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Structure of d(CCCTAGGG): Comparison with Nine Isomorphous Octamer Sequences Reveals Four Distinct Patterns of Sequence-Dependent Intermolecular Interactions

D. B. TIPPIN AND M. SUNDARALINGAM*

Biological Macromolecular Structure, Newman and Wolfram Laboratory of Chemistry, Department of Biochemistry, The Ohio State University, 1060 Carmack Road, Columbus, OH 43210, USA. E-mail: sunda@biot.mps.ohio-state.edu

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Abstract

The self-complementary deoxyoctanuceotide d(CCCTAGGG) crystallizes as an A-type double helix in the space group $P4_32_12$, $a = b = 42.22$ and $c = 24.90$ Å, with one strand per asymmetric unit. Using 1533 unique reflections at 1.9 Å and $I > 2\sigma$, the structure was solved by molecular placement and refined to a final R value of 16.4%. This structure is isomorphous with nine other tetragonal A-DNA octamers, possessing a central pyrimidine/purine step that is fully extended along the backbone with *trans*, *trans* conformations around the C4′—C5′ and O5′—P bonds. A structural water, sandwiched between the π-cloud of the terminal guanine and the N3 atom of G7 in the adjacent duplex, stabilizes an intermolecular base triplet with one hydrogen bond between the terminal cytosine and G6 of an adjacent duplex. Comparative analysis of this structure with the isomorphous A-DNA octamers reveals the importance of base sequence and minor-groove hydration in intermolecular interactions. The minor grooves, which provide both hydrophobic and polar interactions, allow for four patterns of sequence-dependent binding involving interduplex base triplets in which the third base is bonded through a single hydrogen bond. A conserved water molecule appears to be crucial in the stabilization of these intermolecular interactions, which resemble specific recognition motifs found in the crystal structures of the TATA-box/TBP protein complex.

1. Introduction

d(CCCTAGGG) contains the *Avr*II restriction site CCTAGG and represents the tenth member in the richest group of isomorphous DNA structures, the tetragonal A-DNA octamers (Table 1). A central pyrimidine/purine step appears to be prerequisite for crystallization of octamer DNA in $P4_32_12$ as well as essential in establishing the characteristic underwound central base step and extended *trans*, *trans* conformation of the Pu5 sugar-phosphate backbone. The conformation of these octamers has been shown to be predominantly influenced by crystal lattice interactions, with only a minor dependence on base sequence (Ramakrishnan & Sundaralingam, 1993*a*,*b*). Among the helical parameters of the eight reported structures, only the propeller twist and base-pair buckle display any sequence dependency; the twist, rise, slide, inclination, tilt and roll can be readily explained by similarities in the crystal packing forces. Even though many of the helix parameters display little sequence dependency, the intermolecular interactions, *i.e.* crystal packing and base triplets, display considerable sequence dependency. In this study, we have identified four specific intermolecular contacts which can occur among the tetragonal A-DNA family of octamers. These contacts involve the formation of minor-groove base triplets (G·C-G_6, C·G-G_6, C·G-G_{11}, and G·C-G_{11}) between inner-strand purines of one duplex and the terminal base pairs of symmetry-related duplexes. Discovery of a base triplet in d(CCCTAGGG) and its obvious structural importance in stabilizing intermolecular interactions led to the examination of other isomorphous structures, wherein we discovered the ubiquity of base triplets and water molecules in the crystal packing of the tetragonal A-DNA octamers. In this context we report the crystal and molecular structure of d(CCCTAGGG) and discuss intermolecular contacts common to this A-DNA family of octamers.

2. Experimental

2.1. *Synthesis and crystallization*

The oligonucleotide was synthesized *via* solid support phosphoramidite methodology and purified by ethanol precipitation in 2.5 *M* ammonium acetate at 248 K. Tetragonal crystals grew in six days by vapor diffusion at 295 K from a solution of 50 m*M* sodium cacodylate (pH 7.0), 20 m*M* $MgCl_2$, 2 m*M* DNA (single-strand concentration) and 1 m*M* spermine tetrachloride equilibrated against 40%(*v*/*v*) 2-methyl-2,4-pentanediol. A crystal measuring 0.3 × 0.3 × 0.2 mm was mounted in a thin-walled glass capillary along with a drop of mother liquor for intensity-data measurements.

