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Self-Assembled Hexadecanitroxide

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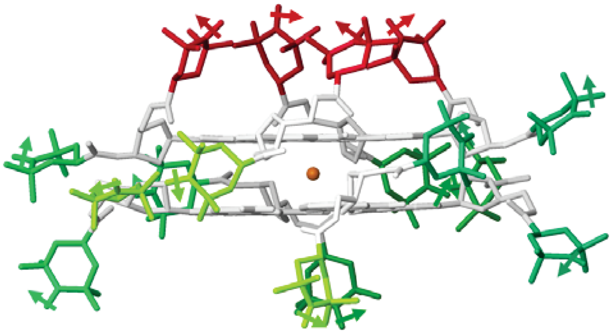
ABSTRACT



A radical-armed guanosine derivative shows drastic magnetic changes by addition (removal) of alkali metal cations corresponding to the reversible assembly (disassembly). In the presence of templating metal ions, the assembly is formed by 8 molecules and 16 open-shell moieties confined in a sphere with a diameter of ca. 30 Å.

Among noncovalent interactions, multiple hydrogen bonds have widely been adopted to control the formation of highly ordered nanoarchitectures[1] because of their directionality, selectivity, and dynamic nature.[2] One versatile multiple hydrogen bonding unit is represented by guanosine. Depending on their substitution pattern, solvent, and cation availability, lipophilic guanosine derivatives spontaneously self-associate to give either H-bonded ribbons or quartet-based columnar structures[3] that can be interconverted by the appropriate external chemical stimulus.[4,5] As it is possible to functionalize the guanosines in the C8 position and/or at the sugar hydroxy functions, they are ideal and promising scaffolds to locate functional units in preprogrammed positions.[4−6]

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(1) See, a few recent examples: (a) Schenning, A. P. H. J.; Meijer, E. W. *Chem. Commun.* **2005**, 3245–3258. (b) Jonkheijm, P.; Miura, A.; Zdanowska, M.; Hoeben, F. J. M.; De Feyter, S.; Schenning, A. P. H. J.; De Schryver, F. C.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 74–78. (c) Würthner, F.; Yao, S.; Heise, B.; Tschierske, C. *Chem. Commun.* **2001**, 2260–2261. (d) Yagai, S.; Mahesh, S.; Kikkawa, Y.; Unoike, K.; Karatsu, T.; Kitamura, A.; Ajayaghosh, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4691–4694. (e) Yagai, S.; Seki, T.; Karatsu, T.; Kitamura, A.; Würthner, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 3367–3371.

(2) Lehn, J.-M. *Supramolecular Chemistry Concepts and Perspectives*; VCH: Weinheim, 1995.

(3) (a) Davis, J. T.; Spada, G. P. *Chem. Soc. Rev.* **2007**, *36*, 296–313. (b) Liu, X.; Kwan, I. C. M.; Wang, S.; Wu, G. *Org. Lett.* **2006**, *8*, 3685–3688. (c) Araki, K.; Yoshikawa, I. *Top. Curr. Chem.* **2005**, *256*, 133–165. (d) Sessler, J. L.; Sathiosatham, M.; Doerr, K.; Lynch, V.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1300–1303. (e) Sivakova, S.; Rowan, S. J. *Chem. Soc. Rev.* **2005**, *34*, 9–21. (f) Lena, S.; Masiero, S.; Pieraccini, S.; Spada, G. P. *Mini-Rev. Org. Chem.* **2008**, *5*, 262–273. (g) Garcia-Arriaga, M.; Hobley, G; Rivera, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 10492–10493.

(4) Graziano, C.; Pieraccini, S.; Masiero, S.; Lucarini, M.; Spada, G. P. *Org. Lett.* **2008**, *10*, 1739–1742.

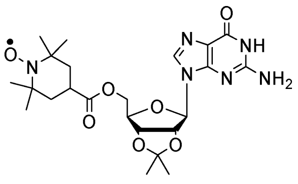
(5) (a) Spada, G. P.; Lena, S.; Masiero, S.; Pieraccini, S.; Surin, M.; Samorì, P. *Adv. Mater.* **2008**, *20*, 2433–2438. (b) Betancourt, J. E.; Martín-Hidalgo, M.; Gubala, V.; Rivera, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 3186–3188.

