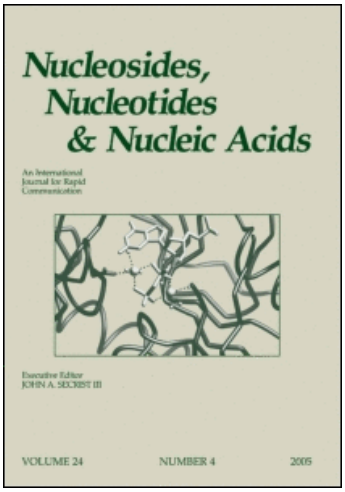

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Oligonucleotides Incorporating 7-(Aminoalkyn-1-yl)-7-deaza-2′-deoxyguanosines: Duplex Stability and Phosphodiester Hydrolysis by Exonucleases

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ABSTRACT

Self-complementary {[5′-d(G-C)$_4$]$_2$} and non-selfcomplementary oligonucleotides [5′-d(TAG GTC AAT ACT) • 3′-d(ATC CAG TTA TGA)] containing 7-(ω-aminoalkyn-1-yl)-7-deaza-2′-deoxyguanosines (**1a**–**c**) (1) and 7-deaza-2′-deoxyguanosine instead of dG were studied regarding their thermal stability as well as their phosphodiester hydrolysis by either 3′ → 5′- or 5′ → 3′ – phosphodi esterase studied by *MALDI-TOF* MS.

Key Words: Oligonucleotides; 7-(Aminoalkyn-1-yl)-1-deaza-2′-deoxyguanosines; Exonucleases.

The introduction of aminoalkynyl-, aminoalkenyl- and aminoalkyl groups to the nucleobases of DNA has an impact on their function, structure and stability. It offers the possibility (i) for the conjugation of DNA and RNA with reporter groups such as

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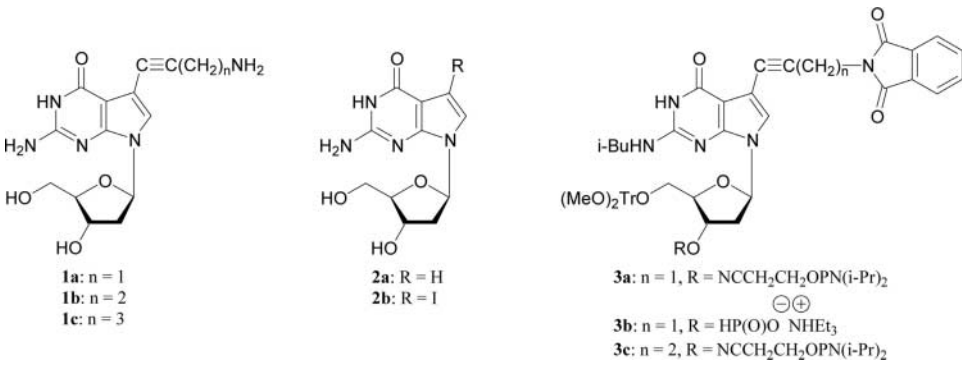
fluorescent residues or charge tags, (ii) to bend the DNA, (iii) to enhance its catalytic repertoire beyond that of ribozymes and aptamers, and (iv) to inhibit regiospecifically the cationic N(7) alkylation of guanine residues by carcinogens.[1]

Here, we report, how the thermal stability of oligonucleotides as well as their resistance against enzymatic phosphodiester hydrolysis by single-strand specific exonucleases are influenced by 7-(ω-aminoalkynyl)-7-deaza-2′-deoxyguanosine residues (**1a**–**c**) with different side length.[2]



Starting from the pivotal intermediate **2b**, Pd(0)-catalyzed *Sonogashira* cross coupling with the corresponding ω-phthalimidoalkynes gave the 7-alkynylated compounds which were then isobutyrylated and subsequently 5′-dimethoxytritylated. The products were then converted into their phosphoramidites **3a**,**c** by a standard procedure; additionally, the phosphonate **3b** was prepared. A phosphoramidite of the 7-(5-aminopentyn-1-yl)-7-deaza-2′-deoxyguanosine has already been published earlier.[3]

