Intramolecular Higher Order Packing of Parallel Quadruplexes Comprising a G:G:G:G Tetrads and a G(:A):G(:A):G(:A):G Heptad of GGA Triplet Repeat DNA*

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GGA triplet repeats are widely dispersed throughout eukaryotic genomes and are frequently located within biologically important regions such as gene regulatory regions and recombination hot spots. We determined the structure of d(GGA)12 (12-mer) under physiological conditions and found the formation of an intramolecular parallel quadruplex for the first time. Later, a similar architecture to that of the intramolecular parallel quadruplex was found for a telomere DNA in the crystalline state. Here, we have determined the structure of d(GGA)24 (24-mer) under physiological conditions. Two intramolecular parallel quadruplexes comprising a G:G:G:G tetrad and a G(:A):G(:A):G(:A):G heptad are formed in d(GGA)24. These quadruplexes are packed in a tail-to-tail manner. This is the first demonstration of the intramolecular higher order packing of quadruplexes at atomic resolution. K⁺ ions, but not Na⁺ ones, are critically required for the formation of this unique structure. The elucidated structure suggests the mechanisms underlying the biological events related to the GGA triplet repeat. Furthermore, in the light of the structure, the mode of the higher order packing of the telomere DNA is discussed.

Several kinds of triplet repeats are found in the human genome. A link to the occurrence of a certain disease has been established for some of triplet repeats. The CCG, CTG, CAG, and GAA repeats are linked to fragile X syndrome, myotonic dystrophy, Huntington’s disease, and Friedreich ataxia, respectively (1–4). It is suggested that these repeats have unusual structures and that the unusual structures cause the extraordinary expansion of the repeats related to the occurrence of the diseases (5, 6). The GGA triplet repeat is widely dispersed throughout eukaryotic genomes (7). The GGA repeat has been identified in portions of human and mouse cellular DNA that cross-hybridize with the internal direct repeat (IR3) repetitive region of Epstein-Barr virus (8). The GGA repeat, together with the GAA repeat, has also been found in micro satellite DNA belonging to the rat polymeric immunoglobulin receptor gene (9). A fragment of the microsatellite DNA containing both the repeats was suggested to attenuate gene expression at the transcriptional and post-transcriptional levels (10). Moreover, the GGA repeat has been identified in various sequences ranging from that of the mouse WASP gene (11), which is a homologue of the gene mutated in the Wiskott-Aldrich syndrome, to regulatory elements governing cell type-specific expression of neural cell adhesion molecule genes (12). The GGA repeat is frequently located within gene regulatory regions and recombination hot spot sites (13). Thus, the biological significance of the GGA repeat is widely recognized, although the link to a certain disease has not yet been clarified. The GGA repeat is capable of forming variable structures (14–18).

We determined the structure of d(GGAGGAGGAGGA) (d(GGA)12) composed of four tandem GGA units under physiological conditions (19). d(GGA)12 folds into an intramolecular quadruplex composed of a G:G:G:G tetrad and a G(:A):G(:A):G(:A):G heptad. Four G-G segments of d(GGA)12 are aligned parallel to each other due to seven successive turns of the main chain at each of the GGA and GAGG segments. This was the first demonstration that DNA can form an intramolecular parallel quadruplex. Later, a similar architecture to that of the intramolecular parallel quadruplex was found for the telomere DNA in the crystalline state (20). We also showed that two quadruplexes of d(GGA)12 form a dimer stabilized through the stacking interaction between the heptads of the two quadruplexes.

Our findings as to GGA triplet repeat DNA, together with the crystallographic result for telomere DNA, indicated the possibility of intramolecular higher order packing of quadruplexes for longer DNA with certain repeating units. To address this point and to elucidate the character of naturally occurring GGA repeat DNA, we studied the structure of d(GGAGGAGGAGGAGGAGGAGGAGGAGGA) (d(GGA)24) under physiological conditions. Here, we present its unique structure. This is the first demonstration of higher order packing of quadruplexes at atomic resolution. The biological events related to GGA triplet repeat DNA can be rationalized in the light of the elucidated structure. Furthermore, our findings provide a support for the hypothetical higher order packing of quadruplexes of telomere DNA and indicate the mode of packing for it.

