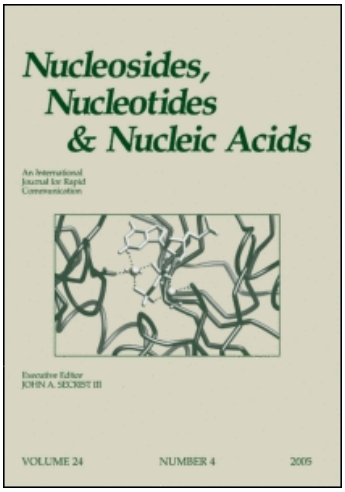

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Effect of Rubidium and Cesium Ions on the Dimeric Quaduplex formed by the *Oxytricha Nova* Telomeric Repeat Oligonucleotide D(GGGGTTTTGGGG)

Flaminia Cesare Marincola[a]; Ada Virno[b]; Antonio Randazzo[b]; Adolfo Lai[a]
[a] Dipartimento di Scienze Chimiche, Università di Cagliari-Cittadella Universitaria di Monserrato, Monserrato, CA, Italy [b] Dipartimento di Chimica delle Sostanze Naturali, Università degli Studi di Napoli "Federico II", Napoli, Italy

To cite this Article Marincola, Flaminia Cesare , Virno, Ada , Randazzo, Antonio and Lai, Adolfo(2007) 'Effect of Rubidium and Cesium Ions on the Dimeric Quaduplex formed by the *Oxytricha Nova* Telomeric Repeat Oligonucleotide D(GGGGTTTTGGGG)', Nucleosides, Nucleotides and Nucleic Acids, 26: 8, 1129 — 1132
To link to this Article: DOI: 10.1080/15257770701521821
URL: http://dx.doi.org/10.1080/15257770701521821

Nucleosides, Nucleotides, and Nucleic Acids, 26:1129–1132, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701521821

Taylor & Francis
Taylor & Francis Group

EFFECT OF RUBIDIUM AND CESIUM IONS ON THE DIMERIC QUADUPLEX FORMED BY THE *OXYTRICHA NOVA* TELOMERIC REPEAT OLIGONUCLEOTIDE d(GGGGTTTTGGGG)

Flaminia Cesare Marincola □ *Dipartimento di Scienze Chimiche, Università di Cagliari–Cittadella Universitaria di Monserrato, Monserrato (CA), Italy*

Ada Virno and Antonio Randazzo □ *Dipartimento di Chimica delle Sostanze Naturali, Università degli Studi di Napoli "Federico II," Napoli, Italy*

Adolfo Lai □ *Dipartimento di Scienze Chimiche, Università di Cagliari–Cittadella Universitaria di Monserrato, Monserrato (CA), Italy*

□ *The DNA sequence d(GGGGTTTTGGGG) consists of 1.5 units of the repeat in telomeres of Oxytricha nova. It has been shown by NMR and x-ray crystallographic analysis that it is capable to form a dimeric quadruplex structure and that a variety of cations, namely K^+, Na^+, and NH_4^+, are able to interact with this complex with different affinity, leading to complexes characterized by different local conformations. Thus, in order to improve the knowledge of this kind of molecule, and in particular to provide further insight into the role of monovalent cations in the G-quadruplex folding and conformation, we have investigated by ^{1}H-NMR the effect of the addition of Rb^+ and Cs^+ to the quadruplex formed by the oligonucleotide d(GGGGTTTTGGGG).*

Keywords Quadruplex; DNA; *Oxytricha nova*; rubidium; cesium

A class of DNA, which has been called G-DNA, contains four guanine residues aligned with each other in a cyclic fashion to form a tetrad array of hydrogen-bonded guanines. The interest in this structures has been fueled by the recognition that telomeres, the 3′ single-stranded guanine-rich overhangs found at the termini of chromosomes, may form G-DNA type structures of potential biological significance.[1,2] In addition to their presence in telomeres, where they may play a role in maintaining the stability and integrity of chromosomes, guanine rich regions are also found within recombination and mutation hot spots[3–7] and in gene regulatory regions.[8] Moreover, G-quadruplex has been found even in several aptamers like the

This work is supported by Italian M.U.R.S.T. and Regione Campania (L.41, L.5).

Address correspondence to Flaminia Cesare Marinicola, Dipartimento di Scienze Chimiche, Università di Cagliari–Cittadella Universitaria di Monserrato, S.S. 554 (bivio per Sestu), I-09042 Monserrato (CA), Italy. E-mail: flaminia@unica.it

thrombin binding aptamer (TBA)[9] and oligonucleotides that turned out to be potent inhibitors of HIV-1 integrase.[10]

G-quadruplexes are stabilized by specific metal ion interactions.[11–13] In fact the central cavity formed by stacked G-tetrads serves as host to a variety of cations. The effect of cations like K^+, Na^+, and NH_4^+, on the dimeric quadruplex formed by the *Oxytricha nova* telomeric repeat oligonucleotide d(GGGGTTTTGGGG) has been already reported.[14] In order to improve the knowledge of this kind of molecule, and in particular to provide further insight into the role of monovalent cations in the G-quadruplex folding and conformation, we have investigated by ^{1}H-NMR the effect of the addition of Rb^+ and Cs^+ ions to the quadruplex formed by the oligonucleotide d(GGGGTTTTGGGG). The solution structure of this oligonucleotide has been determined by an in-depth NMR study.[15,16] It possesses four G-tetrads with guanosines that adopt a *syn-syn-anti-anti* conformation, which results in a quadruplex of alternative wide, medium, narrow, medium width grooves between strands, and possessing two TTTT loops across the diagonal at the edge of the structure (Figure 1).