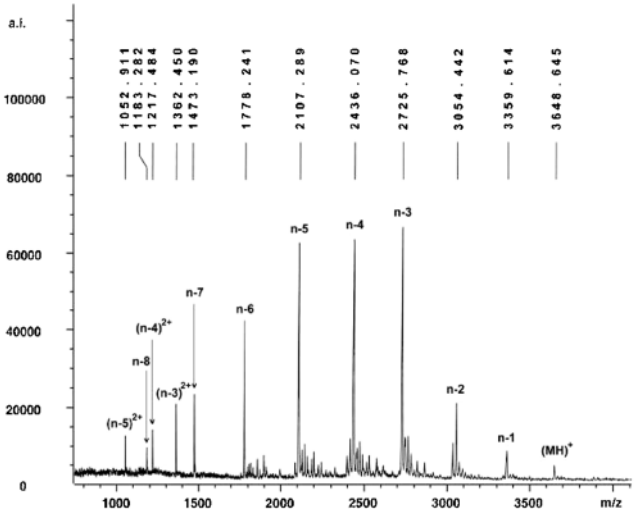


Figure 1. *MALDI-TOF* mass spectrum of a hydrolysis reaction mixture of 5′-d(C**2a**AAC-T**2a2a**C**2a**TC) after treatment with SVPDE.

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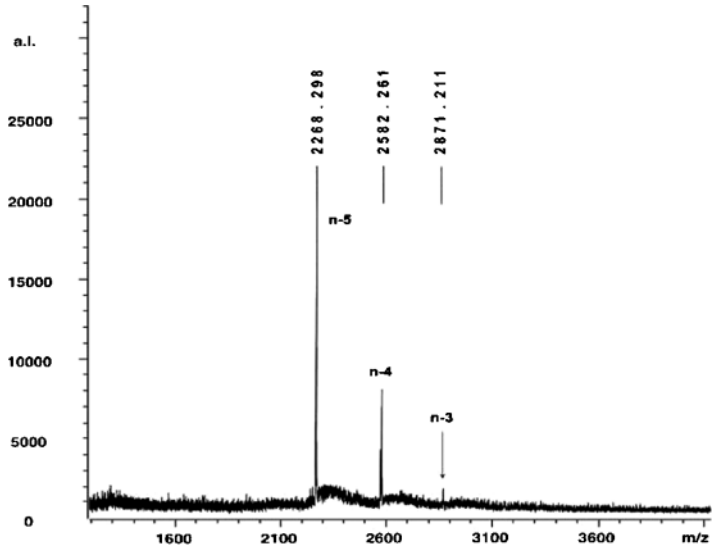

Figure 2. *MALDI-TOF* mass spectrum of a reaction mixture of 5′-d(A**1b**TATT**1b**ACCTA) after treatment with SVPDE.

Oligomers were prepared by solid-phase synthesis using **3a**–**c**; those containing compound **1c** have been published earlier.[3] A comparison of the T_m-values of the **1a**–**c** – modified oligomers exhibits that the incorporation of the 7-(3-aminopropynyl) derivative **1a** leads to an increase of the thermal stability of the duplexes compared to the unmodified parent oligomers. Extension of the length of the nucleobase side chain (**1b**,**c**) lowers the thermal stability stepwise. This is probably due to the gradual approximation of the charged (at pH 7) nucleobase side chain and the negatively charged backbone and therewith the increasing *Coulomb* attraction leading to a shrincage or bending of the double helix with a penalty in stability.

Oligomers containing **2a** are exonucleolytically cleaved without problems (Fig. 1). *MALDI-TOF* mass spectrometry shows that the hydrolysis of oligonucleotides incorporating either **1a** or **1b** by $3' \rightarrow 5'$ specific snake venom phosphodiesterase liberates **1a**-5′-mono-phosphates but not the methylene-extended **1b**-5′-monophosphate. Contrary, the $5' \rightarrow 3'$ – specific bovine spleen phosphodiesterase cleaves off single **1a**- and **1b**-5′-mono-phosphate residues; its action is, however, terminated in the case of oligomers containing two consecutive **1a** or **1b** units (Fig. 2).

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