Table 1. *Tetragonal A-DNA octamers, $P4_32_12$*

Sequence	$a = b$ (Å)	c (Å)	Resolution (Å)	No. of H_2O*	Reference
CCCTAGGG	42.2	24.9	1.9	76	Present work
GCCCGGGC	43.3	24.6	1.8	34	Heinemann *et al.* (1987)
CCCCGGGG	43.4	24.8	2.2	78	Haran *et al.* (1987)
GTGTACAC	42.4	24.8	2.0	86	Jain *et al.* (1989)
CTCTAGAG	42.5	24.3	2.2	34	Hunter *et al.* (1989)
GGGCGCCC	43.3	24.7	1.7	87	Shakked *et al.* (1989)
GTACGTAC	42.5	24.8	2.0	51	Courseille *et al.* (1990)
GTCTAGAC	42.6	24.6	2.5	6	Cervi *et al.* (1992)
GTGCGCAC	42.2	25.1	1.6	84	Bingman *et al.* (1992)
GGCCGGCC	42.1	25.2	2.2	80	Wang *et al.* (1982)

* The number of waters listed is the number per duplex.

Table 2. *Experimental and statistical summaries for d(CCCTAGGG)*

	Tetragonal crystal
Space group	$P4_32_12$ (No. 96)
Cell constants (Å,°)	$a = b = 42.22$ $c = 24.90$ $\alpha = \beta = \gamma = 90.0$
Cell volume (Å^3)	44382
Vol/bp (Å^3)	1387
Crystal dimensions (mm)	0.3 × 0.3 × 0.2
Unique reflections collected	1894 (99.9%)
Unique reflections used in the refinement	1533 at 1.9 Å, $I > 2\sigma$
R factor	16.4%
Bond r.m.s. (Å)	0.013
Angle r.m.s. (°)	3.514

2.2. *Data collection*

Data were collected at 295 K to a resolution of 1.9 Å using a Siemens–Nicolet area detector mounted on a four-circle goniometer and equipped with a rotating-anode X-ray generator powered at 4.5 kW (50 kV × 90 mA). The crystal-to-detector distance was 12.0 cm and the swing angle was 25°. 1894 unique reflections were collected with a single φ scan of 180° at 0.25° intervals, covering 99.9% of the possible reflections at 1.9 Å resolution. 720 frames were processed and scaled using *XENGEN* 2.0 (Howard, 1990), $R_{sym}(I) = 2.91$. See Table 2 for a summary of the data statistics.

2.3. *Refinement*

Coordinates for the starting model d(CCCCGGGG) (Haran, Shakked, Wang & Rich, 1987) were obtained from the Nucleic Acid Database (Berman *et al.*, 1992). All water molecules were removed and atomic thermal parameters were reset to 15 Å^2. Rigid-body refinement using the program *X-PLOR* (Brünger, Kuriyan & Karplus, 1987) yielded an R factor of 36.8%. Further thermal and positional refinement followed by simulated annealing reduced the R factor to 25.8%. The central CG was then mutated to TA using the program *CHAIN* (Sack & Spurlino, 1991) on a Silicon Graphics Elan 4000. The resultant model was refined against data in the 8–1.9 Å shell with $I > 2\sigma$, and difference-density maps were calculated utilizing the program package *PHASES* (Furey, 1992) to locate solvent molecules. Additional cycles of model adjustment and omit maps yielded a total of 38 solvent molecules. The final R factor for 1533 unique reflections was 16.4%, and the model contained 181 DNA atoms and 38 solvent molecules.