**EXPERIMENTAL PROCEDURES**

*Sample Preparation—* d(GGA)12 and mutant oligomers in which each single G residue was replaced by an I residue were prepared as described previously (19). DNA was dissolved in 10 mM sodium phosphate buffer (pH 6.7) containing 3 mM NaN₃ and either 0 or 1–50 mM KCl. The DNA concentrations were 1–40 μM for CD and 0.1–1 mM for NMR.

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* The atomic coordinates and structure factors (code 1OZ8) have been deposited in the Protein Data Bank, Research Collaboratory for Structural Bioinformatics, Rutgers University, New Brunswick, NJ (http://www.rcsb.org/).

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2,2-Dimethyl-2-silapentane-5-sulfonate was used as an internal chemical shift reference. Samples were heated at 95 °C for 5 min, followed by gradual cooling to room temperature prior to the measurements.

**CD and NMR Spectroscopies**—CD spectra and thermal CD melting curves were recorded with a Jasco J-720 spectropolarimeter. The temperature of the solution was raised from 1 to 95 °C at the rate of 1 °C/min. Changes in CD intensity were monitored at 263 nm. The melting temperature was determined by use of the derivative of the melting curve.

NMR spectra were recorded with Bruker DRX600 and DRX800 spectrometers equipped with a quadrupole-resonance probe with X, Y, and Z gradients. The following NMR experiments were used to assign the resonances and to obtain distance and dihedral angle constraints; NOESY, NOESY-TOCSY, 31P-decoupled DQF-COSY, 1H-13C HSQC, 1H-15N HSQC, and 1H-31P HetCor. Spectra were processed with XWIN-NMR (Bruker), NMRPipe (21), and Capp/Pipp/Stapp (22).

**Distance and Dihedral Angle Constraints**—Interproton distances were calculated from NOESY spectra with mixing times of 50 and 200 ms as described previously (19). In total, 750 distance constraints were used for the structure formation. The chemical shift range of 10.7–11.9 ppm for imino proton signals was left unconstrained. No dihedral angle constraints were derived from the distance constraints by more than 6°. The structures were viewed with Insight II (MSI).

**RESULTS**

**K⁺-induced Ordered Structure of d(GGA)₈**—In the absence of K⁺, several broad imino proton signals were observed for d(GGA)₈ (Fig. 1A). This indicates that although d(GGA)₈ seems to form some structure in the absence of K⁺, it is rather unstable. In contrast, 16 sharp signals appeared in the presence of K⁺ (Fig. 1B), indicating the formation of a certain stable ordered structure. The chemical shift range of 10.7–11.9 ppm for these signals suggests that the structure formed is a G:G:G:G quartet-based quadruplex. The sharp signals did not appear when Na⁺ was added instead of K⁺ (Fig. 1C). Thus, K⁺ is critically required for the formation of this stable structure. This is notable from a physiological point of view, because the K⁺ concentration, but not the Na⁺ one, is high, over 100 mM, in the nucleus.

It is known that a parallel quadruplex gives a positive CD band at 260 nm, while an antiparallel one gives a positive CD band at 295 nm either with or without a positive CD band at 260 nm (28, 29). The CD spectrum of d(GGA)₈ in the presence of K⁺ had a positive CD band at around 260 nm without a positive CD band at around 295 nm (Fig. 1D). This suggests that d(GGA)₈ forms a parallel quadruplex. The melting temperature of the structure formed by d(GGA)₈ in the presence of K⁺ was determined to be rather high, 86 °C. This again suggests the formation of a quadruplex, because the melting temperature of a quadruplex is generally very high.

