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A Cation-Directed Switch of Intermolecular Spin−Spin Interaction of Guanosine Derivatives Functionalized with Open-Shell Units

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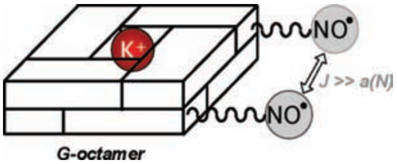
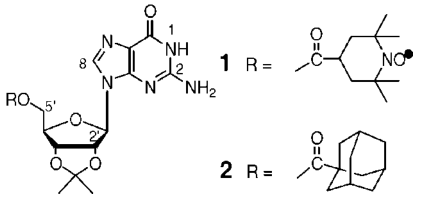
ABSTRACT



The guanosine derivative 1 functionalized with the persistent radical unit 4-carbonyl-2,2,6,6-tetramethylpiperidin-1-oxyl in solution has no particular intermolecular spin−spin interactions; however, in the presence of potassium ions this compound can form a D_4-symmetric octameric assembly $[1_8K]^+$ in which the nitroxyl moieties show a weak electron spin−spin exchange interaction. Since the relative geometry of the radicals is the outcome of K^+-directed self-assembly, the spin−spin interaction can be suppressed by removing the alkaline ion.

Switching of the spin−spin interactions in organic radicals is of particular interest for the development of molecular-scale magnetic devices.[1] When the spin exchange occurs only through-space, complete control of this interaction can be obtained by modifying the spatial arrangement of radical centers.[2] Whereas spin−spin coupling via covalent bonds has been well studied, [3] strong through-space interactions between organic radicals are more difficult to achieve because unpaired spins have to be located at a short distance. Recently, a pH-controlled switching of a spin−spin coupling between two organic radicals placed in a self-assembled cage has been reported;[4] this represents the first example of reversible control by an external stimulus over an intermolecular spin−spin interaction in solution.[5]



Lipophilic guanosines are very versatile self-assembling units. Depending on the experimental conditions, they spontaneously self-associate to give either H-bonded ribbons or quartet-based columnar structures.[6,7] As it is possible to functionalize the guanosines in the 8 position and/or at the sugar hydroxy functions, they are ideal scaffolds to locate

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(1) *Magnetism: Molecules to Materials*; Miller, J. S., Drillon M., Eds.; Wiley-VCH: Weinheim, 2001−2003; Vols. I−IV.

(2) (a) Fujita, W.; Awaga, K. *Science* **1999**, *286*, 261. (b) Itkis, M. E.; Chi, X.; Cordes, A. W.; Haddon, R. C *Science* **2002**, *296*, 1443.

(3) Rajca, A. *Chem. Rev.* **1994**, *94*, 871.

(4) (a) Nakabayashi, K.; Kawano, M.; Fujita, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5322. (b) Nakabayashi, K.; Kawano, M.; Yoshizawa, M.; Ohkoshi, S.; Fujita, M. *J. Am. Chem. Soc.* **2004**, *126*, 16694. (c) See also: Nakabayashi, K.; Ozaki, Y.; Kawano, M.; Fujita, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2046.

(5) Metal-induced conformational modifications in paramagnetic calixarenes have also been reported. Araki, K.; Nakamura, R.; Otsuka, H.; Shinkai, S. *Chem. Commun.* **1995**, 2121.

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functional units in preprogrammed positions, outside highly ordered architectures.[8]

In this paper, we report on the self-assembly of a guanosine derivative functionalized with the persistent radical unit 4-carbonyl-2,2,6,6-tetramethylpiperidin-1-oxyl (**1**). While **1** in solution has no particular intermolecular spin−spin interactions, in the presence of potassium ions this compound can form a D_4-symmetric octameric assembly $[\mathbf{1}_8\mathrm{K}]^+$ in which the nitroxyl moieties show a weak electron spin−spin exchange interaction (Figure 1). Since the relative geometry of the radicals is the outcome of K^+-directed self-assembly, the spin−spin interaction can be suppressed by removing the alkaline ion. To the best of our knowledge, the system described here is the first example of a reversible introduction-suppression of spin−spin exchange in a self-recognizing and self-assembling molecule controlled by the addition/removal of a templating cation.

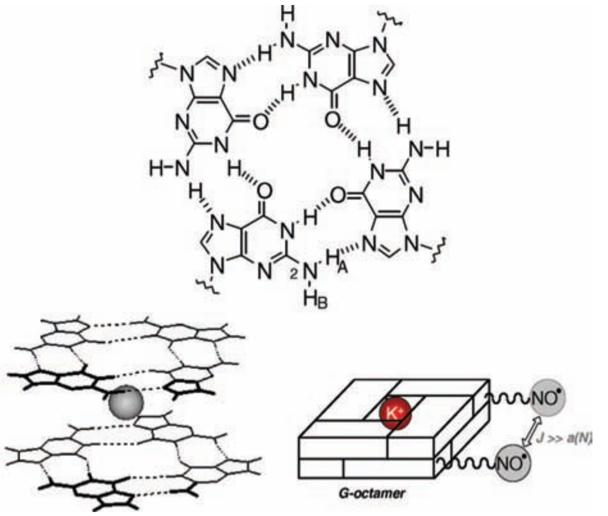

Figure 1. G-quartet motif and the D_4-symmetric stacking of two G-quartets templated by a cation (for clarity, only one nitroxyl per quartet has been shown in the last cartoon).

