

# GC rich DNA oligonucleotides with narrow minor groove width

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**Abstract** Investigation of the width of the minor groove using 500 MHz NMR spectroscopy in three closely related 11-mer B-DNA duplexes shows that the minor groove is narrow in a GC rich oligonucleotide, and that a narrow minor groove is not something endemic to DNAs with persistent repetitions of adenine nucleotides (A-tract DNA). The width of the groove is dictated by local sequence contexts and independent of neighboring A-tract DNA.

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**Key words:** GC rich DNA oligomer; Minor groove width; 2D NMR; 2D NOESY in water; Pyrimidine-purine junction; Purine-pyrimidine junction

## 1. Introduction

There is considerable interest in the intrinsic bending of DNA, and several issues, the influence of fluctuations and the effect of local sequences in DNA curvature among others, remain unresolved [1]. Although the overall structure of DNA with repeating tracts of adenines – A-tract DNA – belongs to the B form, there are significant local structural deviations between A-tract DNA and the B form of random nucleotide sequences [2–5]. The pronounced structural feature of A-tract DNA is the presence of a narrow minor groove and bending at the A-tract. X-ray crystallographic study of oligo(dA)-oligo(dT) [6] and fiber diffraction study of poly(dA)·poly(dT) [7] report a minor groove which is narrow by about 3 Å compared with over 5 Å in standard B-DNA. Similar results were obtained by NMR [8] and energy calculations [9] of poly(dA)·poly(dT) in solution.

In NMR studies, the interstrand NOE between the H2 of adenine and H1' of the 3'-neighboring residue from the complementary strand serves as a good measure of the minor groove width. This distance is of the order of 5.1 Å in standard B-DNA [10], whereas it can be short enough for NOE observations (<5 Å) in A-tracts. Extensive NMR studies [2,11–13] of DNA oligomers having varying lengths of A-tract have demonstrated that the width of the minor groove in the A-tract decreases gradually from the 5' to the 3' direction; that is, the minor groove is widest at the 5' end of the A-tract, compresses gradually, and reaches a minimum plateau near the third or fourth/fifth adenine from the 5' end of the tract. Despite these extensive investigations, there is no systematic study to answer several questions associated with the narrowing of the minor groove. How does a specific sequence affect the narrowing of the groove? Is this effect local and contextual or long range? Is the narrowing limited and endemic to

A-tracts? Can GC rich regions possess narrow minor grooves?

By investigating the structure of three closely related non-selfcomplementary 11-mer DNA duplexes (Fig. 1) by NMR spectroscopy we demonstrate that the width of the minor groove is dependent on the local sequence, and that both AT and GC rich sequences, depending upon local sequence context, may have a narrow or a wider minor groove.

Previously, we studied the parent sequence, code named 'AAA' (Fig. 1), by NMR to seek the effect of the three contiguous adenines on the overall structure and dynamics of the oligomer [14]. As expected, the A<sub>3</sub>·T<sub>3</sub> block forms a special structure with a narrow minor groove and the groove width gradually decreases in the 5'-to-3' direction along the strand of adenines. To our surprise, however, the H2-H1' interstrand distance is found still short in the G13-A14-T9-C10 step (in the GC rich region) which is separated from the A<sub>3</sub> block by one GC pair downstream. On the other hand, we did not see the interstrand H2-H1' NOE contact in a similar G19-A20-T3-C4 step, one GC pair upstream from the block of three As. In the present study, we examine two additional undecamer duplexes, code named 'GAA' and 'GGA' (Fig. 1). The abbreviations 'AAA', 'GAA' and 'GGA' refer to the sequence of the central three residues in the top strand in Fig. 1. The rest of the sequences is identical in the three 11-mer duplexes. The three duplexes are designed to see whether the short interstrand distance observed in the downstream GC rich region in AAA is propagated from the A-tract downstream across a GC pair, or a relatively narrow minor groove is formed intrinsically without the participation of the upstream A-tract. We compare the interstrand H2-H1' NOE cross peaks of the three oligomers and rationalize our observation on the basis of simple mechanistic models that explain the local deformations, and thus the bending of DNA.

