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A Photoresponsive Supramolecular G-Quadruplex

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ABSTRACT

Photoirradiation of a hexadecameric supramolecular G-quadruplex leads to a diastereoselective [2 + 2] cyclodimerization of half of its constituent subunits, which in turn shifts the equilibrium toward the formation of a precise heteromeric octamer.

Responsive molecules are attractive due to their potential to act as components in (supra)molecular machinery.[1] Light is a particularly attractive external stimulus to trigger a specific response due to its low cost and inherent efficiency (i.e., speed of stimulus, lack of waste products).[2,3] Up to now, most reported examples of photoresponsive supramolecules are those that fluctuate between unassembled and assembled states or between precise[4] and polymeric states (e.g., gels, fibers, micelles).[5] Yet, examples of supramolecules in which a precise supramolecule transitions into another remains a significant challenge.[3] Here we describe the phototransformation of a precise homomeric hexadecamer into an equally precise heteromeric octamer.

We have recently evaluated the effects of extrinsic stimuli on the structure and dynamics of precise supramolecular G-quadruplexes (SGQs). SGQs are coaxially stacked (*2*, *3*, *4*, ... *n*) planar hydrogen bonded guanosine tetramers (or tetrads, T) stabilized by a wide variety of hard cations such as potassium (Figure 1). We have, furthermore, shown that SGQs made from 8-aryl-2′-deoxyguanosine (8ArG) derivatives could be induced to transition between two precise supramolecular states, specifically, octamers (*2*T-SGQ) and hexadecamers (*4*T-SGQ). In particular, we have so far shown two independent examples of such systems where a change in the solvent (e.g., solvoresponsive) or a change in the cation promoter (e.g., ionoresponsive) achieved the desired transition (Figure 1a; *i*/*i*′).[6] Here we expand this strategy to include a photoresponsive assembly (Figure 1a; *ii*).

To achieve a photoresponsive SGQ, we designed an 8-chalconyl-2′-deoxyguanosine derivative (**1**) containing a double bond in addition to the 8-(*m*-carbonylphenyl) moiety (Figure 1b). The former was to impart the desired photoresponsiveness, while the latter was expected to direct the reliable formation of a supramolecular hexadecamer ($\mathbf{1}_{16}$). We performed a Claisen–Schmidt condensation (Figure S1), to derivatize the 8-(*m*-acetylphenyl) moiety, thus ensuring the preservation of the critical *m*-carbonyl group.[6d,7a] This leaves the hydroxyl groups on

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[1] Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines - A Journey into the Nano World*; Wiley-VCH: Weinheim, 2003.

[2] Saha, S.; Stoddart, J. F. *Chem. Soc. Rev.* **2006**, *36*, 77–92.

[3] For selected examples of photoresponsive supramolecular systems, see: (a) Yagai, S.; Kitamura, A. *Chem. Soc. Rev.* **2008**, *37*, 1520–1529. (b) Bassani, D. M.; Darcos, V.; Mahony, S.; Desvergne, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 8795–8796. (c) Rakotondradany, F.; Whitehead, M. A.; Lebuis, A.-M.; Sleiman, H. F. *Chem.—Eur. J.* **2003**, *9*, 4771–4780. (d) Yagai, S.; Nakajima, T.; Karatsu, T.; Saitow, K.-i.; Kitamura, A. *J. Am. Chem. Soc.* **2004**, *126*, 11500–11508. (e) Molard, Y.; Bassani, D. M.; Desvergne, J.-P.; Horton, P. N.; Hursthouse, M. B.; Tucker, J. H. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 1072–1075. (f) Yagai, S.; Iwai, K.; Karatsu, T.; Kitamura, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 9679–9683.

[4] A precise supramolecule is one which not only is discrete (i.e., nonpolymeric) but also has a well-defined three-dimensional structure.

[5] For an example of a [2 + 2] photodimerization of thymine-terminated bolaamphiphile within supramolecular fibers, see: Iwaura, R.; Shimizu, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4601–4604.

[6] (a) Martín-Hidalgo, M.; Rivera, J. M. *Chem. Commun.* **2011**, *47*, 12485–12487. (b) Betancourt, J. E.; Rivera, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 16666–16668. (c) Betancourt, J. E.; Martín-Hidalgo, M.; Gubala, V.; Rivera, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 3186–3188. (d) García-Arriaga, M.; Hobley, G.; Rivera, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 10492–10493.

