# Supramolecular Assembly and Metal-Coordination in G-quadruplex Structures

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Jamie Michael Withers

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## Abstract

G-quadruplexes are supramolecular structures formed from the self association of guanine-rich oligonucleotides. They consist of stacks of G-quartets, each of which is made of four guanine bases arranged in a cyclic, planar array and held together through hydrogen bonding. Recent evidence has suggested G-quadruplexes have a biological role. Telomeric DNA, which has been linked to cancer formation and ageing, is capable of forming a variety of G-quadruplex structures. This observation has led to the development of a number of drug candidates that are currently undergoing clinical trials. Although G-quadruplex structure can be controlled to a certain extent by the careful selection of oligonucleotide sequence, this strategy alone is not always sufficient to allow predictable assembly to occur. To address this problem, we investigated metal-coordinating nucleotides as a method of controlling the predictable assembly of G-quadruplexes. Our research was focused on the use of 1,2,4-triazole and cytosine nucleotides in the formation of base pairs and base quartets; their ability to coordinate transition metal ions was examined.

We investigated a variety of intramolecular and intermolecular G-quadruplex assemblies modified with triazole nucleotides, each providing a different environment for metal coordination. We found that 1,2,4-triazole nucleotides were not capable of forming either base pairs or quartets. We were not able to find evidence of a direct interaction between triazole nucleotides and metal-ions under the conditions studied.

The stabilisation of a DNA duplex by coordination of silver(I) ions to cytosine nucleotides was observed. However, this interaction was not useful in directing the assembly of a G-quadruplex structure. In most cases we found that the presence of transition metal ions had a negative impact on the stability of G-quadruplex structures, and that destabilisation occurred before metal coordination could be observed.

Our investigations into the metal-coordinating properties of a 3+1 G-quadruplex based on the 3*htel* sequence have highlighted the significance of the Watson-Crick base pair formed in this assembly. In the absence of this base pair, the G-quadruplex is completely destabilised, however, evidence suggests the formation of a G-triplex instead.

Although we did not observe G-quadruplex assembly directed by metal-coordinating nucleotides, the contents of this thesis may be considered as a basis for the further development of supramolecular oligonucleotide assemblies.

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