It was also found that the melting temperature does not depend on the concentration of d(GGA)₈. This indicates that the structure formed is unimolecular. This conclusion was supported by the result of analysis of the line widths of NMR resonances that are sensitive to molecular weight. The line

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1 The abbreviations used are: NOESY, nuclear Overhauser effect spectroscopy; NOE, nuclear Overhauser effect; TOCSY, total correlation spectroscopy; DQF, double quantum filtered; HSQC, heteronuclear single-quantum coherence spectroscopy; r.m.s.d., root mean square deviation.
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widths for d(GGA)$_k$ (24-mer) were the same as those for d(GGA)$_s$ (12-mer), which exists as a dimer in solution (19).

Resonance Assignments—The non-exchangeable $^1$H, $^{13}$C, and $^{31}$P resonances of d(GGA)$_a$ were assigned as described previously (19) using standard methods (23, 30). As an example, Fig. 2A shows expansion of the NOESY spectrum allowing the sequential assignments of H1’ and H6/H8 through H1’(i – 1)-H6(i)-H8(i)-H1’(i) connectivities. H2’, H2, H5’, H4’, and H5’/H5’ resonances were assigned by means of TOCSY and DQFCOSY spectra. These assignments were confirmed by the sequential H3’(i – 1)-P(i)-H4’/H5’/H5’(i) connectivities in the $^1$H-$^{31}$P HetCor spectrum, the assignments of $^{31}$P resonances being made at the same time (data not shown). The chemical shifts of $^{13}$C resonances were obtained from the $^1$H-$^{13}$C HSQC spectrum. Exchangeable $^1$H resonances were assigned as described previously with the use of mutant oligonucleotides in which each single G residue was replaced by an I residue (19).

**FIG. 2.** NOESY spectra. A, H6/H8-H1’ region of the NOESY spectrum with a mixing time of 200 ms for d(GGA)$_a$ in $^2$H$_2$O containing 10 mM sodium phosphate (pH 6.7), 3 mM NaN$_3$, and 30 mM KCl at 25 °C.

The lines show the H1’(i – 1)-H6/H8(−i)–H1’(−i) connectivities, the intraresidue cross-peaks being labeled. Cross-peaks $a$–$j$ are as follows: $a$, A3H2-A21H1; $b$, A6H5-A18H1; $c$, A9H2-A15H1; $d$, A15H2-A9H1; $e$, A18H2-A6H1; $f$, A21H2-A3H1; $g$, G1H8-G22H1; $h$, G7H5-G16H1; $i$, G13H8-G10H1; $j$, G19H8-G4H1. Expansion of the NOESY spectrum in $^2$H$_2$O at 2 °C, indicating NOEs originating from GNH-C(β) and ANH$_C$(C). Cross-peaks in B are as follows: $a$ and $a'$, G1H9-G4H8; $b$ and $b'$, G4H9-G7H8; $c$, G7NH$_2$-G10H8; $d$, G10NH$_2$-G13H8; $e$, G13NH$_2$-G16H8; $f$, G16NH$_2$-G19H8; $g$, G19NH$_2$-G22H8; $h$, G22NH$_2$-G13H8; $i$ and $a''$, G1NH$_2$-A3H8; $b$ and $b'$, G4NH$_2$-A6H8; $c$, G7NH$_2$-A9H8; $e$, G13NH$_2$-A15H8; $f''$, G16NH$_2$-A18H8; $g$, G19NH$_2$-A21H8; $i$ and $i''$, and $i''$, G1NH$_2$-A3H8; $j$ and $j'$, and $j''$, G4NH$_2$-A6H8; $k$, G7NH$_2$-A9H8; $l$, G13NH$_2$-A15H8; $m$ and $n$, G16NH$_2$-A18H8; $o$, G19NH$_2$-A21H8; $p$ and $p'$, G1NH$_2$-A3H8; and $q$, G4NH$_2$-A6H8. Cross-peaks in C are as follows: $a$ and $a'$, A3H9-G1H1; $b$ and $b'$, A6H9-G4H1; $c$ and $c'$, A9NH$_2$-G7H1; $d$, A15NH$_2$-G13H1; $e$ and $e'$, A18NH$_2$-G16H1; $f$ and $f'$, A21NH$_2$-G19H1.

