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Reversible Interconversion between a Supramolecular Polymer and a Discrete Octameric Species from a Guanosine Derivative by Dynamic Cation Binding and Release

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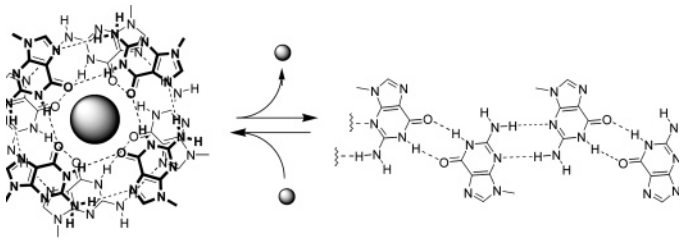
ABSTRACT



The tunable interconversion between two highly ordered supramolecular motifs (G-quartet K^+-templated column and G-ribbon) of a lipophilic guanosine derivative fueled by cation complexation and release in a cryptand [2.2.2] containing guanosine solution is reported. The process is controlled by the sequential addition of acid and base.

Reversibility is a hallmark of supramolecular chemistry.[1] By exploiting the information stored in the molecule, in particular, its preprogrammed propensity to undergo self-recognition and self-association pathways, in combination with the reversibility of its self-assembly under external stimuli such as temperature or chemical environment, it is possible to implement molecule-sized prototypes of dynamic chemical devices.[2] Besides the fundamental interest in controlling motions on the nanoscale, these device prototypes can be important for future data storage.[3]

Lipophilic guanosines are unique building blocks which are capable of self-assembling into different structures depending on the experimental conditions. In the presence of certain cations, they can form G-quartet-based octamers or columnar aggregates (supramolecular polymers) depending on the concentration of the cation and nucleobase.[4] The metal cations are located between the quartets and act as templates (Figure 1).[5,6] In the absence of metal templates, guanosines without a C(8) sterically demanding substituent[7] self-assemble, both in solution and in the solid state, into

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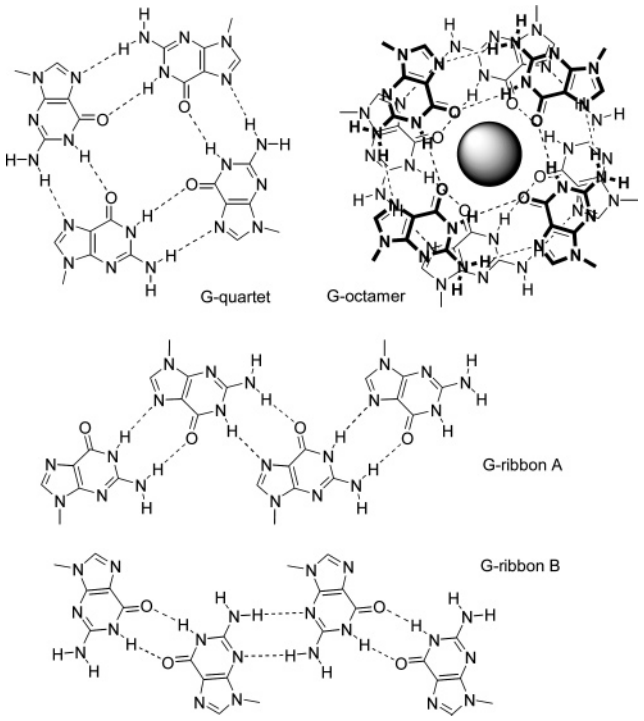
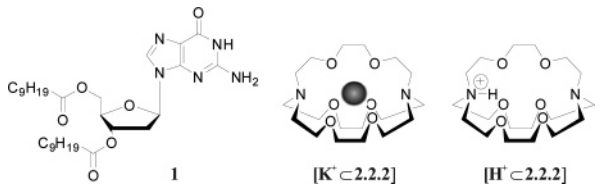


Figure 1. Supramolecular assemblies of guanine moieties: the G-quartet, the metal templated octamer, and two different G-ribbons. Although the A-type is observed in the solid phase and at surfaces, the B-type is thermodynamically stable in chloroform solutions.

ribbonlike architectures (Figure 1).[8−10] These ribbons are interesting structures as they are the building blocks for new lyotropic mesophases formed in organic solvents.[9−11] In the solid state, the ribbons, when grown between gold electrodes, are photoconductive and display also rectifying properties.[12] The peculiar electronic properties were successfully exploited for the fabrication of a field-effect transistor based on electroactive guanosine layers.[13] Moreover, guanine-based architectures, in particular, G-quartets, are well-known to hold potential in anticancer drug design as they can act as enzyme telomerase inhibitors.[4,14] This is in fact particularly relevant because it has been recently demonstrated that there is a link between tumor immortalization and telomerase activity.[15]

Very recently, Ghoussoub and Lehn were able to control the mesoscale dynamic sol−gel interconversion, i.e., from a disordered guanine solution to gel-forming ordered G-quartet architectures, through reversible cation binding and release.[16] However, a great challenge remains to control the switching between two or more highly ordered guanine-based supramolecular motifs making use of an external agent.