## 2. Materials and methods

The undecamers AAA, GAA and GGA were obtained commercially and used without further purification. Deuterated oligomers for all three duplexes where AH8 and GH8 were selectively deuterated were prepared by heating the corresponding oligomers overnight in D<sub>2</sub>O at 80°C at pH 7.5.

For both H<sub>2</sub>O and D<sub>2</sub>O samples, the DNA concentration was 2.0 mM in duplex, and the salt concentration was 100 mM in NaCl (pH 7.0 in 10 mM sodium phosphate buffer with 1 mM EDTA).

1D and 2D NOESY NMR spectra in 90% H<sub>2</sub>O and 10% D<sub>2</sub>O (hereafter referred to as water spectra) were recorded at 500 MHz at 5°C, by the use of the jump-return procedure. The mixing time of the 2D NOESY water spectra was 200 ms. The 2D NOESY spectra in D<sub>2</sub>O were collected at 500 MHz at 5°C at four mixing times, 50, 100, 150, and 300 ms, RD = 1.5 s for NS = 64 with the pulse sequence (RD-90°-t<sub>1</sub>-90°-t<sub>m</sub>-90°-Acq)<sub>NS</sub>. All 2D spectra were Fourier transformed into a matrix (2048 × 2048) with zero filling. NOE intensities were determined by integrating the areas of cross peaks and expressing them as % relative to the diagonal peak intensities. ROESY data have also been collected for AAA.

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### 3. Results and discussions

#### 3.1. Resonance assignment

The assignments of the exchangeable imino protons and the H2 protons were obtained by 1D and 2D NOESY experiments in water. The 2D NOESY spectra for GGA, imino vs. imino region, appear in Fig. 2. The three thymines of this duplex makes two contacts each with guanines. The four cross peaks between the AT and GC imino protons contain six such G-T contacts, three of which overlap in one of the cross peaks as indicated. Thus, T16N3H has two cross peaks, one with the neighboring G15N1H and the other with G6N1H across the strand. Likewise, T9N3H shows two overlapping cross peaks with G13N1H and G15N1H across the strand. T3N3H also has interstrand cross peaks with G19N1H and G21N1H. Note that G6N1H is the only G1H with cross peaks to GC (G5N1H) and AT (T16N3H) pairs. From these patterns one can straightforwardly assign the imino resonances of AT and GC pairs. The chemical shift of the imino proton of the terminal G12 is expected to appear broad due to exchange at a low field as has been demonstrated in other systems by Ulyanov et al. [14] and Sarma et al. [15].

The correct assignment of the AH2 resonances is very crucial to the argument in this paper. Fig. 3 demonstrates how uniquely the three AH2s of GGA are assigned from the 2D

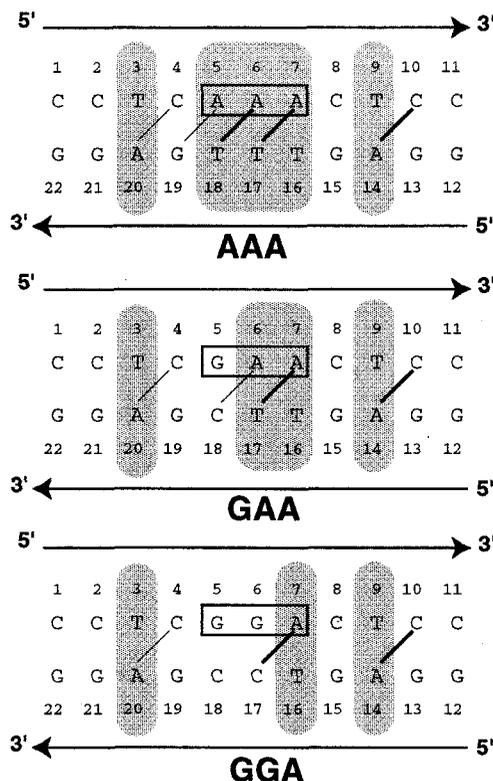


Fig. 1. The three closely related sequences of the 11-mer DNA duplex employed in this study. They are abbreviated as AAA, GAA and GGA, based on the sequence variation at the center. The potential interstrand H2-H1' contacts are shown by slashes; heavy slashes indicate those pairs for which we successfully measured this distance, light slashes indicate the absence of NOE contact, and in these instances distances are beyond 5 Å. In all the oligonucleotides, GH8 and AH8 were deuterated to simplify the spectra and to measure the interstrand AH2-H1' NOEs as accurately as possible.