3. Results and discussion

3.1. *Structural aspects*

d(CCCTAGGG) crystallizes in the tetragonal space group $P4_32_12$, $a = b = 42.22$ and $c = 24.90$ Å, with one strand in the asymmetric unit and four duplexes in the unit cell (Table 2). The DNA duplexes are clustered about the 4_3 screw axes of the unit cell while elliptically shaped solvent channels (10 × 20 Å) run along the 2_1 screw axes. Each duplex makes contact with four neighboring duplexes by abutment of terminal base pairs against the sugar-phosphate backbone of symmetry-related duplexes. d(CCCTAGGG) is isomorphous to other tetragonal A-DNA octamers and has a central pyrimidine/purine base step that is fully extended along the sugar-phosphate backbone with *trans* conformations around the C4′—C5′ and O5′—P bonds. The underwound helical twist (29°) of the central TpA base step improves interstrand stacking within the duplex as well as compensates for the weaker stacking of the overwound (36.5°) flanking base steps, C3pT4 and A5pG6. The helical parameters for d(CCCTAGGG) are similar to previous tetragonal A-DNA octamers and are discussed more fully elsewhere (Ramakrishnan & Sundaralingam, 1993*a*). As in other reported A-DNA octamers, the terminal guanine sugar pucker is C2′ *endo* despite attempts to model it in the C3′ *endo* conformation.

3.2. *Hydration*

On either side of the extended A5 backbone, water molecules bridge the phosphate O atoms of T4 with A5 and G6 with G7, stabilizing the *trans*, *trans* conformation at distances of 2.86 and 3.28 Å, respectively. A structural water found sandwiched between the π-cloud of the terminal guanine, G16, and the N2 and N3 atoms of G7 in an adjacent duplex can be viewed as either stabilizing an intermolecular base triplet or interrupting the formation of a possible base quartet found in A-DNA decamers (Ban, Ramakrishnan & Sundaralingam, 1994). This highly conserved water molecule, which has a thermal parameter of 30 Å^2 is found in seven other A-DNA octamers and maintains hydrogen-bonding distances of 2.77 and 3.14 Å with the N3 and N2 atoms of G7 while sitting 3.24 Å above the base plane of G16 in a symmetry-related duplex (Fig. 1).