Circular dichroism (CD) was initially employed to prove the self-assembly of **1** to give quartet-based structures in $CHCl_3$. Figure 2 (top) shows CD spectra of solutions of **1** recorded before (trace a) and after (trace b) solid−liquid extraction of potassium picrate, K-Pic (i.e., after stirring the guanosine solution with solid K-Pic; see the Supporting Information). In the presence of K-Pic, an intense negative CD coupling is observed in the 250−300 nm region, this feature being diagnostic of an assembly of (at least) two G-quartets chirally rotated.[10,11] Neither temperature (25−60 °C) nor concentration (0.05−10 mM) variations do modify the intensity (and shape) of the CD spectrum, suggesting that, even in the presence of large modification of the experimental conditions, the self-assembled structure is maintained and that almost all guanosine molecules are in the assembled state.

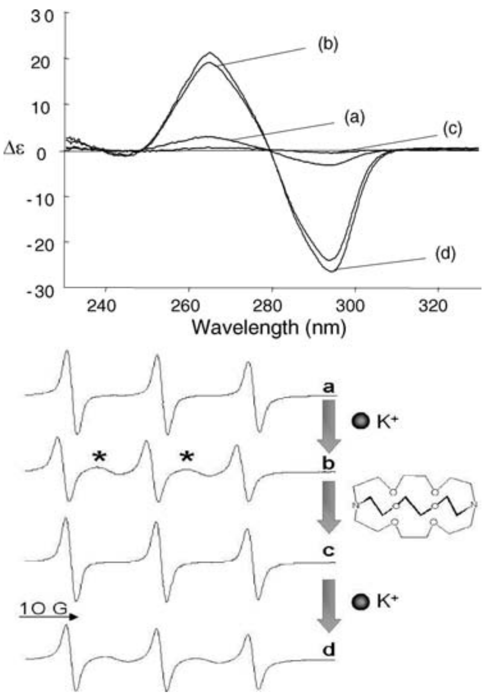

Figure 2. CD (top) and EPR (bottom) spectra of solutions of **1** (0.5 mM) in $CHCl_3$ before (a) and after (b) solid−liquid K-Pic extraction,[9] (c) solution b after water washing and addition of [2.2.2] cryptand 0.25 mM, and (d) solution c after addition of solid K-Picrate (1 mol/mol of [2.2.2] cryptand).

The EPR spectrum of radical **1** (Figure 2, bottom) recorded in chloroform is characterized by three hyperfine lines (trace a) as normally found for a monoradical nitroxide species ($a_N = 15.9$ G, $g = 2.0057$). Solid−liquid extraction of potassium picrate modifies the EPR spectrum into a new spectrum containing five lines (trace b) separated by $a_N/2$ with the width of the second and fourth line much broader than the other ones. The observation of five equally spaced lines clearly suggests the presence in solution of an assembled species in which the nitroxyl moieties are coupled by a through-space spin−spin exchange interaction (J), with $J \gg a_N$.

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(6) (a) Davis, J. T.; Spada, G. P. *Chem. Soc. Rev.* **2007**, *36*, 296. (b) Liu, X.; Kwan, I. C. M.; Wang, S.; Wu, G. *Org. Lett.* **2006**, *8*, 3685. (c) Araki, K.; Yoshikawa, I. *Top. Curr. Chem.* **2005**, *256*, 133. (d) Sessler, J. L.; Sathiosatham, M.; Doerr, K.; Lynch, V.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1300.

(7) Gubala, V.; De Jesús, D.; Rivera, J. M *Tetrahedron Lett.* **2006**, *47*, 1413.

(8) (a) Sreenivasachary, N.; Lehn, J. M. *Proc. Nat. Acad. Sci. U.S.A.* **2005**, *102*, 5938. (b) Kaucher, M. S.; Harrell, W. A., Jr.; Davis, J. T *J. Am. Chem. Soc.* **2006**, *128*, 38. (c) Arnal-Hérault, C.; Banu, A.; Barboiu, M.; Michau, M.; van der Lee, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4268. (d) Zhong, C.; Wang, J.; Wu, N.; Wu, G.; Zavalij, P. Y.; Shi, X. *Chem. Commun.* **2007**, 3148.