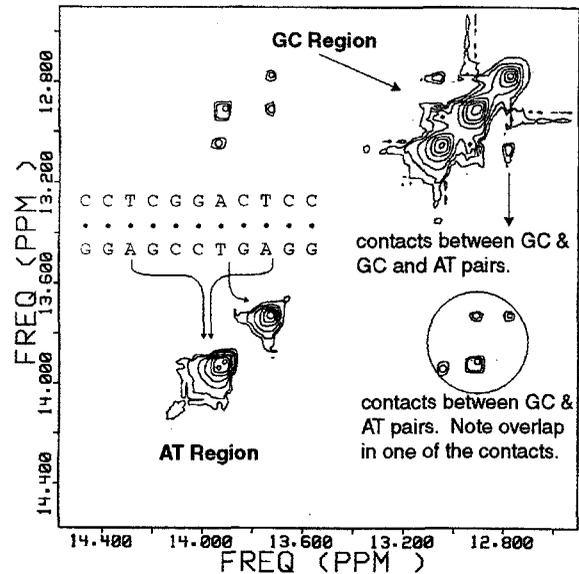


Fig. 2. 500 MHz water 2D NOESY of GGA at 5°C, 200 ms mixing time showing the connectivities between base pairs in the imino region. Note that the resonance at 12.78 ppm shows connectivity to a GC pair and to an AT pair. This is possible only for the G6-C17 pair in GGA. See text for further details.

NOESY spectra in water, once the imino protons are assigned. The contour plot (Fig. 3a) contains the imino-to-base proton region, where the three thymine imino-to-AH2 cross peaks are boxed. The projections below Fig. 3a illustrate the cross peaks from the three thymine imino protons of GGA in water. From the NH of T3 (Fig. 3b), a strong cross peak is observed at 7.75 ppm, indicating that this resonance is from H2 of A20 across the strand. There are also cross peaks to the imino protons of G21 (13.04 ppm) and G19 (12.94 ppm) and to amino protons (not assigned). Similarly, cross peaks from NH of T9 (Fig. 3c) include resonances from imino protons of G15 (12.91 ppm) in addition to the strong peak from H2 of A14. Fig. 3d shows the cross peaks from NH of T16 to H2 of A7, as well as to NH of G15 (12.91 ppm) and G6 (12.78 ppm).

The non-exchangeable protons for GGA and GAA were assigned following the standard connectivities as explained previously in detail for AAA by Ulyanov et al. [14]. A representative connectivity walk for the case of GAA is illustrated in Fig. 4 for base-base and base-H1' regions at the mixing time of 150 ms. The chemical shifts of the protons of GAA and GGA at 5° obtained by the above analysis are listed in Tables 1 and 2. The shift data for AAA have already been reported in [14]. We have not discussed the assignment of imino resonances in the oligomer duplex GAA. The approach employed is very similar to what is described above for GGA and for the parent oligomer AAA described in extenso by Ulyanov et al. [14].

#### 3.2. The 11-mer DNA duplexes AAA, GAA and GGA in aqueous solution belong to the B family

We have provided extensive arguments elsewhere for AAA [14] based on NMR data such as the expected NOESY walks between base protons and H1' as well as that between H3' (e.g. see Fig. 4 for GAA) which show that AAA exists in aqueous solution in the B form. Similar NMR data and arguments conclusively showed that the new 11-mer duplexes