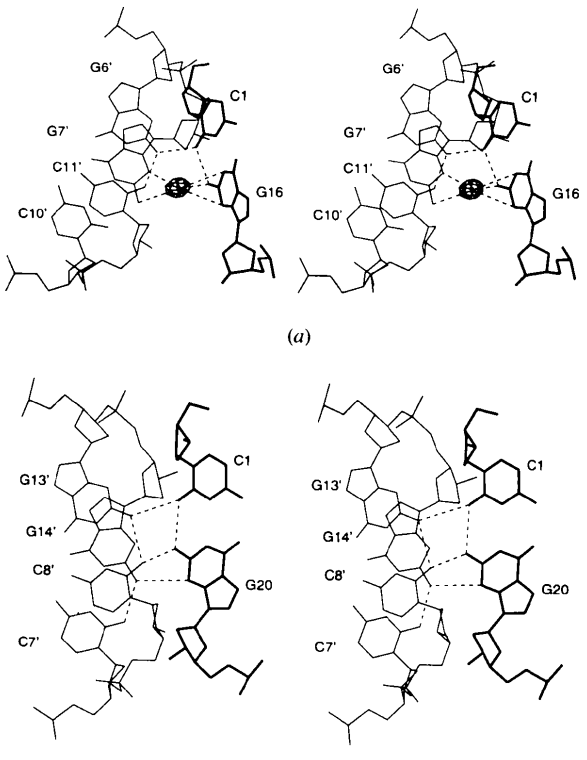

Fig. 1. Crystal packing of (*a*) a typical A-DNA octamer d(CCCTAGGG) and (*b*) a typical A-DNA decamer d(CCGGGCCCGG). (*a*) Stereoview of the crystal packing interactions between the terminal base pair C1·G16 and the minor groove of an adjacent duplex, C10′·G7′ and C11′·G6′. In the base triplet G16·C1-G6′, the O2 atom of C1 is 2.80 Å away from the N2 atom of G6′, while the N2 atoms of G16 is 4.55 Å away from the O2 atom of C11′. The water molecule is within hydrogen-bonding distance (2.77 and 3.14 Å) of the N2 and N3 atoms of G7′ and sits 3.24 Å below the C2 atom of G16. The water is between 3.40 and 3.56 Å from the N1, N2 and N3 atoms of G16. The $F_o - F_c$ density of the sandwiched water is contoured at 5σ. (*b*) In the decamer base quartet, the O2 atoms of C1 lies 3.31 Å from the N2 atom of G13′ while the N2 atoms of G20 lies 2.57 Å from the O2 atoms of C8′. Also, the N3 atom of G20 lies 3.32 Å from the N2 atom of G13′.

Srikrishnan & Parthasarathy have already illustrated the importance of 'sandwiched' water molecules in stabilizing the intermolecular interactions of pyrimidine bases in the crystalline state (Srikrishnan & Parthasarathy, 1976). The minor groove of d(CCCTAGGG) also contains a coplanar hexagonal ring of water molecules at its central base step such that two of the dyad-related water molecules form hydrogen bonds of 2.72 Å with the N3 atoms of the central adenines (Fig. 2). The four innermost water molecules have thermal parameters around 32 $Å^2$, while the two outermost water molecules have thermal parameters around 70 $Å^2$ at full occupancy. Four A-DNA octamers, d(GCCCGGGC), d(GGGCGCCC), d(CCCCGGGG) and d(GGCCGGCC), have four of the six water molecules found in this hexagonal ring. Not surprisingly, they are the four water molecules closest to the minor groove and furthest from the solvent channel. Three other octamers, d(GTACGTAC), d(GTCTAGAC) and d(CTCTAGAG), contain within their structures the two water molecules which make direct contact with the N3 atoms of the purines in positions 5 and 13. It is worth pointing out that only six water molecules are reported in d(GTCTAGAC), two of which correspond to the innermost water molecules in our hexagonal ring. Only in the present structure d(CCCTAGGG) are all six sites occupied by well ordered solvent molecules, with the outer two positions partially occupied. This hexagonal geometry of minor groove waters, as well as pentagonal rings identified in other DNA duplexes (Bingman, Li, Zon & Sundaralingam, 1992; Kennard *et al.*, 1986), are more than likely the remnants of a more ordered pattern of water molecules.

3.3. *Intermolecular packing and pseudo-base triplets*

Previous discussions on crystal packing in A-DNA have focused primarily on van der Waals interactions between the terminal base pairs of one duplex against the aliphatic sugar residues and backbone phosphate

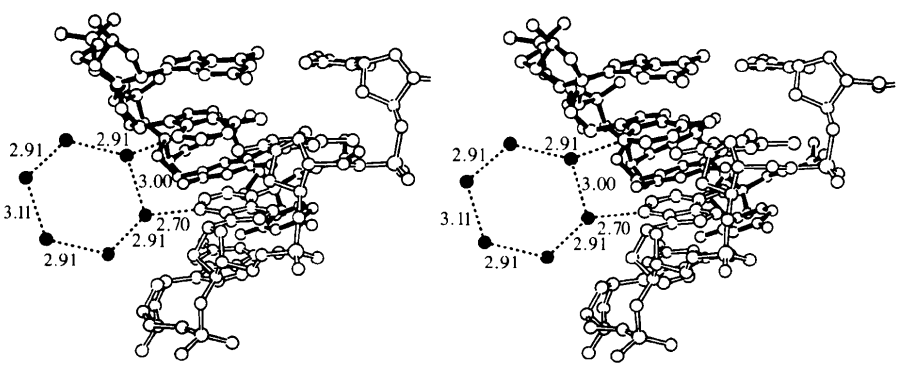

Fig. 2. Stereoview of the coplanar, hexagonal ring of water molecules in the minor groove of d(CCCTAGGG). The top three water molecules are related to the bottom three by a crystallographic twofold. The two closest waters are hydrogen bonded at 2.70 Å to the N3 atoms of the diad-related adenines, A5 and A13. Hydrogen bonds between ring waters range from 2.91 to 3.11 Å. The four innermost water molecules correspond to 4σ peaks in the electron-density map ($F_o - F_c$) while the two outermost water molecules correspond to 2σ peaks.

