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Metallo-responsive switching between hexadecameric and octameric supramolecular G-quadruplexes†

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We report the metallo-responsive high fidelity switching between hexadecameric and octameric supramolecular G-quadruplexes triggered by a change in the metal cation promoter from potassium to strontium, respectively.

Further advances in the development of molecular machinery require the construction of components that alternate their configuration between, at least, two distinct states. Most current examples of artificial supramolecular machinery rely on interconversions between specific configurations of mechanically linked systems (*e.g.*, catennanes, rotaxanes) or within contorted structures (*e.g.*, *cis-trans* isomers, foldamers).^{1–3} A complementary, and comparatively underdeveloped, strategy will take advantage of changes in the oligomeric state (molecularity) of self-assembled supramolecules. In biological systems, fluctuations in the oligomeric state of assemblies provide an efficient way to alter their structure and, thus, their function. For example, changes in the oligomeric state for the protective antigen of the anthrax toxin (heptamer-octamer) provide a means of controlling cytotoxicity.⁴ Analogous changes in RuvA enzymes (tetramer-octamer) enable control of the dynamics of processing DNA in Holliday junctions.⁵

Most responsive multimeric assemblies rely on an all or none strategy where the two available states are assembled or fully disassembled.⁶ An additional challenge is the development of systems where two well-defined oligomeric states (in particular those with molecularities larger than trimers or tetramers) interconvert with high fidelity.^{7,8} The interconversion can be achieved by tuning intrinsic parameters *via* covalent modification of the monomeric building blocks with responsive functional groups (*e.g.*, photo-, redox- or pH-active). Alternatively, such tuning can be achieved through the modulation of extrinsic parameters by altering the surroundings of the supramolecule such as the solvent,^{9–11} temperature,¹² or metal cations.^{13,14} Herein, we present a metallo-responsive supramolecular G-quadruplex (GQ) that switches between a hexadecameric and octameric states in processes triggered by changes in the metal cation from potassium to strontium, respectively (Fig. 1).¹⁵

Supramolecular GQs are formed by the self-assembly of guanine, or related derivatives, that form stacks of planar hydrogen-bonded tetramers in the presence of cations of appropriate size (*e.g.*, Na⁺, K⁺, NH₄⁺).^{16,17} In recent years we have studied the self-assembly of 8-aryl-2'-deoxyguanosine derivatives (8ArGs) and surveyed the effects of modulating intrinsic and extrinsic parameters, on the structure and properties of their corresponding assemblies.^{18,19} Properties such as their selectivity for binding²⁰ and transporting metal cations²¹ can also be modulated by such parameters. Specifically, the 8-(*m*-acetylphenyl)-2'-deoxyguanosine (mAG) scaffold induces the reliable formation of hexadecamers, in both organic¹⁹ and aqueous media,²² even when containing large, and sterically demanding groups such as dendrons.^{23,24} Furthermore, modulation of these parameters has enabled the development of solvo-⁹ and thermo-¹² responsive systems, paving the way to more elaborate supramolecular machinery.

We have shown that titrating a solution of **1** in CD₃CN with KI, initially leads to the formation of the D₄-symmetric

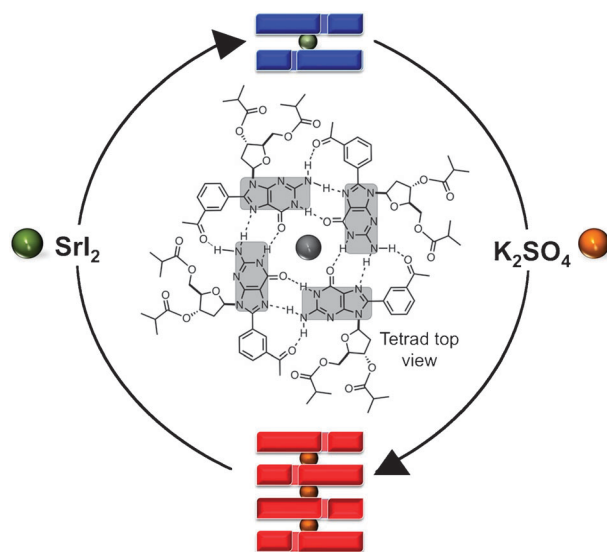


Fig. 1 Schematic representation of the cycle of the metallo-responsive supramolecules formed by **1**, a tetrad of which is represented in the center. Side view depictions of the octamer **1**₈·Sr²⁺ (top, blue) and the hexadecamer **1**₁₆·3 K⁺ (bottom, red). Strontium and potassium cations are represented by green and orange spheres, respectively.