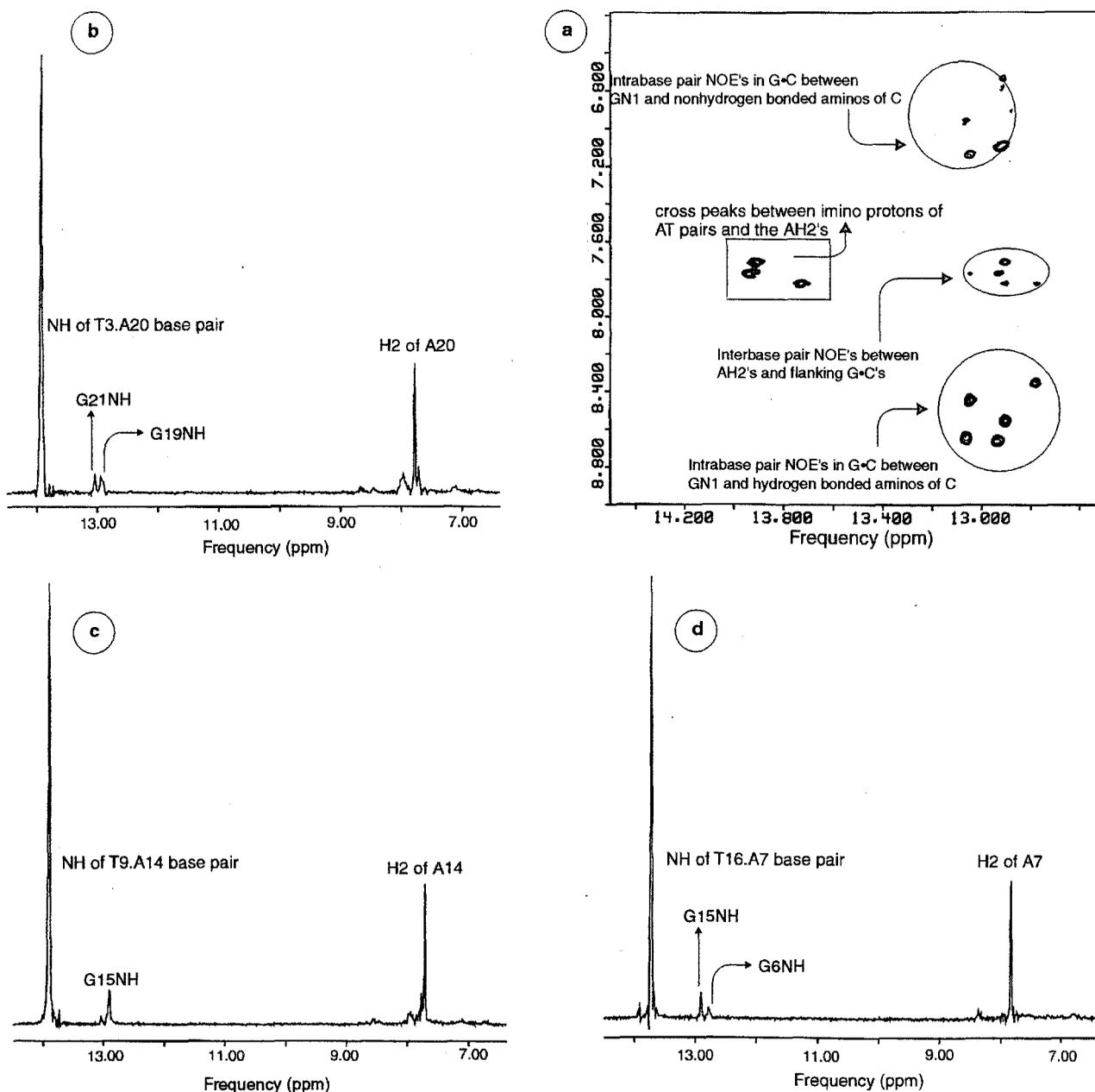


Fig. 3. 500 MHz water 2D NOESY of the 11-mer duplex GGA showing the NOESY cross peaks between the base and imino regions. The origins of various cross peaks are indicated in the diagram. The individual projections illustrate the unambiguous assignments of the three AH2's in this duplex of 22 nucleotides. The spectrum was obtained under the following conditions: jump-return, imino selected, 200 ms mixing time, 5°C.

GAA and GGA also exist in the B form in aqueous solution. In order to be brief and not to repeat arguments from reference [14], we do not present the details why GAA and GGA are in the B form here.