(6) A few selected recent papers: (a) Lena, S.; Masiero, S.; Pieraccini, S.; Spada, G. P. *Chem.—Eur. J.* 2009, Published online: May 6, 2009, DOI: 10.1002/chem.200802506. (b) Sreenivasachary, N.; Lehn, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 5938–5943. (c) Kaucher, M. S.; Harrell, W. A., Jr.; Davis, J. T. *J. Am. Chem. Soc.* **2006**, *128*, 38–39. (d) Arnal-Hérault, C.; Banu, A.; Barboiu, M.; Michau, M.; van der Lee, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4268–4272. (e) Zhong, C.; Wang, J.; Wu, N.; Wu, G.; Zavalij, P. Y.; Shi, X. *Chem. Commun.* **2007**, 3148–3150. (f) Arnal-Hérault, C.; Pasc, A.; Michau, M.; Cot, D.; Petit, E.; Barboiu, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8409–8413. (g) Kumar, A. M. S.; Sivakova, S.; Marchant, R. E.; Rowan, S. J. *Small* **2007**, *3*, 783–787. (h) Otero, R.; Schöck, M.; Molina, L. M.; Lægsgaard, E.; Stensgaard, I.; Hammer, B.; Besenbacher, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 2270–2275.

10.1021/ol901028h CCC: $40.75

Recently we have shown that the scaffolding of the persistent radical unit 4-carbonyl-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), is achieved by taking advantage of the self-assembly templated by potassium ions of the guanosine derivative **1** into a H-bonded network.[4] In the presence of potassium ions, this compound can form in fact a D_4-symmetric octameric assembly $[\mathbf{1}_8\mathrm{K}]^+$ containing eight spin centers showing a weak electron spin−spin exchange interaction. Reversible interconversion, fueled by cation release and complexation, allows the switching between discrete quartet-based assemblies and molecularly dissolved **1** (or its ribbon-like supramolecular oligomers), thus the control of the intermolecular weak spin−spin interactions.

The system described in our previous communication[4] was the first example of a reversible introduction-suppression of a weak spin−spin exchange in a self-recognizing and self-assembling molecule controlled by the addition/removal of a templating cation.[7] Our next challenge was to increase the spin exchange difference between the two states to obtain drastic magnetic changes before and after addition of the metal cation.



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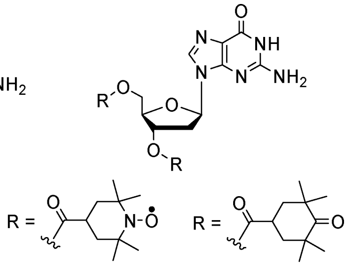

2a **2b**

In this communication, we report on the self-assembly properties of derivative **2a** where two TEMPO units are connected to the guanosine deoxynucleoside at the O5′ and O3′ positions. This target molecule has been chosen for two reasons: (i) in the metal templated assembled species of **2a** the number of paramagnetic units doubles, possibly leading to significant enhancement of magnetic coupling; (ii) passing from ribo-guanosine (such as **1**) to 2′-deoxyguanosine derivatives, the discrete K^+-templated assembly was expected to be C_4-symmetric (the two faces of the G-quartets are heterotopic and, in principle, the two quartets in the octamer can be arranged in three different orientations, see Figure 1, C_4-symmetric head-to-tail, and D_4-symmetric head-to-head or tail-to-tail)[6a,8] and this structural variation could originate a different (higher) spin−spin interaction.

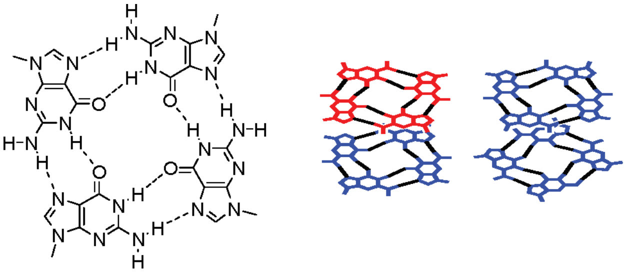

Figure 1. G-quartet motif and a schematic representation of D_4 and C_4-symmetric octamers. Red and blue color refers to the two heterotopic faces of the G-quartet.

We will show that **2a**, despite the presence of two bulky substituents, forms indeed a K^+-templated octameric assembly giving rise to very strong spin−spin interactions comparable to those observed in very concentrated monoradical solutions. This finding is consistent with the proposed structure consisting of 16 radical units confined within the complex.

Because steric hindrance potentially introduced by the double substitution in O5′ and O3′ could destabilize supramolecular assemblies, CD spectroscopy was initially employed to prove the self-assembly of **2a** to give quartet-based structures in $\mathrm{CH_2Cl_2}$ upon K-Pic extraction.