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the ribose available for attaching functional elements such as hydrophilic groups,[6d] fluorophores,[7b] and dendrons.[6a,7c,7d]

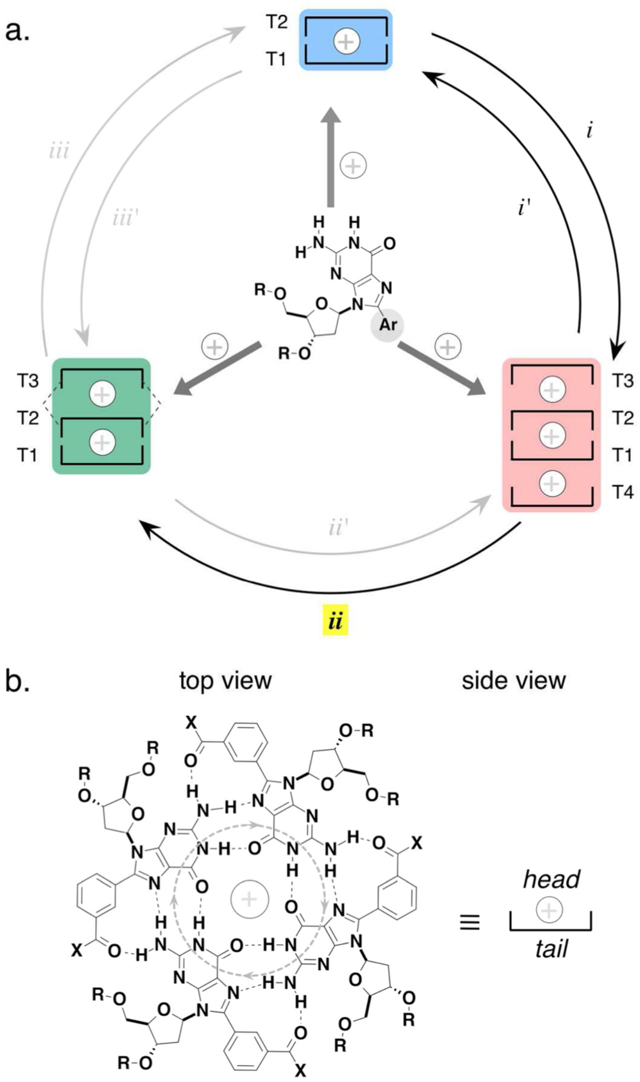
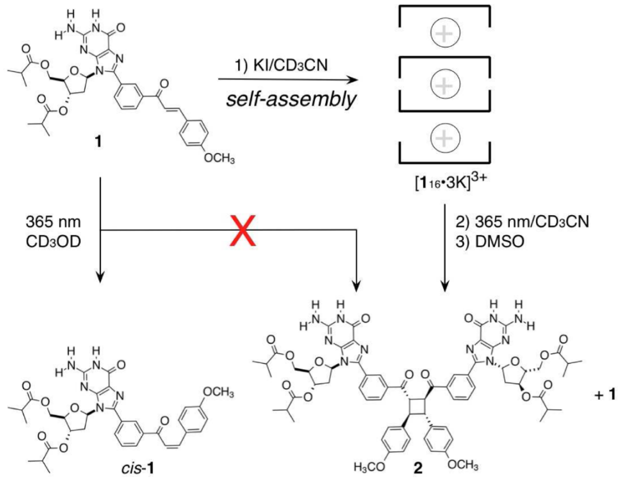


Figure 1. (a) Schematic depiction of the interconversion of various SGQs formed by 8ArG derivatives using external stimuli. The circles with a + sign represent a cation such as K^+; the *2*T-SGQ, *3*T-SGQ, and *4*T-SGQ are highlighted (respectively) in blue, green, and red. The dotted lines between T2 and T3 represent potential covalent bonds between subunits as is the case in the present work. The dark arrows represent achieved modes of transforming different types of SGQs (process *ii* highlighted in yellow is the subject of the current report), while the arrows in gray (*ii*′, *iii*, *iii*′) are unachieved transformations. (b) Chemical and cartoon depictions of a generic 8ArG tetramer (e.g., $\mathbf{1}_4$•K^+; X = chalconyl moiety and R = isobutyryl as shown in Scheme 1) indicating its two diastereomeric sides. The head is the side shown, which has a clockwise rotation (circular dashed arrows) around N1H to O6 hydrogen bonds.