### 3.3. Measurements of distances between H2 of adenines and H1' protons across the minor groove

The groove widths of the three duplexes, AAA, GAA and GGA, were monitored by the interstrand H2-H1' distances measured in those duplexes, where H8 protons of adenine and guanine were deuterated. The main purpose of the deuteration was to minimize the overlap of H2 proton resonances by H8 protons so that the small interstrand cross peaks between H2 of adenine and H1' could be observed. These cross

peaks in the case of GAA are identified in Fig. 4. The H2-H1' inter-proton distances were obtained from the initial build-up rates of the NOESY cross-peak intensities measured as the integration of the cross peak slices at mixing times of 50, 100, 150 and 300 ms. The equation  $r = r_{\text{ref}}(\text{noe}_{\text{ref}}/\text{noe})^{1/6}$  was used to calculate the distances, where  $r$  is the distance of interest,  $r_{\text{ref}}$  is a fixed distance, and  $\text{noe}$  and  $\text{noe}_{\text{ref}}$  are the corresponding NOEs. The cytosine H6-H5 distance of 2.44 Å was used as the fixed reference. The build-up curves for the H6-H5 NOEs for the three duplexes are approximately linear up to the 100 ms mixing time. The initial build-up curves for the cytosines in GAA and GGA coincide well with in each molecule, giving slopes of  $0.176 \pm 0.009$  and  $0.203 \pm 0.007\%/ms$ , respectively, and these values have been



Table 2  
Proton chemical shifts (ppm) of the 11-mer duplex GGA (Fig. 1) in solution at 5°C with TSP as an internal standard

	H6/H8	H2/H5 CH3	H1'	H2'	H2''	H3'	H4'
C1	7.79	5.85	5.90	2.34	2.54	4.65	4.11
C2	7.76	5.65	6.00	2.23	2.54	4.82	4.11
T3	7.51	1.65	6.10	2.23	2.54	4.89	4.10
C4	7.46	5.65	5.53	1.99	2.32	4.85	4.30
G5	7.85	–	5.48	2.64	2.73	4.98	4.33
G6	7.76	–	5.60	2.61	2.65	4.65	4.37
A7	8.15	7.82	6.19	2.69	2.88	5.15	4.47
C8	7.26	5.15	5.75	1.97	2.49	4.64	4.19
T9	7.44	1.52	6.06	2.15	2.54	4.87	4.19
C10	7.54	5.66	5.99	2.14	2.44	4.85	4.22
C11	7.48	5.43	6.15	2.31	2.25	4.56	3.97
G12	7.83	–	5.64	2.54	2.73	4.84	4.65
G13	7.83	–	5.53	2.67	2.78	4.83	4.36
A14	8.13	7.68	6.15	2.74	2.94	5.08	4.49
G15	7.58	–	5.86	2.45	2.75	4.89	4.41
T16	7.23	1.20	6.04	2.12	2.45	4.88	4.25
C17	7.54	5.56	5.99	2.23	2.47	4.85	4.23
C18	7.44	5.59	5.41	1.99	2.32	4.85	4.09
G19	7.92	–	5.42	2.69	2.74	4.83	4.18
A20	8.10	7.75	6.00	2.66	2.87	5.05	4.43
G21	7.64	–	5.59	2.34	2.48	4.96	4.36
G22	7.64	–	6.09	2.42	2.34	4.61	4.21

est in AAA were reported earlier by us [14] from single point NOESY experiment. The currently reported distances in Fig. 5 for AAA from multiple NOESYs are slightly larger than those reported earlier.

### 3.4. The minor groove width can be narrow in GC rich regions and the width is dependent on local sequence context and independent of upstream narrow groove of A-tracts

The most remarkable observation in Fig. 5 is that in GAA, the blocks G6A7·T16C17 and T9C10·G13A14 in GC regions show H2-H1' distances in the range of 4 Å, clearly revealing a narrow minor groove. This observation clearly rules out the notion that a narrow minor groove is something endemic to A-tract DNA. It indeed could be present in GC rich regions.

Further, the observation that in all three 11-mer duplexes, AAA, GAA and GGA, the H2-H1' distance in the block T9C10·G13A14 is in the range of 4–4.5 Å (Fig. 5). This observation in all three oligomers rules out any explanation of this observation in AAA and GAA on the basis of the effect of the narrow minor groove at the A-tracts upstream. Narrowness of the minor groove and consequent bending must be dictated by the local context of the sequences.

