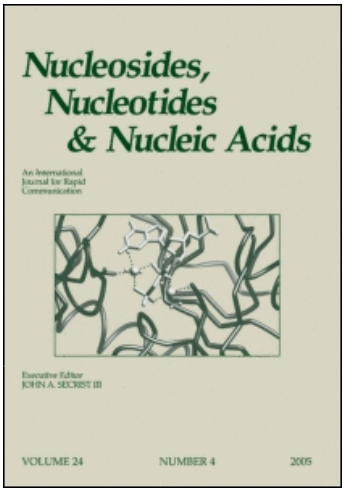


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# The Biochemical Significance of Parallel DNA Duplexes

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## ABSTRACT

Structural and synthetic model are given for (modified) parallel DNAs with non-Watson and Crick duplex formation.

*Key Words:* Parallel bases; Phosphatemethylated DNA; Hydroxymethylphosphonate DNA; Quadruplexes.

X-ray crystallographic studies on acetylated DNA or RNA nucleosides show modes of hydrogen-bonded pairing which differ from the antiparallel coupling as found in the Watson and Crick model. It was established that 3′,5′-di-*O*-acetyl thymidine crystallizes in a parallel base-paired conformation with two equivalent N(3)-H ··· O(4) hydrogen bonds which displays a *twofold rotational symmetry*.[1,2] This conformation is also present in solution. Similar observations were made for methylphosphotriester DNA showing parallel T=T N(3)-H ··· O(4) pairing, and C=C N(4)-H ··· N(3) pairing only for $S_P$ chirality.[3–5] This exclusive methylation resulted in an extended investigation of the methylphosphotriester DNA of the T-hexamer showing the unique properties of a parallel right-handed duplex.[6] Recently the significance of parallel duplex formation has been found in the ends of chromosomes capped by telomers consisting of a GGGG tetrad alignment in the presence of $K^+$ ions with a *fourfold rotational symmetry* in consequence of

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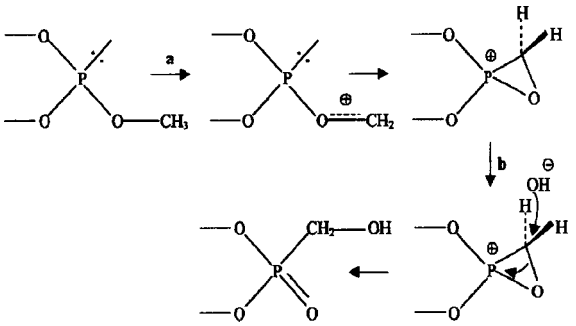
N(2)-H ··· N(7) and N(1)-H ··· O(6) hydrogen bonding.[7] The latter mode is exclusively found in the parallel formation of T=T pairing. In connection with the function of telomerase it may be of importance to note that the cationic oligopeptide octadeca (L-lysine) is able to induce parallel duplexes with T=T and C=C base pairs in natural oligomers as $dT_{10}$, $dC_{10}$, $d(C_6T_6)$, and $d(T_6C_2T_2)$.[8] It may be of interest to mention that the crystal structure of 2′-deoxy-3′,5′-di-*O*-acetyl guanosine in comparison with 3′,5′-di-*O*-acetyl thymidine shows an *asymmetric* unit consisting of two independent molecules. The G bases are linked by the N(1)-H ··· N(7) and N(2)-H ··· O(6) hydrogen bonds to form a virtually planar system.[9] The other purine base A may form a parallel arrangement just like the parallel C=C pairing with a *twofold rotational symmetry* consisting of only one pair of N(6)-H ··· N(1) hydrogen bonds. For that reason A-quadruplexes are impossible. The crystal structure of 2′-deoxy-3′,5′-di-*O*-acetyl adenosine differs from a parallel duplex because the N(6)-H ··· N(1) hydrogen bonding is accompanied with N(6)-H ··· N(7) bridging.[10] Severe criticism of the possible formation of parallel duplexes was based on a *synthetic* procedure. Different from our synthesis of methylphosphotriester DNA of the T-hexamer a methoxyl group at P(III) was used as protecting agent. The phosphite was converted into the methylphosphotriester with *t*-butyl hydroperoxide.[11] However, in the case of a methoxyl group at P(III) it is clear that we are dealing with a very reactive primary carbon as methyl, resulting in a competition with P(III) toward *t*-butyl hydroperoxide. This aspect has not been recognized.[11] With all data available as UV hyperchromicity, the melting curves with $^1$H NMR, the FAB mass spectroscopic numbers, and the $^1$H NMR characterization it is clear that in this case we are dealing with a hydroxymethylphosphonate DNA which is an isomer of methylphosphotriester DNA. The mechanism for the formation of hydroxymethylphosphonate DNA is given in the reaction Sch 1.

In fact this conversion is based on an intramolecular Michael addition followed by an Arbuzov-Michaelis reaction. The initial intermediate formed after hydride abstraction by *t*-butyl hydroperoxide under formation of *t*-butyl alcohol can be considered as a highly activated formaldehyde and thus accessible for (intramolecular) nucleophiles. The isomerization toward the corresponding natural DNA thereby following the procedure of the solid-phase synthesis can be described by the formation of a P(V) trigonal bipyramidal (TBP) geometry. The intramolecular electron




***Scheme 1.*** **a** = *t*-BuOOH/$CH_2Cl_2$; **b** = $OH^-$.

displacement is in according to the dynamic properties of a P(V) TBP structure.[12] Compounds which show resemblance with methylphosphonate DNAs are strongly hindered by their backbone structure for duplex formation.[13] This explains the absence of self-association of the hydroxymethylphosphonate derivative $d([T_P(O)CH_2OH]_5T)$ the isomer of the methylphosphotriester derivative $d([T_P(O)O\text{-}CH_3]_5T)$. An interesting point remains the difference in stabilization of parallel duplex formation with non-Watson and Crick base-pairing. In the case of T=T and C=C pairing this unusual hybridization could be effectuated by methylation of the phosphate linkages or by peptides via well-defined local charge interactions. These examples clearly show the 3D role of peptides on stabilization of DNA duplexes. Although shielding of the negative charge of the phosphodiester linkages is of importance, it could be shown that parallel duplex formation is absent under high salt conditions. Apparently under these conditions the anionic shielding is less effective than methylation of phosphodiester linkages and/or cationic complexation with peptides. Another well-defined example is the antiparallel right-handed DNA (B-DNA) conversion in the antiparallel left-handed DNA (Z-DNA).[14] In that case phosphatemethylation and increase of salt concentration gives the same result because the right-handed duplex is already present with the alternating CG sequence necessary for the conversion into the Z-form. On the other hand the role of the alkali metal ions in the stabilization of the G-quadruplexes is very selective. In contrast to $Na^+$, $K^+$ ions induce a parallel arrangement. The $K^+$ ions are positioned between the stacked G-quartets and complexed with eight of the carbonyl oxygens in a bipyramidal antiprismatic arrangement. Furthermore this separation of charge is very effective in diminishing the repulsion between the negatively charged strands. In some respect there is correspondence with the valinomycin-$K^+$ complex, a cyclic polypeptide-like molecule, consisting of a threefold repeating sequence in which the $K^+$ ion is coordinated to the oxygens of the carbonyl groups of six valine residues. Furthermore valinomycin has nearly a 20,000-fold preference for $K^+$ over $Na^+$[15].



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