Formation of Two G-G:G-G Tetrads and Two G(A):G(A) G-Heptads and Their Mutual Arrangement—The formation of the G2-G5-G8-G11 and G14-G17-G20-G23 tetrads was concluded on the basis of GNH/NH$_2$-G8H (Fig. 2B) and GNH-GNH NOEs; the NOEs commonly observed for both tetrads are shown in Fig. 3A. The formation of the G1-A3:G4-A6: G7(A9):G10 and G13(A15):G16(A18):G19(A21):G22 heptads was concluded on the basis of GNH/NH$_2$-A8H (Fig. 2B), ANH$_L$-GH1 (Fig. 2C), GNH$_2$-ANH$_2$, and G8H-A8H NOEs, in addition to GNH$_2$-G8H and GNH-GNH ones; the NOEs commonly observed for both heptads are shown in Fig. 3B. A12 and A24 are not involved in either the tetrads or the heptads.

The arrangement of two heptads was determined on the basis of the strong AH2-AH1’/2” NOEs between A3 and A21, A6 and A18, and A9 and A15, and the medium to weak GH8-GH1’ ones between G1 and G22, G4 and G19, G7 and G16, and G10 and G13 (Fig. 2A). Thus, the overall structure of d(GGA)$_a$ was concluded to be as shown in Fig. 3C.

**Structure of d(GGA)$_a$—**The applied constraints and the structural statistics for the 20 final structures are summarized in Table I. The root mean square deviations (r.m.s.d.s) of the 20 final structures versus the mean structure for all heavy atoms were 0.35 ± 0.13 Å.

Fig. 4A shows a stereo view of the superposition of the 20 final structures. A representative structure with the lowest energy is shown in Fig. 4B, a trace of the sugar-phosphate main chain being indicated by a tube for clarity. Two tetrad and two heptads can be seen (Fig. 4, C–E), as already discussed qualitatively. A12 is located close to the upper heptad, although it is not involved in the heptad. A24 is stacked on G23.

A turn at a G1-G2-A3 trinucleotide segment, which is composed of a sheared G1A3 base pair and a single G2 residue at the top, is followed by another turn at a G2-A3-G4-G5 segment except for the G11-A12-G13-G14 and G22-

The authors conclude that the structure of d(GGA)$_a$ is characterized by a compact arrangement of G-G:G-G tetrads and G(A):G(A) G-Heptads, consistent with the observed NOESY and HSQC spectra. The structure is stabilized by hydrogen bonding and van der Waals interactions, leading to a highly ordered architecture.
G23-A24 segments. In the cases of the canonical B- and A-forms, the backbone dihedral angles are as follows; \( \alpha' \), \( \beta \), \( \gamma \), \( \delta \), and \( \zeta \) (31). Deviation from the canonical dihedral angles of \( \alpha' \), \( \beta \), and \( \gamma \) was found for all A residues. Deviation of \( \alpha' \) and \( \beta \) was found for G4, G7, G10, G11, G16, G19, and G22. Deviation of \( \zeta \) was found for almost all G residues. The combination of these deviated dihedral angles results in the successive turns of the backbone. These successive turns cause the four G-G segments, i.e. the G1-G2, G4-G5, G7-G8, and G10-G11 segments, to be aligned.
parallel to each other. As a result, the G1–G11 portion of d(GGA)₈ forms an intramolecular parallel quadruplex (Figs. 3C and 4B). Similarly, the G13-G14, G16-G17, G19-G20, and G22-G23 segments are aligned parallel to each other, and the G13–G23 portion forms another intramolecular parallel quadruplex. The two quadruplexes are packed in a tail-to-tail manner through stacking between the two heptad planes, the orientation of G-G segments of one quadruplex being opposite to that of the other quadruplex (Figs. 3C and 4B).

The stacking between the tetrad and heptad planes is shown in Fig. 4, A and D. The five-membered ring of one guanine base is stacked on the six-membered ring of the other guanine base for each G-G segment. The A3, A6, A9, and A15 bases are stacked on the G2, G5, G8, and G11 sugars, respectively, which is characteristic of the structure of a GNA trinucleotide loop and consistent with the extreme upfield shift of H₄/G₁₁₀₃₂ (2.62–2.84 ppm) and the moderate upfield shift of H₃/G₁₁₀₃₂ (4.56–4.66 ppm) of these G residues (32, 33). Stacking of the two heptads is shown in Fig. 4E. The G1, A3, G4, A6, G7, A9, and G10 bases are stacked on the G22, A21, G19, A18, G16, A15, and G13 ones, respectively.