atoms in the minor groove of an adjacent duplex. However, burial of potential hydrogen-bond donors and acceptors would exact a large energetic penalty (Bingman *et al.*, 1992). Two ways to avoid this enthalpic penalty is through the formation of intermolecular base multiples and solvation by water molecules. Both means of dealing with this potentially unfavorable situation are seen in the tetragonal family of A-DNA octamers. Fig. 1 shows in detail the crystal packing of d(CCCTAGGG) and, consequently, the manner in which the base triplet and structural water molecule stabilize the intermolecular interactions of adjacent duplexes in the crystal lattice. For comparison purposes, Fig. 1(*b*) provides a stereoview of an intermolecular base quartet found in both the A-DNA chimeric decamer d(CCGGC)r(G)d(CCGG) (Ban *et al.*, 1994) and the A-DNA decamer d(CCGGGCCCGG) (Tippin & Sundaralingam, unpublished work),

The packing motif for d(CCCTAGGG) involves stacking of the terminal C·G base pair against the sugar-phosphate backbone of a symmetry-related duplex, forming an intermolecular base triplet between C1 and G6 in a neighboring G6·C11 base pair (Fig. 3). The O2 atom of C1 lies in the plane of the G6·C11 base pair, 2.81 Å away from the N2 atom of G6. A similar triplet interaction is observed in two other A-DNA octamers, d(CTCTAGAG) and d(CCCCGGGG). In all, four classifications of end packing are predicted for the tetragonal A-DNA octamers (G·C-G_6, C·G-G_6, C·G-G_{11}, and G·C-G_{11}), but only three are actually observed (Fig. 3). Two of these involve the formation of adjacent-strand base triplets, whereby adjacent strands of opposite polarity interact on the same sides of their minor grooves (I and II), and two involve the formation of cross-strand base triplets, whereby cross strands of similar polarity interact from opposite sides of their minor grooves (III and IV). The type of base triplet formed is highly dependent on the arrangement of hydrogen-bond donors and acceptors in the minor groove. In classes I and II, adjacent-strand triplets are formed by intermolecular contacts between the 5′-terminus of the parent duplex and the sixth residue, G6, in a symmetry-related duplex. In classes III and IV, cross-strand triplets are formed by intermolecular contacts between the 5′-terminus of the parent duplex and the 11th residue, G11 or A11, in a symmetry-related duplex. In each case a purine at position 6 or 11 is responsible for mediating intermolecular interactions between adjacent duplexes. The term 'triplet' is purposefully chosen to distinguish these single-hydrogen-bond interactions between intermolecular base pairs from the two-hydrogen-bond 'triples' seen in the A-DNA decamers (Ban *et al.*, 1994).

The first class of base triplets is observed in sequences whose first base is a cytosine and whose sixth base is a guanine, G·C-G_6. These include d(CCCTAGGG), d(CTCTAGAG) and d(CCCCGGGG). An adjacent-strand triplet is formed by packing of the terminal cytosine, C1, into the minor-groove side of G6 in a symmetry-related duplex, whereby the O2 atom of C1 serves as the hydrogen acceptor and the N2 atom of G6 serves as the hydrogen donor. The angle between intermolecular base pairs is around 114° [(I) in Fig. 3]. In the sequences d(GTCTAGAC), d(GCCCGGGC) and d(GGCCGGCC) the first base is a guanine instead of a cytosine, giving rise to the second class of base triplets, C·G-G_6. In this class, the N3 atom on the minor groove side of G1 serves as the hydrogen acceptor and binds the N2 atom on the minor-groove side of G6 [(II) in Fig. 3]. The interplanar angle formed by this intermolecular interaction is about 117°. Note that this particular interaction of bases involves base atoms of the 5′-terminus not involved in Watson–Crick hydrogen bonds; consequently, only one of the bases involved in the intermolecular contact can participate in bifurcated hydrogen bonding, *i.e.* G6. In class I triplets, both bases involved in intermolecular contacts, C1 and G6, exhibit bifurcated hydrogen bonds of the minor-groove atoms involved in Watson–Crick base paring. Sequences with purines in both positions one and six, *i.e.* class II triplets, cannot form base triplets with the minor-groove atoms responsible for Watson–Crick hydrogen bonding because of the absence of complementary donor–acceptor combinations: G1(N2) and G6(N2) are both hydrogen donors and could not form the hydrogen bond necessary to establish base triplets.

