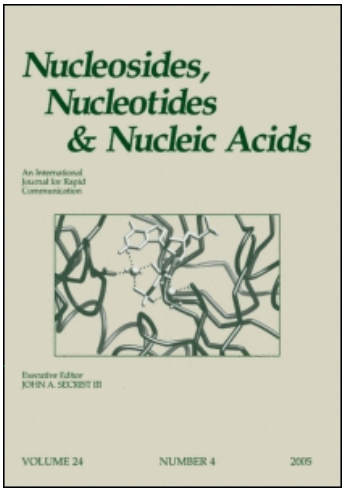

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UNUSUAL MONOMOLECULAR DNA QUADRUPLEX STRUCTURES USING BUNCH-OLIGONUCLEOTIDES

Giorgia Oliviero, Jussara Amato, Nicola Borbone, Aldo Galeone, Michela Varra, Gennaro Piccialli, and Luciano Mayol ▫ *Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli Federico II, Napoli, Italy*

▫ *The chemical synthesis of several G-rich bunch-oligonucleotides and the structural characterization of the corresponding monomolecular G-quadruplexes (**I–IV**) have been reported. The synthetic method allow the achievement of monomolecular DNA quadruplex structures having unusual and predeterminable oligodeoxyribonucleotide (ODN) strand orientation.*

Keywords G-Quadruplex, Bunch-ODN, Solid-Phase Synthesis

INTRODUCTION

DNA quadruple helices based on G-quartets (G-quadruplexes) have aroused widespread interest not only for their substantiated presence in many biologically important regions of the genome but also because such structures form the scaffold of several aptamers provided with useful biological properties.[1–6] G-quadruplexes can be classified on the basis of the number of self-associating strands one, two, or four strand and are further distinguished by the orientation of the strands to each others (parallel or antiparallel).[7]

The monomolecular complexes, largely involved in biomolecular events are, almost exclusively, of antiparallel type, showing a higher stability than bi- or tetramolecular counterparts. On the contrary, tetramolecular complexes, whose formation is characterized by unfavorable kinetic and thermodynamic parameters, show the four strands in a parallel orientation. Generally, only the quadruplexes having an adequate stability are suitable for structural investigations.

In this frame the achievement of stable quadruplex models, having predeterminable strand orientation or less stable quartets could be useful for biological and structural studies. The intermolecular formation of parallel structures in vitro is very slow and may require high ODN concentrations. These unfavorable kinetic