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octamer $\mathbf{1}_8\text{-K}^+$ (from 0.0313 to 0.125 equiv of KI), leading to the formation of the hexadecamer $\mathbf{1}_{16}\cdot 3\text{K}^+$ after the addition of 0.5 equiv of KI.⁹ Similarly, the addition of SrI_2 (0.125 equiv) to a solution of $\mathbf{1}$ (30 mM) in CD_3CN reveals a single set of signals corresponding to the octamer $\mathbf{1}_8\cdot\text{Sr}^{2+}$. In contrast, higher concentration of Sr^{2+} decreases the fidelity and appears to destabilize the octamer (as previously reported for other GQs),²⁵ but does not induce the formation of a hexadecamer. DOSY experiments in CD_3CN are consistent with the formation of $\mathbf{1}_8\cdot\text{Sr}^{2+}$, giving a $D = (7.0 \pm 0.2) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ at 298 K, which corresponds to a hydrodynamic radius (R_H) of 9.2 Å. The constitution of $\mathbf{1}_8\cdot\text{Sr}^{2+}$, is further supported by vapour pressure osmometry (VPO) and HR-ESI MS (CD_3CN with 0.125 equiv of SrI_2). The former provides a molecular weight in solution of 4566 Da (ESI†, Table S2), whereas the latter reveals a clean spectrum with a base peak at m/z 2145.7058 corresponding to $\mathbf{1}_8\cdot\text{Sr}^{2+}$ (ESI†, Fig. S3).

Surprisingly, in CD_3CN with 0.5 equiv of KI, increasing proportions of SrI_2 shifts the equilibrium from the hexadecamer $\mathbf{1}_{16}\cdot 3\text{K}^+$ towards $\mathbf{1}_8\cdot\text{Sr}^{2+}$ (Fig. 2). The octamer $\mathbf{1}_8$ is detectable after the addition of just 0.03 equiv of SrI_2 (Fig. 2) and it becomes the main species after the addition of 0.125 equiv of such salt. Although the cations of potassium and strontium have similar ionic radii (1.51 and 1.26 Å, respectively),²⁶ in acetonitrile, their distinct charge densities seem to dictate the resulting molecularity of the assemblies of $\mathbf{1}$. Whereas, a hexadecamer can accommodate three consecutive potassium cations in its internal channel, the corresponding arrangement with divalent strontium cations is untenable due to the increased electrostatic repulsion.^{27,28}

The addition of KI to $\mathbf{1}_8\cdot\text{Sr}^{2+}$ does not lead to the formation of $\mathbf{1}_{16}\cdot 3\text{K}^+$ (ESI†, Fig. S7), and the persistence of the former,

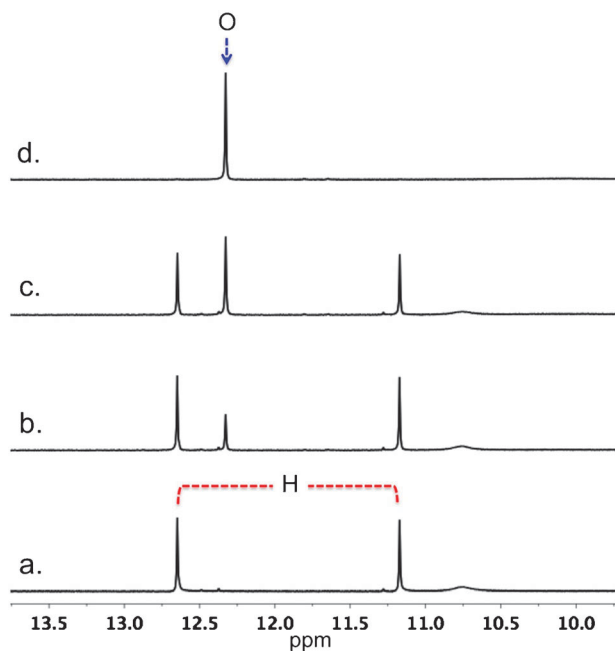


Fig. 2 ^1H NMR (500 MHz, 298.2 K) spectra for $\mathbf{1}$ (30 mM) in (a) CD_3CN with 0.5 equiv of KI, 97% of hexadecamer (H) $\mathbf{1}_{16}\cdot 3\text{K}^+$; (b) 0.0313 equiv of SrI_2 , 79% H and 19% octamer (O) $\mathbf{1}_8\cdot\text{Sr}^{2+}$; (c) 0.0625 equiv of SrI_2 60% H and 39% O; (d) 0.125 equiv of SrI_2 100% O.