We report here on the tunable interconversion between discrete supramolecular assemblies from a lipophilic guanosine, i.e., G-ribbons and G-quartet columns, fueled by cation complexation and release. The G-quartet structures are harnessed by the presence of a coordinated potassium cation: this offers the possibility of triggering a reversible ribbon−quartet interconversion by controlled sequential addition and removal of K^+. The cryptand [2.2.2] offers an efficient complexation of K^+ to yield the cryptate [$K^+ \subset$ 2.2.2].[17] Upon protonation of one of the bridgehead nitrogens, the bound K^+ can be released, leading to the formation of [$H^+ \subset$ 2.2.2]. Such an approach was proven to be successful to trigger the reversible conversion between a coiled and stretched conformation in an oligomeric pyridine−pyrimidine derivative.[18]

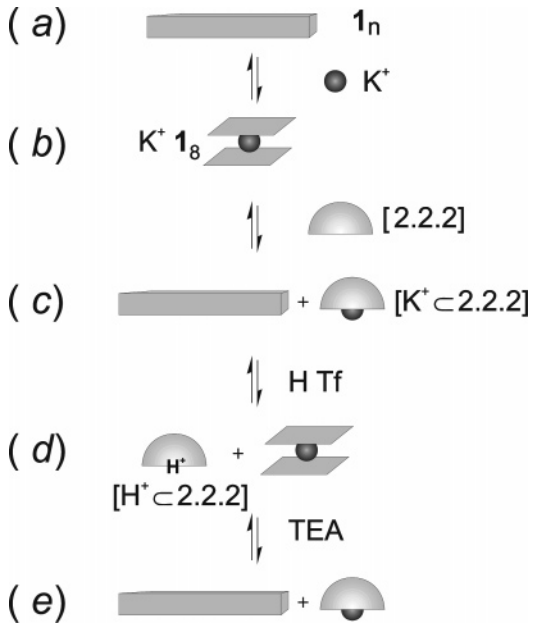


Figure 2. The stepwise reversible interconversion between the ribbon $\mathbf{1}_n$ and the octamer $K^+\mathbf{1}_8$.

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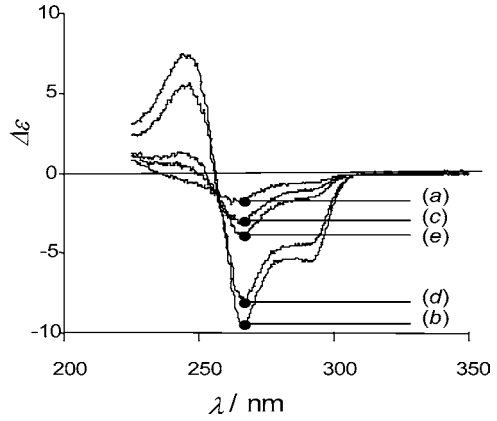

Figure 3. Observation of the reversible ribbon−octamer interconversion in a solution of **1** (13.5 mM) in $CDCl_3$ (path length = 0.01 cm) by CD spectroscopy. (a) Initial sample ($\mathbf{1}_n$); (b) after addition of 1.7 mM potassium picrate ($K^+\mathbf{1}_8$); (c) after addition of 4.2 mM cryptand [2.2.2] ($\mathbf{1}_n$); (d) after addition of 4.2 mM HTf ($K^+\mathbf{1}_8$); and (e) after addition of 4.2 mM Et_3N ($\mathbf{1}_n$).

