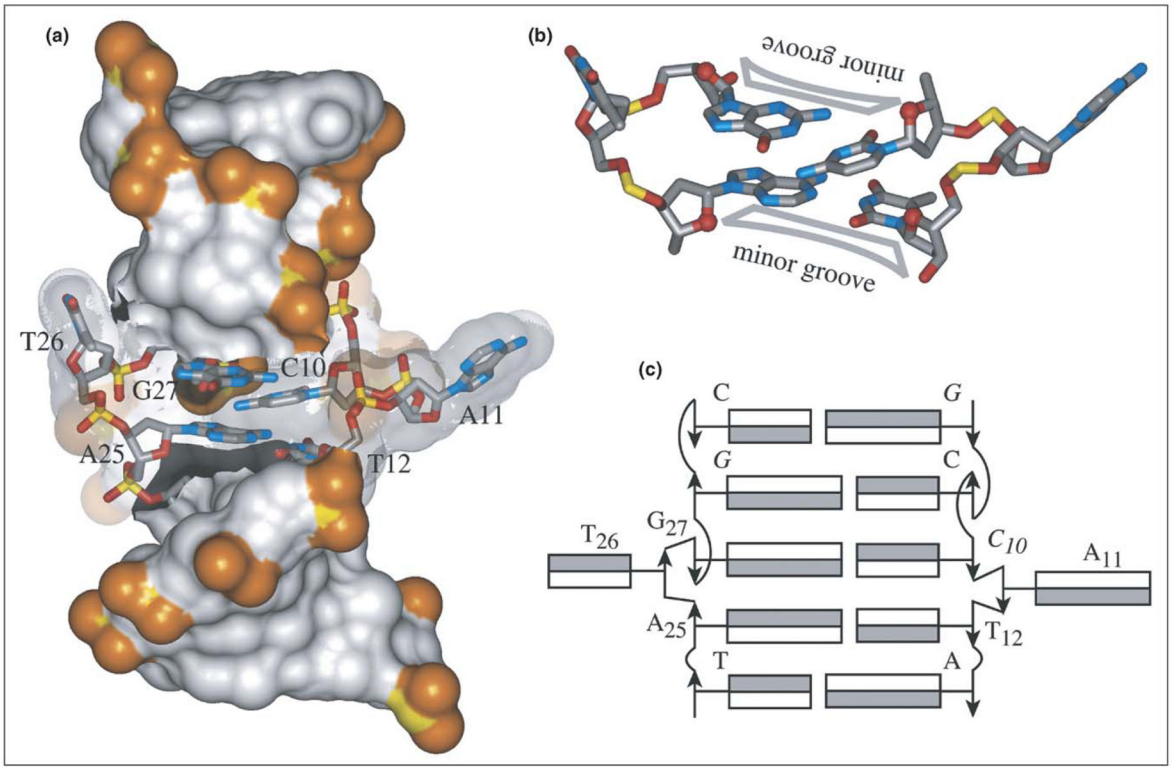

Figure 6.

Structure of the B-Z DNA junction [62••]. Views highlighting **(a)** flipped-out bases of the junctional pair, **(b)** opposing minor grooves flanking looped-out bases of the junctional pair, and **(c)** stacking arrangement of base faces at junctional and flanking sites.

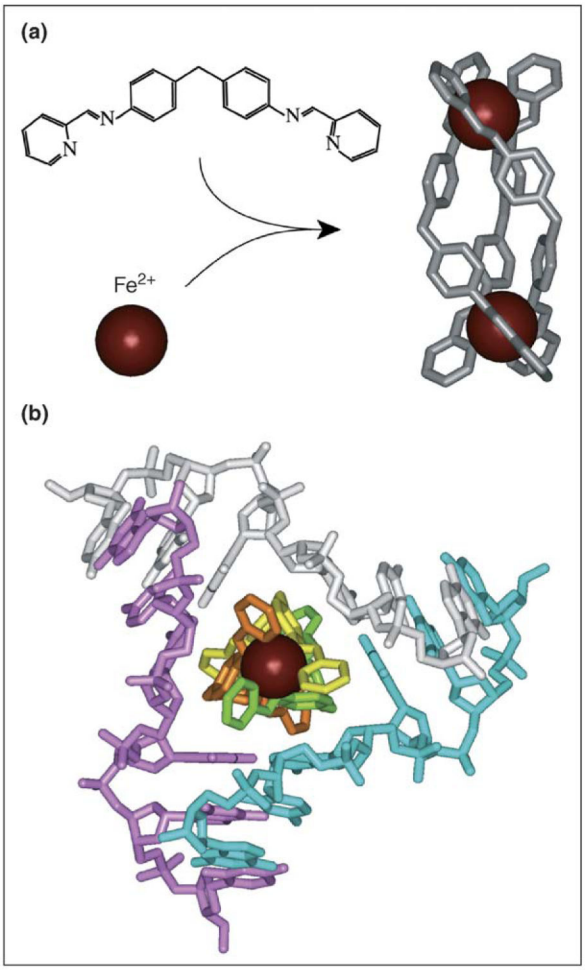

Figure 7.

Recognition of a three-way DNA junction by a metallosupramolecular helicate. **(a)** $[Fe_2L_3]^{4+}$ (L = $C_{25}H_{20}N_4$) tetracationic supramolecular helicate, with the Fe^{2+} ions represented as red spheres. **(b)** Structure of a three-way DNA junction bound to $[Fe_2L_3]^{4+}$. Three DNA strands are colored cyan, magenta and gray, respectively.