All G residues take on the anti conformation with respect to the glycoside bond, while all A residues, except for A12 and A24, take on the high anti-conformation. All G residues take on the B-form sugar conformation (around C₁'-exo), while all A residues, except for A12 and A24, take on the A-form sugar conformation (around C₃'-endo). The high anti and C₃'-endo conformations of the six A residues are supposed to be preferable for the series of turns and/or for good stacking interactions.

Weak to medium NOEs were observed between A6H₂ and G7H₈, A9H₂ and G₁₀H₈, A₁₈H₂ and G₁₉H₈, and A₂₁H₂ and G₂₂H₈. These NOEs could be very strong, if A6, A9, A18, and A21 take on the syn conformation, forming hydrogen bonds, i.e. G₄NH₂·A₆N₁ and G₄N₃·A₆NH₂, G₇NH₂·A₉N₁ and G₇N₃·A₉NH₂, G₁₆NH₂·A₁₈N₁ and G₁₆N₃·A₁₈NH₂, and G₁₉NH₂·A₂₁N₁ and G₁₉N₃·A₂₁NH₂, respectively. Therefore, there is the possibility that there is a small fraction of the syn conformation for A6, A9, A18, and A21, being in fast exchange with the major high anti conformation on an NMR time scale.

Comparison of the Structures of d(GGA)₈ and d(GGA)₄—The structures of d(GGA)₈ and d(GGA)₄ are shown schematically in...
Fig. 5. Comparison of the structures of d(GGA)$_8$ (24-mer) (A), d(GGA)$_4$ (12-mer) (B), and the telomere DNA, d[AGGG(TTAGGG)$_3$], in the crystalline state (C).

From the viewpoint of symmetry, the formation of an octad composed of four G and four A bases may seem to be natural. A12 of d(GGA)$_4$ (12-mer) does not fold back to the heptad plane, and thus the octad is not formed (Fig. 5B). This was explained by that the terminal A12 of d(GGA)$_4$ does not have a following G residue that would pull it to the heptad plane (19). In the case of d(GGA)$_8$ (24-mer) (Fig. 5A), it is conceivable that A12 may associate with the upper heptad, resulting in the formation of an octad. However, all NMR data for d(GGA)$_8$ were against the existence of the sheared G10:A12 base pair that is needed for the formation of an octad, although the position of A12 was determined to be close to the upper heptad (Fig. 4B). A12 must bridge the upper and lower quadruplexes. It seems that A12 cannot be involved in the octad to play this role due to structural restriction. The terminal A24 does not fold back to the heptad, either, for the same reason as for d(GGA)$_4$. Thus, an octad is not formed for d(GGA)$_8$ either.

From the viewpoint of achieving maximum stacking interactions, the relative arrangement of the two heptads of d(GGA)$_8$ can be rationalized. For example, if the lower heptad is rotated by either 90° or 180°, one A base of each heptad cannot be involved in the stacking interaction, which is energetically less stable and thus unfavorable.

Each monomer of d(GGA)$_4$ forms an intramolecular parallel quadruplex (Fig. 5B). Matsugami et al. (19) first demonstrated that DNA can form the intramolecular parallel quadruplex. Later, an intramolecular parallel quadruplex was found for a telomere DNA in the crystalline state (20). These structures have indicated the intramolecular higher order packing of quadruplexes. In this study, we have demonstrated for the first time that the intramolecular higher order packing of quadruplexes actually occurs and the mode of the packing at atomic resolution is discussed. The intramolecular packing of the two quadruplexes for d(GGA)$_8$ is achieved through the stacking interaction between the heptads of each quadruplex (Fig. 5A). As a result, the two quadruplexes are arranged in a tail-to-tail manner. Alternatively, if the G13:A15:G16:A18:G19:A21:G22 heptad is stacked on the G2:G5:G8:G11 tetrad, with A12 bulging out, then the two quadruplexes are arranged in a head-to-tail manner. However, this does not occur for d(GGA)$_8$, because heptad-heptad stacking in a tail-to-tail manner is energetically much more stable and favorable than heptad-tetrad stacking in a head-to-tail manner.