The addition (see Figure 2) of 1/8 equiv of potassium picrate to a chloroform solution of the guanosine derivative[19] **1** transforms the supramolecular ribbon[8] $\mathbf{1}_n$ (of B type, see Figure 1) into the octameric complex $K^+\mathbf{1}_8$.[5] Upon subsequent addition to $K^+\mathbf{1}_8$ of 2.5 equiv of [2.2.2], the potassium complex reverts to the original G-ribbon $\mathbf{1}_n$ (because of the small difference between the stability constants of [$K^+ \subset$ 2.2.2] and $K^+\mathbf{1}_8$, the conversion from $K^+\mathbf{1}_8$ to $\mathbf{1}_n$ requires an excess of cryptand). Upon addition of 1 equiv of trifluoromethanesulfonic acid (HTf), K^+ is released from the cryptate and the octameric complex $K^+\mathbf{1}_8$ is regenerated. In contrast to Lehn et al.,[16,18] who obtained the release of K^+ by protonation of both the nitrogen atoms of the cryptand, we added only 1 equiv of acid. In fact, upon addition of more than 1 equiv, the octameric species $K^+\mathbf{1}_8$ is no longer the most abundant self-assembled species in solution, as revealed by CD and ^{1}H NMR spectroscopies. Adding thereafter 1 equiv of triethylamine (TEA) deprotonates [$H^+ \subset$ 2.2.2]; the free cryptand recaptures K^+, and the G-ribbon

(19) The guanosine derivative **1** was synthesized according to the procedure reported in ref 10. A 13.5 mM deuteriochloroform solution of **1** was prepared and left to stand for a week at +4 °C (solution a). On this solution, both CD (Jasco J710, path length = 0.01 cm) and ^{1}H NMR (Varian 400 MHz) spectra were recorded (curves a in Figures 3 and 4) at room temperature. A volume of solution a was shaken at 20 °C with an equal volume of a 1.68 mM aqueous solution of potassium picrate; the two phases were kept in contact at +4 °C for 2 days; afterwards, the organic phase was recovered (solution b) and CD and ^{1}H NMR spectra were recorded (curves b, Figures 3 and 4). A portion of 7 mL of solution b was added to 11.0 mg (0.029 mmol) of [2.2.2] (1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo-[8.8.8]hexacosan, Aldrich), and the system was stirred overnight at room temperature (solution c): CD and ^{1}H NMR spectra were then recorded (curves c, Figures 3 and 4). An aliquot of 6 mL of solution c was added to 3.73 mg (0.025 mmol) of trifluoromethanesulfonic acid (Aldrich) and stirred for 1 h (solution d). CD and ^{1}H NMR spectra were recorded (curves d, Figures 3 and 4). A portion of 300 μL (0.021 mmol) of a 70 mM deuteriochloroform solution of triethylamine (redistilled from CaH_2) was added to 5 mL of solution d and stirred for 1 h: CD and ^{1}H NMR spectra were recorded (curves e, Figures 3 and 4). Upon addition of the acid, the equilibration between the two self-assembled species required ca. 30 min, whereas after addition of the base, it takes ca. 20 min.