The ^{1}H NMR spectrum of **1**, in the presence of KSCN (0.5 equiv, in CD_3CN), revealed a pair of peaks between 11 and 13 ppm corresponding to the two types of N1Hs characteristic of a D_4-symmetric *4*T-SGQ or hexadecamer (Figure 2a). The 2D NOESY spectrum also shows key signature cross peaks in the 7−13 ppm region, corresponding to the hydrogen bonded guanine moieties in the G-quadruplex core (Figure S21). Electrospray ionization mass spectrometry (ESI-MS) provided further evidence for the formation of $[\mathbf{1}_{16}\bullet 3K]^{3+}$ by showing a peak at *m*/*z* 3471.8918 (Figure 2). These results show that the enhanced steric crowding in the periphery of **1** does not interfere with its self-assembly, underscoring the importance of the *m*-carbonyl group in directing the assembly of a *4*T-SGQ.

Scheme 1. Photoreaction Products Obtained by Irradiating 8-Chalconyl-2′-deoxyguanosine Derivative **1** as a Monomer or after Its Self-Assembly into Hexadecamer $\mathbf{1}_{16}$•$3K^{+a}$



[a] Irradiation of monomer **1** does not produce **2**, as indicated by the crossed out arrow.

Photoirradiation (30 min; 365 nm) of **1** in methanol (unfavorable conditions for self-assembly) resulted in a *trans*−*cis* isomerization with a photoequilibrium of ca. 60% *cis*-**1** as confirmed by UV−vis spectroscopy and ^{1}H NMR (Scheme 1; Figures S7−S10).[8,9] In contrast, photoirradiation of $\mathbf{1}_{16}$ (20 min, in CD_3CN) lead to the disappearance of all the signature peaks with the concomitant broadening of the remaining visible signals (Figures 3 and S18). Initially it seemed as if the formation of *cis*-**1** had induced the disassembly of $\mathbf{1}_{16}$,[10] but a day later it became clear that this was not the case because the ^{1}H NMR spectrum revealed the emergence of a species with sharp signals,

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(7) (a) Gubala, V.; Betancourt, J. E.; Rivera, J. M. *Org. Lett.* **2004**, *6*, 4735–4738. (b) Rivera, J. M.; Martín-Hidalgo, M.; Rivera-Ríos, J. C. *Org. Biomol. Chem.* **2012**, *10*, 7562–7565. (c) Rivera, L. R.; Betancourt, J. E.; Rivera, J. M. *Langmuir* **2011**, *27*, 1409–1414. (d) Betancourt, J. E.; Rivera, J. M. *Org. Lett.* **2008**, *10*, 2287–2290.

(8) Irradiation for up to 60 min leads to no significant changes relative to shorter irradiation times. *cis*-**1** decays slowly back to **1** (Figure S10).

(9) Spada reported that the *cis*−*trans* isomerization of an 8-styryl-2′-deoxyguanosine derivative leads to the reversible assembly−disassembly of the corresponding octameric supramolecule. Lena, S.; Neviani, P.; Masiero, S.; Pieraccini, S.; Spada, G. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 3657–3660.

(10) An experiment using a 1:1 mixture of **1**:*cis*-**1** (Figure S17) indicates that even at these proportions *cis*-**1** does not disrupt hexadecamer formation.

which became dominant after several more days. An interesting feature of this new species was the triple set of signals, which offered the first hint of an assembly with three tetrads or a *3*T-SGQ (Figures 2b, 3). The question remained, however, as to what type of *3*T-SGQ was it.

The peak pattern of the NMR of the new species (Figures 2b and S19),[11] and the observed mass of m/z 2613.6326 (Figures 2 and S20), led us to hypothesize that the isomerization toward *cis*-**1** induced the formation of a dodecamer. This possibility was quickly dismissed due to the near absence of *cis*-**1** in the ^{1}H NMR in DMSO-d_6 (a solvent that disrupts the assembly), in addition to the observed 1:1 ratio of **1** with a new species (**2**) that showed a double set of signals (Scheme 1, Figure 3b). Further HPLC-MS analysis of **2** demonstrated it to have twice the mass of **1** (Figures S6, S14) supporting its assignment as a covalent dimer (Scheme 1). Further NMR experiments with **2** confirmed the presence of a cyclobutyl moiety, likely formed via a [2 + 2] photocycloaddition between the double bonds in the chalconyl moiety.