### 3.5. The effect of the immediate flanking sequences at the pyrimidine-purine junction or within oligo purine-oligo pyrimidine runs

Distributed among the three oligonucleotides in Fig. 1 are eight GA·TC steps (2 in AAA, 3 in GAA and 3 in GGA). Out of these eight steps, four (1 in AAA, 1 in GAA and 2 in GGA) show H2-H1' distances in the range of 4–4.5 Å; the remaining four (1 in AAA, 2 in GAA and 1 in GGA) show distances beyond 5 Å. This observation clearly illustrates the significance of local sequence context dictating the width of the minor groove at least in GC rich oligomers.

Even though these observations cannot be rationalized by a single all encompassing universal concept, they can indeed be rationalized, case by case, depending upon the sequence context. Note that the three GA·TC blocks upstream

(G19A20·T3C4) in the three separate oligomers consistently have H2-H1' distances larger than 5 Å; on the other hand, the three GA·TC blocks downstream (G13A14·T9C10) consistently show a shorter distance of 4–4.5 Å.

The upstream GA·TC is localized adjacent to a Y<sub>n</sub>-R<sub>m</sub> junction whereas the downstream GA·TC is within a continuous run of purines, and this purine run later becomes part of a R<sub>n</sub>-Y<sub>m</sub> junction. According to the formalism of Zhurkin et al. [16] and Yanagi et al. [17] due to pronounced buckles Y<sub>n</sub>-R<sub>m</sub> and R<sub>n</sub>-Y<sub>m</sub> junctions have different cup angles, the former looks like a 'butterfly' with a negative cup, the latter appears 'rhombic' with a positive cup. According to Zhurkin et al. [16], the magnitude of the buckle angle is considerably less at the junctions ('flattening'), and increases as one travels towards the end of the duplex. The NMR data by Ulyanov et al. [18] on the selfcomplementary duplex GGATCC provide experimental support for these predictions. The flattening of the buckle of C4 at the Y<sub>n</sub>-R<sub>m</sub> junction within the butterfly (formed by C4A5·T18G19 in AAA; C4G5·C18G19 in both GAA and GGA) is considerably more than the flattening of the buckle of C10, situated away from the R<sub>n</sub>-Y<sub>m</sub> junction and

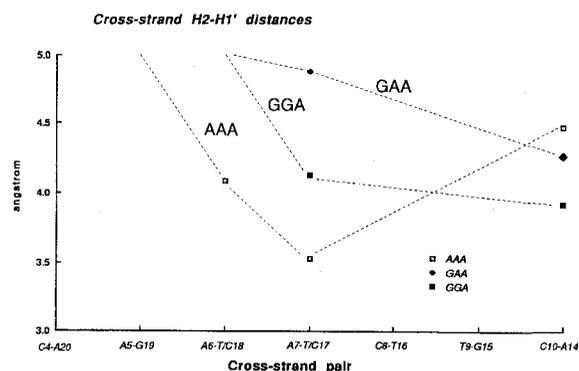


Fig. 5. Plot of interstrand H2-H1' distance against the corresponding cross-strand pair. This distance reflects the width of the minor groove. See Fig. 1 for sequence and numbering scheme.

the rhombic structure (formed by A7C8·G15T16 in all three oligomers) within the oligo(R)·oligo(Y) runs. Because C10 is considerably more buckled than C4 we are able to observe the H2A14-H1'C10 distance of 4–4.5 Å. The lack of sufficient buckle at C4 makes the H2A20-H1'C4 distance more than 5 Å.

The middle of the GAA 11-mer duplex contains the G5A6·T17C18 step, and the observed distance between H2A6 and H1'C18 is beyond 5 Å. This can be rationalized on the mechanistic formalism presented above, viz., C18 is at a  $Y_n$ - $R_m$  junction, and its buckle is considerably flattened increasing the distance between H2A6 and H1'C18. The mechanistic scheme proposed above also explains the observed short H2A7-H1'T17 in AAA and GAA and H2A7-H1'C17 in GGA because the pyrimidine track is expected to have strong buckles.