Here we report the ^{1}H-NMR titration experiments of the quadruplex $[d(GGGGTTTTGGGG)]_2$ originally containing 50 mM Na^+. The titration profiles with RbCl and CsCl turned to be completely different (Figure 2). The addition of CsCl caused no changes in the chemical shifts of the oligonucleotide (Figure 2a). The addition of RbCl (Figure 2b) up to a total concentration of 15 mM did not cause any significant proton spectra

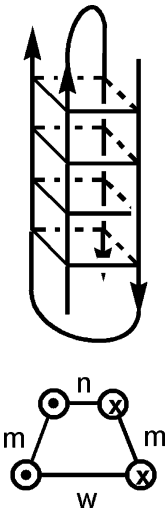

FIGURE 1 Schematic illustration of $[d(GGGGTTTTGGGG)]_2$ quadruplex structure. Strand direction along each edge of the quadruplex is indicated by arrows. Top view is reported below. Types of grooves are indicated as narrow (n), medium (m), and wide (w). Strand polarity is indicated by the arrow tails (crosses) and heads (points) in circles.

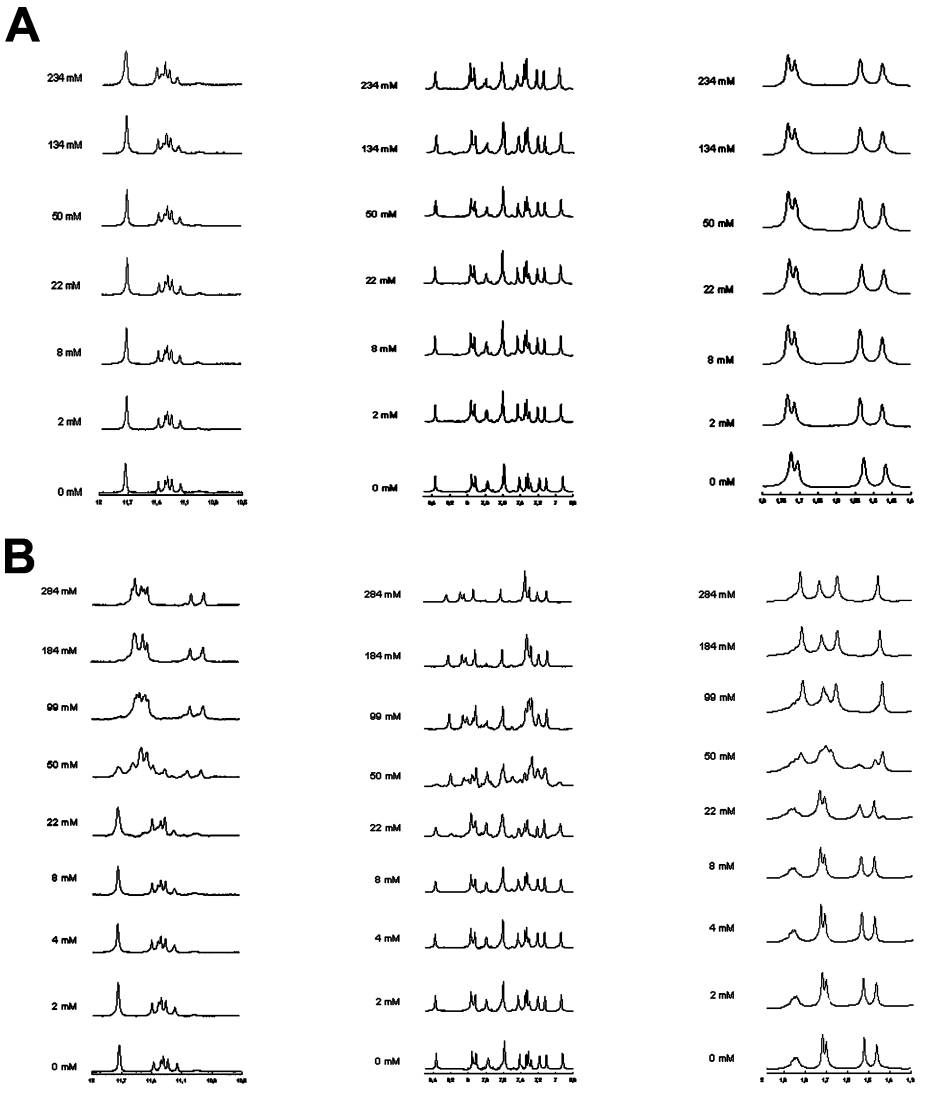

FIGURE 2 Titration (T = 298 K, 400 MHz) with CsCl (a) and RbCl (b) of 1.5 mM solution of $[d(GGGGTTTTGGGG)]_2$. The CsCl and RbCl millimolar concentrations are shown along the side of spectra.