The cross-strand base triplets, classes III and IV, arise if the 5′-terminus of the parent duplex packs against the complementary strand of a symmetry-related duplex, interacting with the 11th base instead of the sixth base. In the case of d(GTGTACAC), d(GGGCGCCC) and d(GTGCGCAC), cross-strand triplets are formed through the interaction of the N3 atom in G1, acceptor, with the N2 atoms in G11, donor, giving rise to the third class of base triplets, C·G-G_{11} [(III*a*) in Fig. 3]. The angle formed by the intermolecular base pairs is approximately 120°. A variation on the third class of base triplets is represented by a single sequence, d(GTACGTAC), in which a cross-strand triplet forms between the N2 atom of G1 and the N3 atom of A11 [(III*b*) in Fig. 3; Table 3]. The resulting hydrogen-bond geometry for d(GTACGTAC) is less favorable than that found in the crystal packing of other tetragonal A-DNA octamers. Because the N2 H atoms of G1 are restricted to the base plane, the N2 H atom involved in the formation of the base triplet C·G-A projects above the AT base plane, resulting in a weaker intermolecular hydrogen bond. In (III*b*) of Fig. 3, the intermolecular hydrogen bond is drawn between the N2 of G1 and the N3 of A11, the N2 H atom

involved in the intermolecular contact extends above this plane but still makes an acceptable angle with N3 for hydrogen-bond formation. Because of the high propeller twist, −18°, of the T6·A11 base pair, it is difficult to estimate the angle of interaction by reporting the angle between the intermolecular base planes, which comes out to be 113.5°. A better approximation of this angle is the angle between the plane of the terminal base pairs and the base plane of A11, itself, which is 122.6°. The fourth class of triplets forms cross-strand triplets and is predicted to occur for octamer sequences beginning with cytosine