Circular dichroism is diagnostic of either the formation of G-quartet based assemblies[9] or the stacking polarity of two contiguous G-quartets.[10] In fact, the tetramers do not stack in register, but are rotated with respect to each other to give, in the 230−300 nm region, characteristic of the $\pi-\pi^*$ transitions of guanine chromophore, a double signed exciton-like CD signal. This couplet, whose sign allows the assignment of the stacking helicity (handedness), exhibits opposite signed bands at ca. 260 and 240 nm for the head to tail (C_4-symmetric) stacking while both bands are blue-shifted by 20−30 nm in the D_4-symmetric stacking.[10]

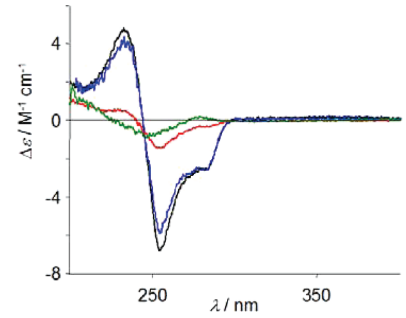

Figure 2. CD spectra of **2a** (5 mM) before (red line) and after (black line) K-Pic extraction. CD spectra of **2a**/K-Pic complex sample after dilution to 0.5 mM (blue line) and after addition of 4 equiv [2.2.2] cryptand (green line).

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(7) Self-assembled spin cage containing four radical centers have also been reported: Nakabayashi, K.; Ozaki, Y.; Kawano, M.; Fujita, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2046–2048.

(8) C_4-symmetric octamers are described, for example, in: (a) Marlow, A. L.; Mezzina, E.; Spada, G. P.; Masiero, S.; Davis, J. T.; Gottarelli, G. *J. Org. Chem.* **1999**, *64*, 5116–5123. D_4-symmetric octamers are described, for example, in: (b) Martić, S.; Liu, X.; Wang, S.; Wu, G. *Chem.—Eur. J.* **2008**, *14*, 1196–1204. (c) Kaucher, M. S.; Lam, Y.-F.; Pieraccini, S.; Gottarelli, G.; Davis, J. T. *Chem.—Eur. J.* **2005**, *11*, 164–173.

(9) Paramasivan, S.; Rujan, I.; Bolton, P. H. *Methods* **2007**, *43*, 324–331. Gottarelli, G.; Spada, G. P.; Garbesi, A. In *Comprehensive Supramolecular Chemistry*; Sauvage, J.-P.; HosseiniM. W., Eds.; Pergamon: Oxford, 1996; Vol. 9, pp 483−506.

(10) (a) Gray, D. M.; Wen, J.-D.; Gray, C. W.; Repges, R.; Repges, C.; Raabe, G.; Fleishhauer, J. *Chirality* **2008**, *20*, 431–440. (b) Gottarelli, G.; Masiero, S.; Spada, G. P. *Enantiomer* **1998**, *3*, 429–438. (c) Gottarelli, G.; Lena, S.; Masiero, S.; Pieraccini, S.; Spada, G. P. *Chirality* **2008**, *20*, 471–485.

Figure 2 shows CD spectra of solutions of **2a** recorded before (red trace) and after (black trace) solid−liquid extraction of potassium picrate K-Pic (i.e., after stirring the guanosine solution with solid K-Pic—see Supporting Information). While the solution of **2a** shows a weak Cotton effect corresponding to the guanine chromophore, in the presence of K-Pic an intense negative CD coupling with the negative and positive components at around 265 and 245 nm, respectively, is observed: this feature is diagnostic of a C_4-symmetric assembly of (at least) two G-quartets chirally rotated. Intensity and shape of the CD spectrum do not change with concentration, in the range 8−0.5 mM (see Figure 2, blue trace), suggesting that in these conditions the self-assembled structure is maintained. The molar ratio between **2a** and K-Pic has been determined spectrophotometrically to be >8:1 (see Supporting Information). These findings suggest that the assembly is a C_4-symmetric octamer formed by two head-to-tail stacked G-quartets.