When the GGA unit is further repeated, formation of the structure shown in Fig. 5A is expected for the other 24-mer region, too. The structures formed for each 24-mer region may further pack through the stacking interaction between the tetrad of each structure.

The GGA triplet repeat is abundant in eukaryotic genomes (7), and is frequently located within biologically important regions such as gene regulatory regions and recombination hot spot sites (11–13). Thus, the biological significance of the GGA repeat is widely recognized. The GGA repeat shows considerable genetic polymorphism due to genetic instability (7, 34). This genetic instability is supposed to originate from DNA...
slippage during DNA replication and/or frequent recombination of the repeats (35). The structure elucidated in this study can be used to rationalize the occurrence of these events. In the course of replication, double-stranded DNA is locally melted to yield single-stranded DNA for use as a template for DNA synthesis. In this case, the GGA strand is expected to form the unique intramolecular structure we found, when the high concentration of K+ over 100 mM, in the nucleus is considered. The structure is very stable, as revealed by its high melting temperature of 86 °C. It was also found for d(GGA)4 that the unique structure is formed, the addition of the complementary strand, d(TCC)4, is not effective for the formation of a duplex (19). The unique structure remained even in the presence of the complementary strand. The formed structure could cause the slippage during DNA replication, which results in a gain or loss of repeats and thus genetic instability.

Alternatively, intermolecular association of two double-stranded DNAs through the packing of two quadruplexes formed in each DNA, as shown in Fig. 5B, may also occur and facilitate the recombination. This idea is coincident with the fact that the GGA repeat is frequently located in recombination hot spot sites. The facilitated recombination may also be responsible for the genetic instability of the GGA repeat. Furthermore, the intermolecular association at the GGA repeat may play a role in the pairing of homologous chromosomes during meiosis. The idea of pairing through a quadruplex has already been proposed for the G stretch (37–40). It is known that the synopsis formation between homologous chromosomes in meiosis usually begins at telomere DNA, but that it sometimes starts at loci inside a chromosome.

It is expected that the unique intramolecular structure shown in Fig. 5A is formed in the course of transcription as well, because DNA is locally melted in this case, too. The formed structure is supposed to be an obstacle for an RNA polymerase to proceed, which could explain the attenuation of gene expression at the transcriptional level (10). We have revealed that RNA with the related sequence also can form a similar intramolecular parallel quadruplex (36). This RNA structure is very stable, too, the melting temperature being 86 °C (36). Therefore, it is expected that the unique structure in the transcribed mRNA becomes an obstacle for the translation machinery to associate with and/or proceed along mRNA in the course of translation, which may lead to the attenuation of gene expression at the post-transcriptional level (10).

The structure elucidated in this study can also provide a clue as to the higher order packing of the telomere DNA. A quadruplex of telomere DNA only contains the tetrad, not the heptad (Fig. 5C). Therefore, the arrangement of the two quadruplexes in a head-to-tail manner, in which the G26-G32-G38:G44 tetrad of the second quadruplex is stacked on the G4-G10:G16-G22 tetrad of the first quadruplex, with a T23-T24-A25 segment serving as a linker, seems to be likely for d[AGGG-(TTAGGG)n], as proposed by Parkinson et al. (20). Because of the lack of the heptad, the tail-to-tail arrangement of the two quadruplexes, in which the G26-G32:G38:G44 tetrad is stacked on the G2-G8:G14-G20 tetrad, with folding back of the T23-T24-A25 segment, seems less likely, although it is not impossible.

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Intramolecular Higher Order Packing of Parallel Quadruplexes Comprising a G:G:G:G Tetrad and a G(:A):G(:A):G(:A):G Heptad of GGA Triplet Repeat DNA
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