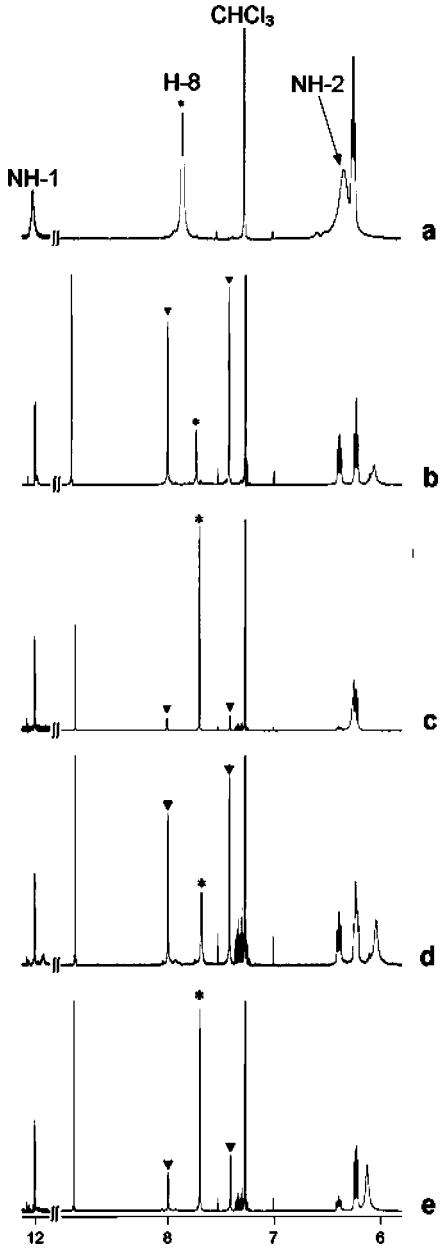

Figure 4. Observation of the reversible ribbon−octamer interconversion in a solution of **1** (13.5 mM) in $CDCl_3$ by ^{1}H NMR spectroscopy; only the downfield portion of the spectra (5−13 ppm) is shown. (a) Initial sample ($\mathbf{1}_n$); (b) after addition of 1.7 mM potassium picrate ($K^+\mathbf{1}_8$); (c) after addition of 4.2 mM cryptand [2.2.2] ($\mathbf{1}_n$); (d) after addition of 4.2 mM HTf ($K^+\mathbf{1}_8$); and (e) after addition of 4.2 mM Et_3N ($\mathbf{1}_n$). The stars and triangles mark the H(8) signals for the ribbon and octamer species, respectively.

$\mathbf{1}_n$ is formed again. The interconversion may be repeated by sequential addition of acid and base.[20]

Circular dichroism (CD) and ^{1}H NMR can both be exploited to monitor the ribbon−octamer $\mathbf{1}_n \gg K^+\mathbf{1}_8$ interconversion. In fact, CD spectroscopy has been successfully

(20) The cycle was repeated three times without apparent degradation of the system; however, the salt formation prevents the possibility of an indefinite repetition of the switching.

used to study the cation-directed assembly of homoguanylic and guanosine-rich oligonucleotides,[21] as well as that of lipophilic guanosines.[22] Although the CD spectrum of $\mathbf{1}_n$ in the region of the intense $\pi-\pi$ transitions of the guanine chromophore at ca. 260 nm is monosignate and weak (Figure 3, trace a), the stabilization of stacked G-quartet-based structures induced by the K^+ ion introduces a negative exciton signal (Figure 3, trace b). The adjacent quartets are, in fact, rotated by a well-defined angle:[5] this causes the interaction between the transition moments located in the different G-quartets originating the bisignate couplet.[23] The sequential addition of cryptand, acid, and base leads to spectra that resemble the initial spectrum $\mathbf{1}_n$ (Figure 3, trace c), $K^+\mathbf{1}_8$ (Figure 3, trace *d*), and $\mathbf{1}_n$ again (Figure 3, trace e), respectively.[24]

^{1}H NMR spectroscopy has been employed to characterize the assembled species in chloroform solutions of **1**.[5,6,8,10,22] Although the species $\mathbf{1}_n$ exhibits one set of signals,[10,25] the complex $K^+\mathbf{1}_8$ shows two sets of signals in a 1:1 ratio:[5,22] one set corresponds to molecules belonging to one quartet, and the other corresponds to molecules of the other, nonequivalent, quartet. In particular, the region between 5 and 13 ppm, corresponding to the H(1), H(8), and NH(2) signals, represents an unambiguous signature of the ribbon−octamer conversion: the broad H(8) and H(1) signals at 7.9 and 12.1 ppm, respectively, in $\mathbf{1}_n$ (Figure 4, trace a) are replaced by two sharp H(8) signals (in an approximate 1:1 ratio) at 7.4 and 8.0 ppm and by two sharp H(1) resonances at 12.1 ppm when the supramolecular complex $K^+\mathbf{1}_8$ is the dominant species (Figure 4, trace b). As observed also by CD spectroscopy, the sequential addition of cryptand, acid, and base (Figure 4, traces c−e) allows the switching between the two signatures of the ribbon and the octamer.[26]

In summary, we have shown the ionic modulation of the reversible interconversion between two highly ordered supramolecular motifs of a guanosine derivative. This supramolecular dynamer can be of importance as a model system to mimic the formation−annihilation of G-quartet-based architectures, which might be of biological significance, in the frame of nucleic acid telomerase.

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Supporting Information Available: ^{13}C and ^{1}H NMR spectra of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) The recovery of the signals of the initial spectrum $\mathbf{1}_n$ and of $K^+\mathbf{1}_8$ is not complete for the existence of multiple equilibria after acid/base addition.

(25) The chemical shift of H(2) at 6.3 ppm is indicative of the existence of a supramolecular ribbonlike architecture in solution (see ref 10) involving the H(2) protons.

(26) The NMR signals of the ribbons (in particular, those of H(8) and NH(2)) in the presence of cryptate (traces c and e of Figure 4) are sharper as compared to those of the starting spectrum (trace a of Figure 4). This could reflect the differences in the bulk properties of the system (e.g., polarity) and/or the size (and polidispersity) of the ribbon after addition of cosolutes (cryptand, acid, and base).