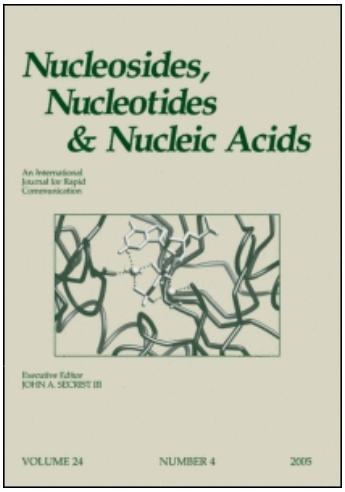

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4-Guanidino-2-pyrimidinone Nucleobases: Synthesis and Hybridization Properties

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4-Guanidino-2-pyrimidinone Nucleobases: Synthesis and Hybridization Properties

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ABSTRACT

N-Alkylated 4-guanidino-2-pyrimidinone-containing nucleosides, in which the guanidine group mimics the double hydrogen bond donor pattern of protonated cytosine, were introduced in polypyrimidine sequences to explore their triple-helix forming capabilites. UV and CD melting experiments showed that strands containing these base analogues did not form triplex complexes.

Key Words: Modified oligonucleotide; Solid phase synthesis; *H*-phosphonate; 4-Guanidino-2-pyrimidinone; Triple helix.

Triple helix-forming oligonucleotides have been shown to produce regulatory effects in biological media, but their possible pharmacological application is still very limited.[1] For example, the formation of parallel triple helices is hampered in physiological conditions because cytosine needs to be protonated to form C^+(G.C) triads (Sch. 1a). Several analogues have been designed to overcome this pH dependence.[2] 4-Guanidino-2-pyrimidinone (Sch. 1b) is thought to mimic the double hydrogen bond donor pattern of protonated cytosines, so we decided to explore its use in triple

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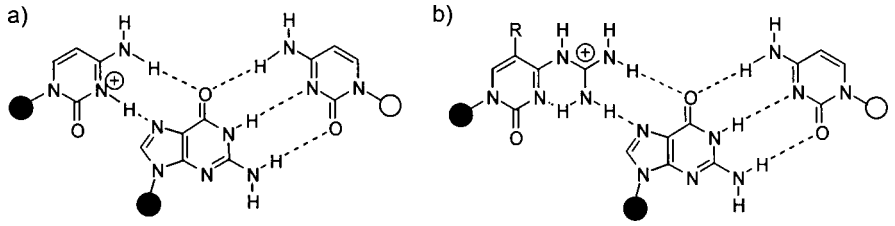
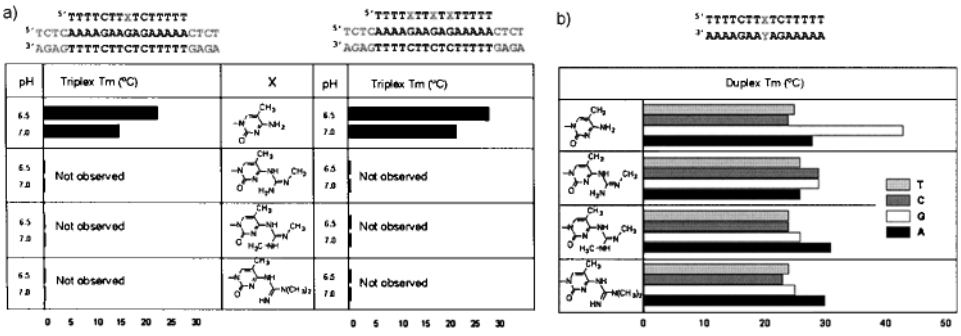


Scheme 1. Nucleobase triads in triple-helix parallel motifs formed by (a) protonated citosine or (b) 4-guanidino-2-pyrimidinone.

helix-forming oligonucleotides. Since the guanidine group is more basic than cytosine, triplexes are expected to form at lower pH. Behr and cowokers have described the synthesis of the 4-guanidino-2-pyrimidinone nucleoside, and the introduction in oligonucleotides of closely-modified base analogues.[3,4] Here we present our results on the introduction of 4-guanidino-2-pyrimidinone nucleobases in oligonucleotides and the study of their hybridization properties.

We recently developed a synthetic scheme[5] to prepare guanidino-derivatized nucleoside *H*-phosphonates. These derivatives were used to synthesize pyrimidine strands containing one to three modified nucleobases to check their triple-helix forming capabilities. Modified strands were hybridized with the complementary duplex and their stability was evaluated by UV melting experiments at two different pH values (pH 6.5 and pH 7.0, Sch. 2a). In contrast to oligonucleotides containing 5-methylcytosine, no triplex transitions were observed for any guanidine-containing oligonucleotide. Subsequent analyses by CD clearly confirmed this result. The inability of guanidine-modified oligonucleotides to form triplexes was unexpected, since *N*-methyl-2-pyrimidinone should, in principle, be able to bind to a G.C base pair. However, the distortion caused by the lack of isomorphism with canonical pyrimidine triads might account for this result. We also studied the hybridization properties of the guanidine analogues in duplexes (Sch. 2b), but no special preferential binding to any of the natural nucleobases was observed for either of them. Work is in progress to further analyse the hybridization properties of these analogues.



Scheme 2. UV melting experiments for (a) triplexes and (b) duplexes containing 4-guanidino-2-pyrimidinone nucleobases.

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