even after adding an excess of KI, is consistent with its higher thermal stability ($T_m \geq 333.2 \text{ K}$). This stabilization effect of strontium cations have been attributed to a stronger coordination between C6-carbonyl groups.^{25,29} In order to achieve a reversible metallo-responsive behaviour, and revert the cycle from an octamer to a hexadecamer, we decided to use sulphate as a counter anion for potassium capable of sequestering the strontium cations from $\mathbf{1}_8\cdot\text{Sr}^{2+}$. The addition of 0.125 equiv of K_2SO_4 to the octamer $\mathbf{1}_8\cdot\text{Sr}^{2+}$ induces it to switch back to the hexadecamer $\mathbf{1}_{16}\cdot 3\text{K}^+$ (ESI†, Fig. S8). A precipitate of SrSO_4 is observed due to the strong ionic pair formation. Further addition of SrI_2 reverts once again the cycle inducing the switch of the hexadecamer to the octamer (ESI†, Fig. S9). Two full cycles were performed, as illustrated in Fig. 3 with no obvious signs of fatigue in the system.

Direct addition of K_2SO_4 to a solution of $\mathbf{1}$ in acetonitrile leads to the formation of $\mathbf{1}_8\cdot\text{K}^+$ (ESI†, Fig. S10), but even an excess of this salt does not promote the formation of $\mathbf{1}_{16}\cdot 3\text{K}^+$. Potassium sulfate enables the interconversion of $\mathbf{1}_8\cdot\text{SrI}_2$ to $\mathbf{1}_{16}\cdot 3\text{KI}$ by increasing the chemical potential and eventual net outward flow of strontium cations from within the octamer to the bulk solution (where it precipitates as SrSO_4). This process, however, needs the presence of a soft counter anion like iodide to increase the activity of the cation in solution enabling the high fidelity self-assembly into GQs.³⁰ Precipitation of SrSO_4 enables completion of the cycle by leaving potassium as the only cation available to promote the formation of the hexadecamer $\mathbf{1}_{16}\cdot 3\text{K}^+$.

Here we have shown for the first time how alternating the metal cation promoter enables the control, and reversible switching, between two well-defined supramolecular GQs. This metallo-responsive system represents our latest addition to a toolbox of active supramolecular GQs that already contains solvo-⁴ and thermo-⁷ responsive systems. We expect these to be valuable in the development of versatile supramolecular machinery.

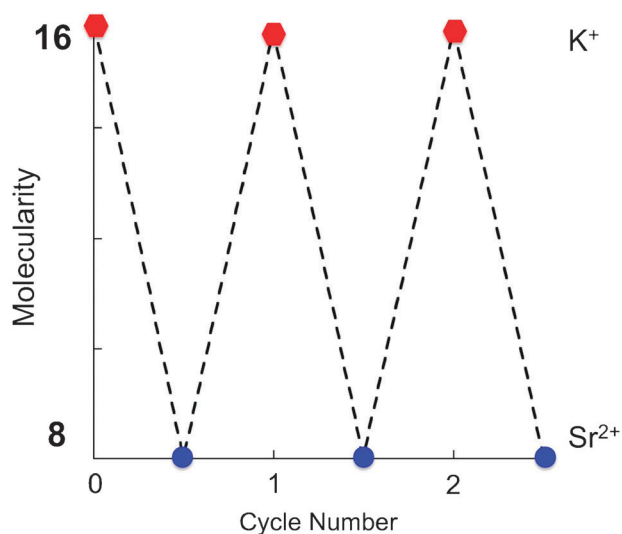


Fig. 3 Changes in the molecularity of the assemblies of $\mathbf{1}$ induced by alternating the metal cation between potassium (red hexagons) and strontium (blue circles).

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