However, it does not explain why consistently in all three oligomers we observe a distance beyond 5 Å between AH2 and CH1' for the T3C4·A20G21 steps, while in the A5A6·T17T18 in AAA, the H2A6-H1'T18 distance is close to 4 Å. All these dinucleotide steps are at  $Y_n$ - $R_m$  junctions, and according to the above Zhurkin formalism [16], the observed distances should be beyond 5 Å. This obviously means that there are other structural factors that also control the width of the minor groove or special provisions must be made when T is at the  $Y_n$ - $R_m$  junction.

### 3.6. On the buckle of thymine at $Y_n$ - $R_m$ junctions

In the paper which exclusively dealt with the parent oligomer AAA [14], we described in extenso how Calladine steric clashes [19–21] in the minor groove between purines in the opposite strands of the block YA·TR and subsequent slide and roll of base pairs increase the interstrand H2-H1' distances. This was invoked to rationalize the lack of observed NOE between H2A5 and H1'G19. We further invoked that in  $A_n$ · $T_n$  blocks, the thymine is heavily buckled [16] and used this to explain the observed short distances detected between H2A6-H1'T18, H2A7-H1'T17 and H2A14-H1'C10 in the AAA duplex. Such arguments can also explain the short observed distances in the new oligomers GAA and GGA (Fig. 1, heavy slashes).

However, we were unable to rationalize certain contradictions and internal inconsistencies in Ulyanov et al. [14]. Why did we observe, in AAA, NOE between H2A6-H1'T18 in the A5A6·T17T18 block at the  $Y_n$ - $R_m$  junction while no NOE was observed between H2A20-H1'C4 in the G19A20·T3C4 block at the  $Y_n$ - $R_m$  junction? Note that in the former a T18 is at the  $Y_n$ - $R_m$  junction whereas in the latter there is a C4.

It was to solve this puzzle that we constructed the analog GAA where T18 in AAA is replaced by C18, and indeed when the replacement was made, no NOE was detected between H2A6 and H1'C18 indicating the distance to be beyond 5 Å. This means three things:

1. A cytosine at the  $Y_n$ - $R_m$  junction could be easily flattened, in the terminology of Zhurkin et al. [16], and obviously such flattening increases the distance between the H1' of this cytosine and the H2 of A across the groove one nucleotide downstream. In the collection of the three oligonucleotides in this report, we have four such examples: C4 in AAA, GAA, GGA and C18 in GAA.

2. The flattening of the cytosine at the  $Y_n$ - $R_m$  junction takes place irrespective of the presence of a contiguous track of thymines upstream of the C. For example GAA.
3. A thymine at the  $Y_n$ - $R_m$  junction remains strongly buckled, and such buckling decreases the distance between the H1' of this thymine and the H2 of A across the groove one nucleotide downstream. One cannot conclude now whether the intransigence of a T to flattening at the  $Y_n$ - $R_m$  junction is due to the presence of a track of Ts immediately upstream or is something endemic to an AT pair, that is, will the T in a sequence such as 5'-CCTR<sub>n</sub>·Y<sub>n</sub>AGG be buckled?

Because of its observation in several cases, it appears that conclusion 1 above is very certain. With respect to conclusions 2 and 3, it will be necessary to construct several closely related oligomers very similar to AAA, GAA and GGA, and investigate their structure before drawing firm conclusions.

### 3.7. A GC rich oligonucleotide duplex with narrow minor groove

In the case of GGA, there are only three A·T pairs distributed individually in a GC rich matrix, and potentially there are three interstrand H2-H1' contacts, H2A7-H1'T17, H2A14-H1'C10 and H2A20-H1'C4 (Fig. 1, GGA). We were able to observe only the first two in the range of 4–4.1 Å, not the third one.

Since there are no  $A_n$ · $T_n$  blocks at the center, it is quite clear that narrow minor grooves at the level of oligonucleotides can be formed without participation of an A-tract. The mechanistic scheme as discussed above explains the experimental observation. It is not possible currently to determine by NMR spectroscopy the width of the minor groove at each dinucleotide step in a molecule such as GGA because the method is based on distances involving adenine H2. Hopefully future developments in NMR will make this possible and may demonstrate that each of the dinucleotide steps in the tracks consisting of  $R_n$ - $Y_m$  junction in GC rich oligomers has heavily buckled pyrimidines causing the compression of the minor groove.

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