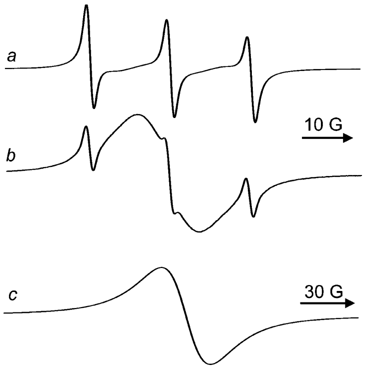

Figure 3. ESR spectra of **2a** (0.5 mM) before (a) and after (b) K-Pic extraction. (c) ESR spectrum recorded at 77 K in CH_2Cl_2 glass in the presence of K^+.

Figure 3 shows ESR spectra recorded on **2a** in CH_2Cl_2 (before, trace a, and after, trace b, K-Pic extraction). In the absence of metal cations, the spectrum is characterized by three equally spaced lines with a broadening between them, this being an indication that intramolecular spin exchange is occurring. In sharp contrast, the ESR spectrum recorded after solid−liquid extraction of potassium picrate shows mainly one broad signal whose integrated intensity corresponds to the initial amount of radicals. The broadening (peak to peak line width = 12 G) of the signal is independent of concentration and temperature, and thus interassembly interactions and motional broadening can be discounted. This spectrum is reminiscent of those obtained from very concentrated nitroxide solutions (>0.05 M).[11] Since the spectrum was obtained at 0.5 mM concentration, the signal broadening is ascribed to the proximity of spin centers of **2a** within the framework of the octamer. This signal may contain not only a triplet transition but also other multiplet transitions from higher spin states arising from multiple interactions between the 16 radical units.

At 77 K in CH_2Cl_2 glass, the spectrum of the octamer (see Figure 3, trace c) showed only a featureless single peak in the g ≈ 2 region and a weak $|\Delta m_s| = 2$ peak at 1660 G. The observation of a $|\Delta m_s| = 2$ transition also support the presence of intermolecular spin−spin interaction. However, the signal of $|\Delta m_s| = 2$ transition is very weak, indicating that these transition probabilities are extremely small as a result of a small D-value of the high spin−spin states from the octamer. Accordingly to previous investigation[11,12] on symmetric tetraradical, we attributed the lack of resolvable zero field splitting to the time-averaged symmetry of the complex (*vide infra*).

Reversible interconversion between uncomplexed and octameric forms was demonstrated by addition of four equivalents of [2.2.2] cryptand to a solution containing the assembly. Under these conditions the EPR and CD spectra returned to the original signals (see Figure 2, green trace, and Supporting Information).[13]

Because of the presence of two paramagnetic units, the ^1H NMR spectra of **2a** are characterized by a very low spectral resolution and their analysis turned out far more complicated than for derivative **1**. Therefore we prepared and characterized by CD and NMR compound **2b** in which the paramagnetic moiety is replaced by the closed-shell structurally related 3,3,5,5-tetramethyl-4-oxocyclohexanecarboxylate fragment. Because of the much higher resolution of NMR spectra, a full characterization of the assembly could be obtained for this derivative.

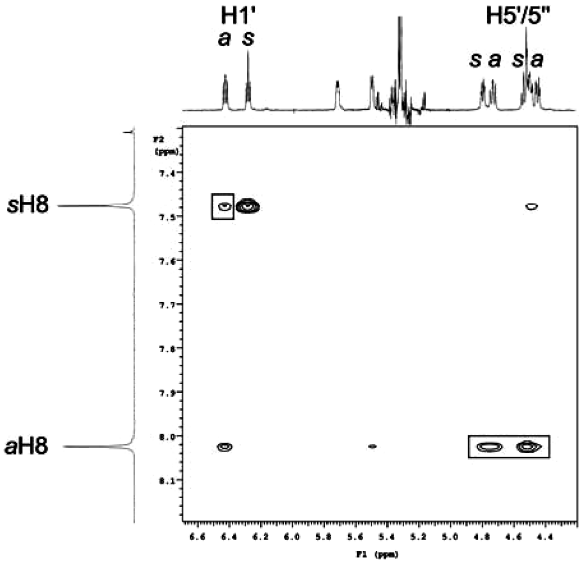

Figure 4. Portion of the 600 MHz NOESY spectrum of the octameric complex between **2b** and K-Pic, recorded at rt in CD_2Cl_2 (mixing time 150 ms) showing the interquartet correlations.