change. Surprisingly, at concentration of RbCl above 15 mM, a new set of proton signals could be observed, whose intensities rose by increasing the amount of RbCl, with the concomitant falling off of the original signals which completely disappeared at RbCl concentration of 100 mM. This could be interpreted assuming that the resonances of the quadruplex gradually moved from their Na^+ to their Rb^+ form chemical shift, and that, above 20 mM, Rb^+ ions are more affine to the quadruplex formed by the *Oxytricha nova* telomeric repeat than the Na^+ ions.

These preliminary results could shed more light to understand the influence of the monovalent cations on the $[d(GGGGTTTTGGGG)]_2$ quadruplex structure and stability. The different affinities of different cations can be used, in principle, to modulate the structures of aptamers based on the scaffold possessed by $[d(GGGGTTTTGGGG)]_2$, and/or for the development of new structural motif to be used in the natotechnology field.

An NMR study devoted to study the structural changes due to the binding of Rb^+ is currently in progress in our laboratories.

REFERENCES

1. Henderson, E.R.; Blackburn, E.H. An overhanging 3′ terminus is a conserved feature of telomeres. *Mol. Cell. Biol.* **1989**, 9, 345–348.
2. Blackburn, E.H. Structure and function of telomeres. *Nature (London)* **1991**, 350, 569–573.
3. Nikaido, T.; Yamawaki-Kataoka, Y.; Honjo, T. Nucleotide sequences of switch regions of immunoglobulin C epsilon and C gamma genes and their comparison. *J. Biol. Chem.* **1982**, 257, 7322–7329.
4. Jeffreys, J.; Wilson, V.; Thein, S.L. Hypervariable 'minisatellite' regions in human DNA. *Nature (London)* **1985**, 314, 67–73.
5. Collier, D.A.; Griffin, J.A.; Wells, R.D. Non-B right-handed DNA conformations of homopurine.homopyrimidine sequences in the murine immunoglobulin C alpha switch region. *J. Biol. Chem.* **1988**, 263, 7397–7405.
6. Hastie, N.D.; Allshire, R.C. Human telomeres: fusion and interstitial sites. *Trends Genet.* **1989**, 5, 326–331.
7. Akman, S.A.; Lingeman, R.G.; Doroshow, J.H.; Smith, S.S. Quadruplex DNA formation in a region of the tRNA gene supF associated with hydrogen peroxide mediated mutations. *Biochemistry* **1991**, 30, 8648–8653.
8. Nickol, J.M.; Felsenfeld, G. DNA conformation at the 5′ end of the chicken adult beta-globin gene. *Cell.* **1983**, 35, 467–477.
9. Bock, L.C.; Griffin, L.C.; Latham, J.A.; Vermaas, E.H.; Toole J.J. Selection of single-stranded DNA molecules that bind and inhibit human thrombin. *Nature* **1992**, 355, 564.
10. Jing, N.; Hogan M.E. Structure-activity of tetrad-forming oligonucleotides as a potent anti-HIV therapeutic drug. *J. Biol. Chem.* **1998**, 273, 34992–34999.
11. Fahlman, R.P.; Sen, D.J. Cation-regulated self-association of 'synapsable' DNA duplexes. *J. Mol. Biol.* **1998**, 280, 237–244.
12. Töhl, J.; Eimer, W. Interaction of a G-DNA quadruplex with mono- and divalent cations A force field calculation. *Biophys. Chem.* **1997**, 67, 177–186.
13. Wang, K.Y.; Gerena, L.; Swaminathan, S.; Bolton, P.H. Determination of the number and location of the manganese binding sites of DNA quadruplexes in solution by EPR and NMR. *Nucl. Acids Res.* **1995**, 23, 844–848.
14. Schulze, P.; Nicholas V.H.; Smith, F.W.; Feigon, J. The effect of sodium, potassium and ammonium ions on the conformation of the dimeric quadruplex formed by the Oxytricha nova telomere repeat oligonucleotide $d(G_4T_4G_4)$. *Nucl. Acids Res.* **1999**, 27, 3018–3028.
15. Smith, F.W.; Feigon, J. Quadruplex structure of *Oxytricha* telomeric DNA oligonucleotides. *Nature* **1992**, 356, 164–168.
16. Smith, F.W.; Feigon, J. Strand orientation in the DNA quadruplex formed from the *Oxytricha* telomere repeat nucleotide $d(G_4T_4G_4$-quadruplex) in solution. *Biochemistry* **1993**, 32, 8682–8692.