(9) 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. In fact, addition of cryptand [2.2.2], which efficiently binds K^+ (and Na^+), leads to a very weak spectrum as expected for an uncomplexed guanosine derivative.

(10) Kaucher, M. S.; Lam, Y.-F.; Pieraccini, S.; Gottarelli, G.; Davis, J. T. *Chem. Eur. J.* **2005**, *11*, 164.

(11) (a) Setnička, V.; Urbanová, M; Volka, K.; Nampally, S.; Lehn, J.-M. *Chem. Eur. J.* **2006**, *12*, 8735. (b) Gottarelli, G.; Lena, S.; Masiero, S.; Pieraccini, S.; Spada, G. P. *Chirality* **2008**, *20*, 471.

The EPR spectrum in the presence of potassium ions shows considerable narrowing of the second and fourth lines when the temperature increases (see Figure S12, Supporting Information), this being an indication that an intramolecular motion is fast modulating the exchange interactions. However, even at 60 °C, when the width of the second and fourth lines tends to be closer to those of the outermost lines, the ratio of integrated line intensities still differs essentially from the theoretically predicted 1:2:3:2:1 ratio. The observed distribution of line intensities can be explained[12] as the result of the superposition of two EPR spectra due to different paramagnetic species which are exchanging slowly in the EPR time scale: one due to a noninteracting ($J = 0$) nitroxide unit while the other is due to nitroxide fragments that can either interact ($J \gg a_N$) or not ($J = 0$) depending on their mutual orientation.[13] For the latter species, the fast modulation of J due to the conformational freedom of the side chains carrying the nitroxide moieties is responsible for the line broadening.

Because of the presence of paramagnetic units, the ^{1}H NMR spectra are characterized by a very low spectral resolution (see Figure 3, top). Nevertheless, some information can be inferred. In particular, after extraction of K-Pic, one amino proton N2−H shifts considerably from ca. 6.5 ppm (in DMSO $\delta = 6.6$ ppm, see Figure S1, Supporting Information) to 9.4 ppm (see Figure 3, top, trace b): this downfield resonance for N2−H_A is characteristic of G-quartet formation where this proton is involved in the cyclic H-bond scheme.[14] The complex obtained after K-Pic extraction shows a molar ratio **1**/K^+ of 2:1 suggesting an empirical formula of [$\mathbf{1}_8K_4$](Pic_4). On the other hand, by washing the solution with water a new species with a molar ratio **1**/K^+ of 8:1, corresponding to [$\mathbf{1}_8K$](Pic), is formed. These two 2:1 and 8:1 complexes show very similar spectral features: they have similar CD, NMR, and EPR spectra (see the Supporting Information).[15] Despite line broadening, both ^{1}H NMR spectra of the complexes with 2:1 and 8:1 molar ratio are characterized by only one set of signals; this is consistent with D_4-symmetric octameric species (two G-quartets stacked in either a head-to-head or a tail-to tail orientation).[14,16]

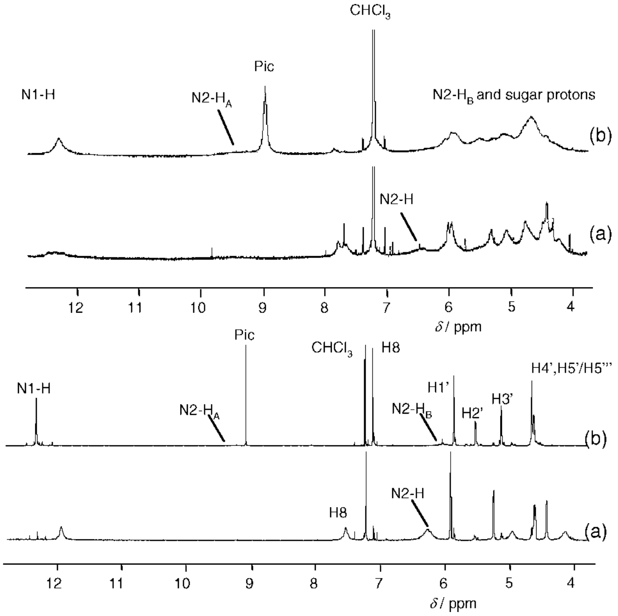

Figure 3. Low-field portions of ^{1}H NMR spectra of solutions of **1**, top, and **2** (10 mM), bottom, in $CDCl_3$ before (a) and after (b) solid−liquid K-Pic extraction.

We also prepared and characterized compound **2** in which the paramagnetic moiety is replaced by the diamagnetic structurally related adamantyl fragment. Because of the much higher resolution of NMR spectra (Figure 3, lower part), a full characterization of the assembly could be obtained for this derivative. Based on CD and NMR data (see Figure 3 and the Supporting Information), we can conclude that in the presence of K^+ both derivatives **1** and **2** self-associate into two stacking all-syn G-quartets in a tail-to-tail or head-to-head arrangement with the metal ion sitting in the central cavity, to form a D_4-symmetric octamer. Both derivatives can associate three additional K-Pic molecules more loosely.