The proton spectrum of a CD_2Cl_2 solution of **2b** after K-Pic extraction (see Supporting Information) is characterized by the doubling of almost all of the signals. Integration

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[11] Wertz, J. E.; Bolton, J. R. *Electron Spin Resonance*; Chapman and Hall: New York, 1986.

of the picrate signal at 8.75 ppm and H8 signals (8.03 and 7.48 ppm) supports a 8:1 stoichiometry for the complex. The signal doubling is thus consistent with a C_4-symmetric octamer. This is confirmed by NOESY spectra (Figure 4 and Supporting Information), which show the features of an octamer composed of an all-*anti* quartet stacked on top of an all-*syn* quartet in an head-to-tail relative orientation.[7] In particular, the characteristic interquartet correlations between *syn*-H8 (7.48 ppm) and *anti*-H1′ (6.43 ppm) and between *anti*-H8 (8.03 ppm) and *syn*-H5′/H5″ (4.79 and 4.53 ppm) can be observed.

Shape and intensity of CD spectra of **2b** (before and after K-Pic extraction) are quite similar to those of **2a** (see Supporting Information) suggesting a similar self-assembly behavior.

Based on CD and NMR data we can conclude that in the presence of K^+ both derivatives **2a** and **2b** self-associate into two stacking G-quartets in a head-to-tail arrangement with the metal ion sitting in the central cavity, to form a C_4-symmetric octamer.

To obtain a more detailed picture of the geometry of the octamer, stochastic dynamics (SD) simulations were performed by using the AMBER* force field of Macromodel 7.0 program. Initially, a Monte Carlo conformational search was carried out by rotating all rotable bonds and by preserving all-*anti* quartet stacked on top of an all-*syn* quartet in an head-to-tail relative orientation. The most stable conformation found by this procedure was then used in the dynamic simulation. The simulations were run at 300 K with time steps of 1 fs and an equilibrium time of 500 ps before dynamic run. The total simulation time was set to 5000 ps in order to achieve full convergence. Molecular dynamics calculations (see Figure 5 and Supporting Information) confirm the C_4-symmetric nature of the octamer and indicate the presence of four triradical modules protuding from the two tetramers and pointing outside the assembly (in green) and a tetraradical module located on top of the all-*anti* quartet (in red). In the triradical module the nitroxide are arranged in isosceles triangles. In each triangle, the distance between the oxygen atoms of the three nitroxides is in the range 9.5−10.5 and 6−7 Å, which is expected to lead to three spin−spin interactions with high J values. The tetraradical unit is, instead, arranged in a rombic fashion with an average distance between radical oxygen atoms of 7.5 Å, which is expected given a strong spin−spin interaction between all of them.

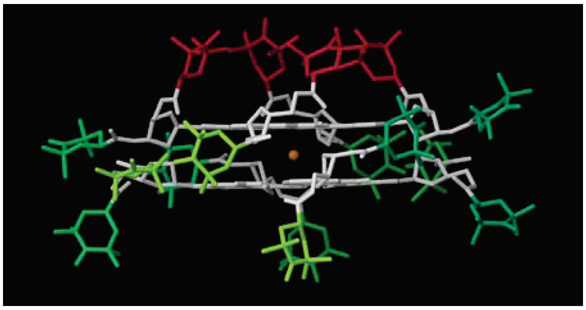

Figure 5. Structure of the octamer that refer to the time interval of dynamic simulation between 2000th to the 2250th ps.

Although self-assembly of a paramagnetic guanosine in the presence of alkali metal ions has already been reported, here we have shown the advantages of obtaining a supramolecular hexadecanitroxide from **2a**, a derivative with two open-shell moieties; in particular, ESR line-broadening due to dipolar and/or exchange effects is more remarkable because of increasing pathways of the radical−radical contact. The present work should be regarded as the first example of a radical-armed self-assembling scaffold showing drastic magnetic changes by addition-removal of diamagnetic alkali metal cations.[14]

Acknowledgment. We thank MIUR, through their National Research Programmes (PRIN), for financial support.

Supporting Information Available: Experimental details; CD, NMR, ESR spectra; video file of MD. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Rajca, A.; Mukherjee, S.; Pink, M.; Rajca, S. *J. Am. Chem. Soc.* **2006**, *128*, 13497–13507. (b) Kirste, B.; Grimm, M.; Kurreck, H. *J. Am. Chem. Soc.* **1989**, *111*, 108–114.

(13) The low-intensity negative couplet present also before K-Pic addition in the CD spectrum is due to Na^+ (or K^+) contamination resulting from the synthetic procedure.

(14) Metal-induced magnetic exchange coupling in paramagnetic azacrowns have also been reported. Igarashi, K.; Nogami, T.; Ishida, T. *Chem. Commun.* **2007**, 501–503.