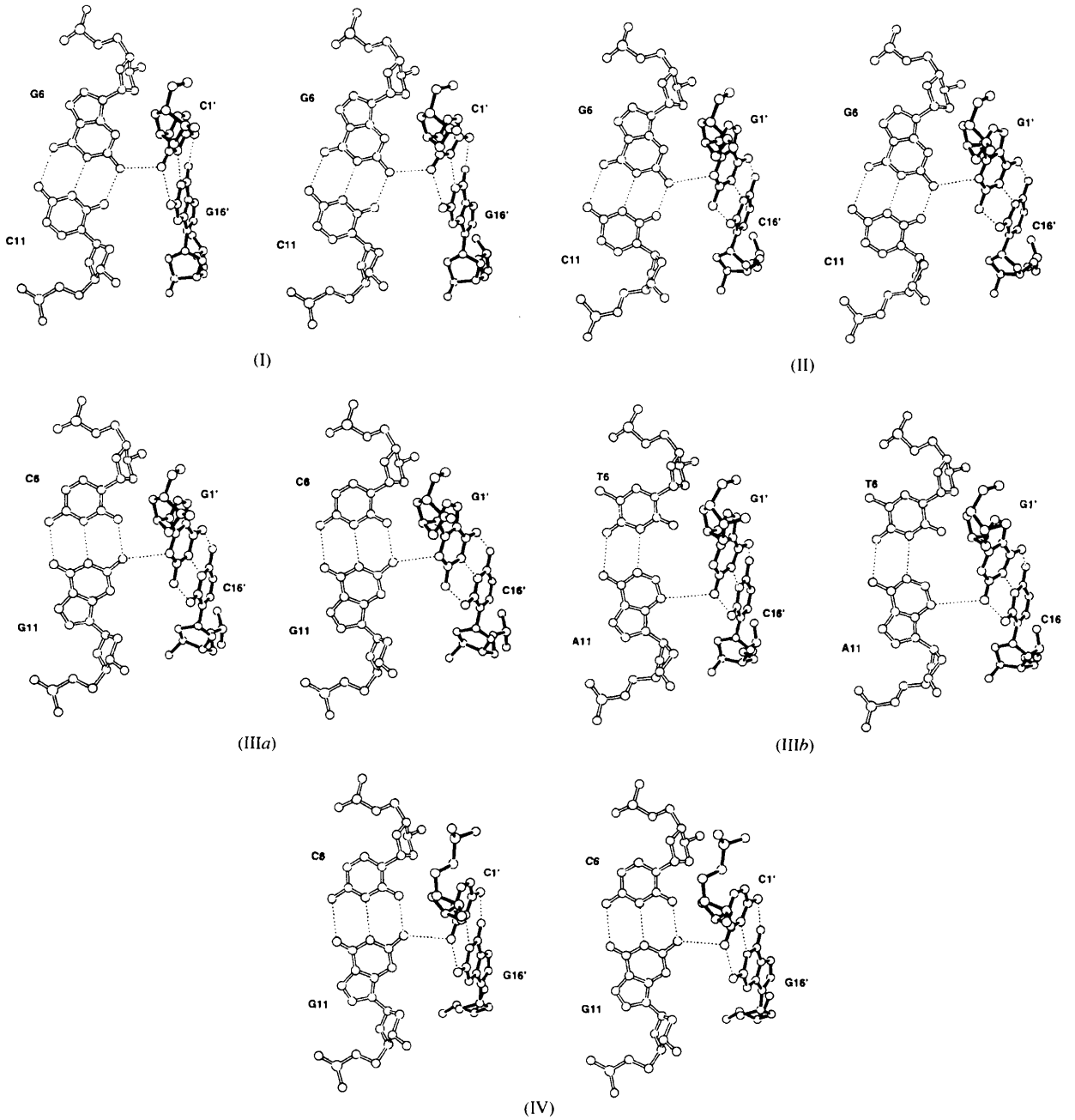

Fig. 3. Stereoviews of the four classes of pseudo-base triplets. Types I–III are observed in the tetragonal A-DNA family of octamers; type IV is postulated. (I) d(CCCTAGGG), (II) d(GTCTAGAC), (III*a*) d(GGGCGCCC), (III*b*) d(GTACGTAC), (IV) postulated d(C*X*GpypuC*X*G) sequence. Classes I and II represent adjacent-strand triplets. Classes III and IV represent cross-strand triplets. In classes I and II, base triplets form between adjacent strands of opposite polarity. In classes III and IV, base triplets form between cross strands of similar polarity. In I and IV bifurcated hydrogen bonds occur between two Watson–Crick atoms. In II and III a single bifurcated hydrogen bond occurs between one Watson–Crick atom and a base-plane N atom.

Table 3. *Intermolecular pseudo-base triplets and their hydrogen-bond distances*

Y = pyrimidine, R = purine. Bases involved in intermolecular bonding are underlined. C·G and G·C refer to terminal base pairs, and innerstrand guanines are numbered. X refers to any base type.