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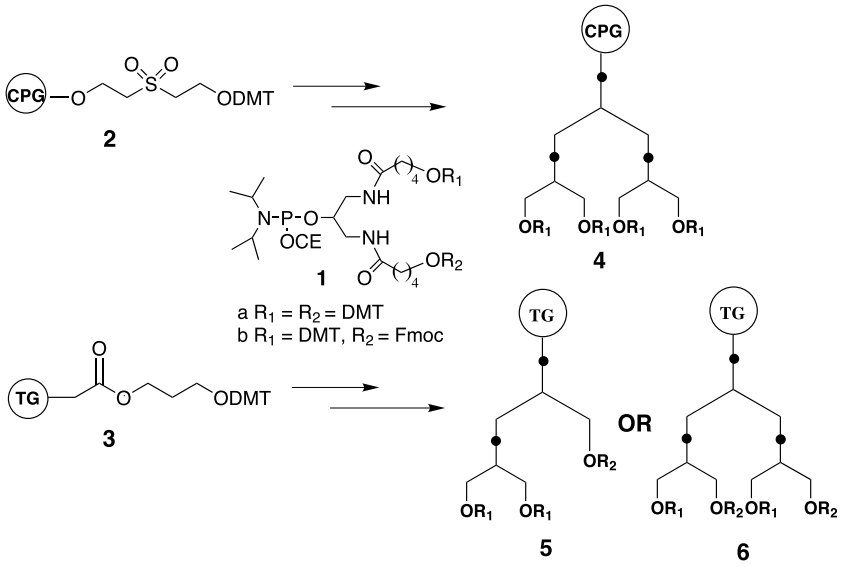
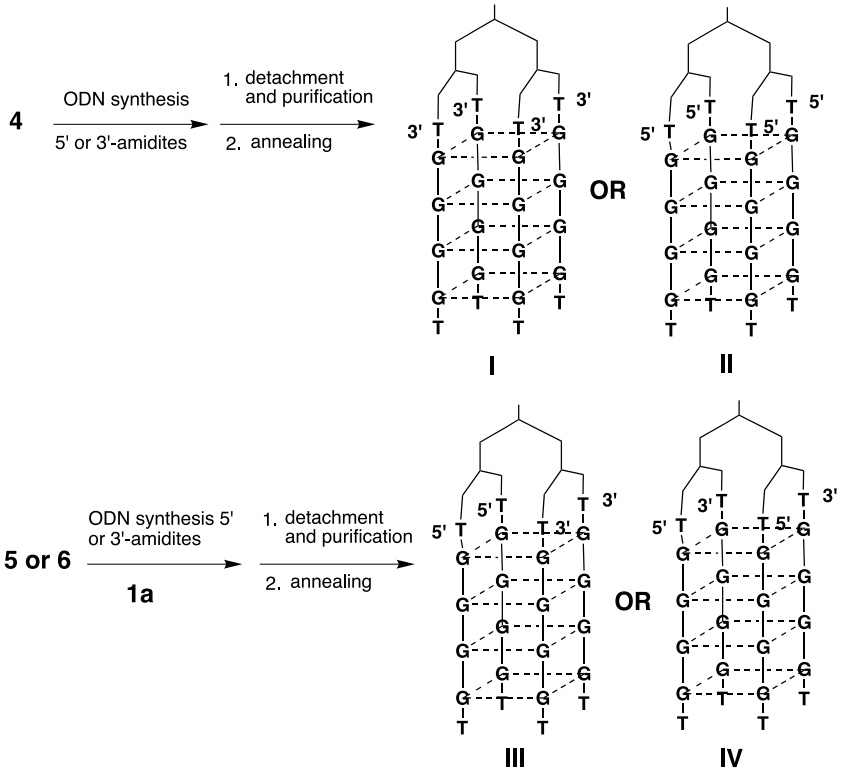


SCHEME 1 General synthetic procedure for the functionalization of the solid supports 2 and 3 with the bunch-spacers 1a or 1b.



SCHEME 2 Synthetic procedure for the quadruplexes I–IV.

and thermodynamic parameters could be disadvantageous in view of their potential therapeutic use.

We recently synthesized a new class of ODNs analogues, which we called bunch-ODNs,[8] capable to form very stable monomolecular G-quadruplex structures. The structural feature of these analogues is the presence of four ODN strands whose 3′-ends are linked together by a tetra-branched spacer (bunch-spacer). Our solid-phase synthetic strategies uses a commercially available bifunctional linker (**1a–b**, Scheme 1) having symmetrical or orthogonal protected alcoholic functions. As solid support we employed the commercially available CPG-resin **2** or a suitable functionalizated carboxy-TentaGel-resin **3** which allow the release of the bunch-ODNs by mild basic treatment. Using a tailored synthetic pathway (Scheme 2), which uses nucleotides 3′ or 5′ phosphoramidite building blocks, the bunch-quadruplexes d[(TGGGGT)]$_4$ **I–IV** having a predetermined strands orientation, were obtained.

The correct structure of the bunch-ODNs was ascertained by ^{1}H NMR and MALDI data. Furthermore, the structure and the stability of the G-quadruplexes (**I–IV**) were investigated by CD thermal denaturation and ^{1}H NMR experiments at variable temperature. Preliminary results indicate that all bunch-ODNs are capable to adopt a G-quadruplex structure and that the bunch-spacer leads to a more stable complex (**I**) when linked to 3′-ODN ends.

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