As far as the open-shell side chains are concerned, EPR experiments indicate the presence of two different types of nitroxidic units. As in the presence of K^+ all guanosine molecules are associate in the octameric form,[17] the two different nitroxide units can be attributed to different conformations adopted by the paramagnetic side chains which are exchanging slowly in the EPR time scale (but fast in the NMR time scale).

As the G-quartet structures are templated by the potassium cation, this offers the possibility of triggering a reversible interconversion between uncomplexed and octameric forms by controlled sequential addition and removal of potassium cations.[19] Such an approach has been applied to compounds **1** and **2** (see the Supporting Information) and has been proven to be a successful trigger for the reversible conversion between through space uncoupled and coupled nitroxides. The macrocyclic [2.2.2] cryptand is known to offer an efficient complexation of potassium to yield the correspond-

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(12) Pardon, V. N.; Kokorin, A. I.; Zhidomirov, G. M.; Zamaraev, K. I. *Mol. Phys.* **1975**, *30*, 695.

(13) An estimate of interspin distance can be obtain by measuring the relative intensity of the $|\Delta m_s| = 1$ and $|\Delta m_s| = 2$. Eaton, S. S.; More, K. M.; Sawant, B. M.; Eaton, G. R *J. Am. Chem. Soc.* **1983**, *105*, 6560. Rohde, O.; Pong Van, S.; Kester, W. R.; Hayes Griffith, O. *J. Am. Chem. Soc.* **1974**, *96*, 5311. Unfortunately, we were not able to detect any signal for the half-field transition up to 77 K.

(14) Marlow, A. L.; Mezzina, E.; Spada, G. P.; Masiero, S.; Davis, J. T.; Gottarelli, G. *J. Org. Chem.* **1999**, *64*, 5116.

(15) The possibility for guanosine derivatives to extract more potassium or sodium than required by the templation in the inner cavity as well as the effect of water washing have been already described.[7,10]

(16) Forman, S. L.; Fettinger, J. C.; Pieraccini, S.; Gottarelli, G.; Davis, J. T. *J. Am. Chem. Soc.* **2000**, *122*, 4060.

(17) After solid−liquid extraction lipophilic guanosines exist only in aggregated complexes in non polar solvents (e.g., $CDCl_3$), while in more polar solvents (e.g., CD_3CN) NMR spectra do show an equilibrium mixture of alkali ion templated complexes and "monomeric" species in slow exchange on the NMR chemical shift time scale.[6,10,14,18]

(18) Gubala, V.; Betancourt, J. E.; Rivera, J. M. *Org. Lett.* **2004**, *6*, 4735.

(19) Pieraccini, S.; Masiero, S.; Pandoli, O.; Samorì, P.; Spada, G. P. *Org. Lett.* **2006**, *8*, 3125.

ing cryptate. Actually, addition of four equivalents of the [2.2.2] cryptand to a solution containing $[\mathbf{1}_8\mathrm{K}]^+$ complex reverts the EPR spectrum to the original three line signal, while the exciton couplet in the CD spectrum vanishes (see Figure 2). A subsequent addition of an equivalent (with respect to the cryptand) amount of solid K-Pic restores the EPR and CD spectroscopic features of self-assembled **1**.[20] In addition, ^{1}H NMR spectroscopy confirms that the self-assembly process is reverted after addition of [2.2.2] cryptand (see Figures S16 and S17, Supporting Information).

In summary, the ability of guanosine derivatives to self-assemble in the presence of alkali ions to give ordered columnar structures has been exploited for modulating the electron spin−spin exchange interaction of nitroxyl probes. The reversible formation of the octameric complex $[\mathbf{1}_8\mathrm{K}]^+$ introduces a spin−spin interaction between neighbor paramagnetic units that is suppressed by removing the alkaline ions. These results demonstrate for the first time that open-shell guanosine derivatives can be used to prepare molecular scale magnetic devices. The possibility of increasing the strength of spin−spin interaction, the number of radical units, the complexity of the supramolecular architecture and the improvement of the switching ability is under investigation.

Acknowledgment. This work was supported by MiUR (through the PRIN program).

Supporting Information Available: Synthetic procedures and characterization; experimental details (including NMR and NOESY spectra of the complexes). This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] Addition/removal of K^+ can also be controlled by protonation/deprotonation of [2.2.2]cryptand.[19] However, increasing the acidity of the solution leads to the disappearance of the EPR signal, because of the reduction of the nitroxide moiety to a diamagnetic unit. Nevertheless, CD experiments showed that reversible conversion between octameric and uncomplexed forms is still operating under these conditions (see Figure S14, Supporting Information).