Adjacent-strand triplets		
Sequence	Intermolecular distance (Å)	Class average (Å)
I C·G-G_6		
d(CCCTAGGG)	2.80	
d(CCCCGGGG)	3.06	
d(CTCTAGAG)	3.16	3.00
II C·G-G_6		
d(GTCTAGAC)	3.06	
d(GCCCGGGC)	3.18	
d(GGCCGGCC)	3.24	3.16
Cross-strand triplets		
III C·G-G_{11}		
d(GGGCGCCC)	3.27	
d(GTGCGCAC)	3.42	
d(GTGTACAC)	3.49	3.39
d(GTACGTAC)	3.55	3.43
IV C·C-G_{11}		
d(CXGYRCXG)	—	—

(pyrimidine) and containing a guanine (purine) at the third position in the single strand, *i.e.* the 11th position in the duplex strand, G·C-G_{11}. The sequence would be of the form d(CXGYRCXG), where Y = pyrimidine, R = purine and X = either purine or pyrimidine and would give rise to base triplets in which both sides of the intermolecular bond would form bifurcated Watson–Crick hydrogen bonds with interplanar angles of approximately 115° [(IV) in Fig. 3]. The range of interplanar angles identified for the base triplets in the tetragonal family of A-DNA octamers, 114–123°, is within the range of minor-groove base multiples reported in the recent analysis of an A-DNA decamer, 110–130° (Ban *et al.*, 1994).

Attempts to crystallize proposed class IV sequences have so far met with little success, resulting in oils or precipitates. Some of our failures may be because of lack of conformational homogeneity in potential class IV duplexes. Sequences of the form d[C(CGCGCG)G] may not form stable A-DNA duplexes because of the left-handed forming potential of the core $(CG)_3$ base steps. However, sequences of the form d[C(CGCGCC)G], which do not have any particular stretch of base pairs that would tend to form left-handed Z-DNA, have still resisted all attempts at crystallization.

Table 3 lists the intermolecular distances formed by the four types of base triplets for ten sequences in the A-DNA family of octamers. In general, adjacent-strand base triplets form stronger intermolecular hydrogen bonds than cross-strand base triplets, and within the family of adjacent-strand triplets, G·C-G triplets (class I) form stronger intermolecular hydrogen bonds than C·G-G triplets (class II) do.

3.4. *Biological relevance*

Base multiples involving the major groove are well known modalities for the stabilization and regulation of DNA in biological systems. These include guanine quartets in telomeric DNA and base triples in triple-stranded DNA. Base multiples involving minor-groove interactions are seen in a number of A-DNA crystal structures and appear to be crucial in their stabilization (Ramakrishnan & Sundaralingam, 1993*b*). In biological systems, these same base multiples could occur in condensed forms of DNA such as chromatin and packaged viral DNA where the ends could be brought into close proximity with the core duplex, or alternatively, the core duplex could be kinked to such a degree that a central G·C base pair might be exposed to form intramolecular base triplets with base pairs elsewhere in the DNA. The octamers analyzed in this study are bent by approximately 15° and, therefore, require minimal distortion of the helix axis to form the types of single hydrogen base triplets which make up classes I to IV.

The large number of structures (ten) in this family of A-DNA duplexes has allowed the characterization of four distinct patterns of minor-groove end-terminal recognition, which has been shown to be entirely dependent on the base sequence. The way in which intermolecular hydrogen bonding in this family of octamers adjusts to changes in the terminal base pairs (C·G *versus* G·C) and the inner base sequence is relevant to the minor-groove base-pair recognition of DNA by proteins and drugs. Previous studies have pointed out that packing of terminal base pairs against the sugar-phosphate backbone in A-DNA minor grooves is analogous to the stacking of phenylalanine side chains in the TATA-binding protein (TBP) against the minor groove of the TATA-box sequence (Eisenstein & Shakked, 1995). Moreover, the intermolecular triplets in the tetragonal A-DNA octamers, formed by the interaction of the N2 of guanine with a symmetry-related O2 of cytosine (class II and III) or a symmetry-related N3 of guanine (class I and IV), are analogous to those interactions between asparagine or threonine side chains of TBP and the N3 of adenine or the O2 of thymine in the TATA box. This analogy is further strengthened by the fact that the minor groove of the TATA box in the TBP/TATA-box complex is wide and shallow just like the minor grooves of the A-DNA octamers.

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