The reason why irradiation of $\mathbf{1}_{16}$ enables a [2 + 2] cycloaddition reaction is the increased proximity of four pairs of chalconyl double bonds in the supramolecule (Figure 3a).[12,13] The formation of a single diastereomer of **2** and the negligible formation of *cis*-**1** are indicative of the kinetic stability, well-defined spatial orientation of the double bonds, and the relatively crowded environment within $\mathbf{1}_{16}$. Molecular modeling studies suggest the stereochemistry around the cyclobutyl moiety in **2** is the so-called δ-truxinate[14] due to the relative orientation of the olefins prior to the dimerization (Figure S26). Minimization of the dimer by itself, followed by its superposition over the structure of $\mathbf{1}_4\mathbf{2}_4$, shows minimal deviations in the overall geometry of the subunits (Figure S26). Those small deviations, however, are likely responsible for the reluctance of **2** to form a homomeric octamer due to its reduced flexibility relative to **1**. The association of two different tetrads ($\mathbf{1}_4 + \mathbf{2}_4$) provides enough flexibility to accommodate the increased rigidity of the subunits of **2**.

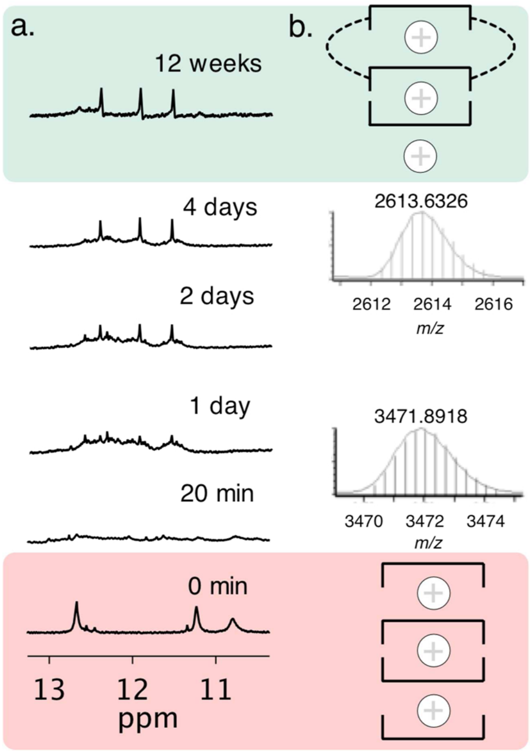

Figure 2. Phototriggered transformation of $\mathbf{1}_{16}$ into $\mathbf{1}_4\mathbf{2}_4$ as a function of time. (a) Partial ^{1}H NMR (500 MHz, CD_3CN, 0.5 equiv KSCN, 298 K) showing the region corresponding to the N1H peaks. (b) Cartoon depiction of the corresponding SGQs $[\mathbf{1}_{16}\bullet 3K]^{3+}$ and $[\mathbf{1}_4\mathbf{2}_4\bullet 3K]^{3+}$; the measured and calculated isotope patterns obtained from ESI-MS are included above and below (respectively) the corresponding cartoon depictions.

After irradiation, many of the potential supramolecular states, including, for example, the heteromeric dodecamer $\mathbf{1}_8\mathbf{2}_4$ or the homomeric octamer $\mathbf{2}_8$, are not favored.[15] This is likely a combination of the detrimental strain imposed by the cyclobutyl moiety combined with the putative entropic advantage of a heteromeric assembly over a homomeric one. More specifically, isolated dimer **2** (with 0.5 equiv of KSCN in CD_3CN) self-assembles with very poor fidelity leading to a complex mixture of assemblies (Figure S24), yet, adding 1 equiv of **1** leads to the relatively slow formation of $\mathbf{1}_4\mathbf{2}_4$ (Figure S25). The many transient peaks observed right after the irradiation of $\mathbf{1}_{16}$ (Figure 2; Figures S18, S19), and up until the new equilibrium is established, points to a rough energy landscape (thus, the relatively long equilibration process) containing multiple metastable assemblies (i.e., kinetic traps) where $\mathbf{1}_4\mathbf{2}_4$ represents a significantly deeper well to shift the equilibrium with high fidelity.[16] The proportion of subunits (1:1) is precisely determined by not only the information encoded

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[11] (a) Rivera-Sanchez, M. d. C.; Andújar-de-Sanctis, I.; García-Arriaga, M.; Gubala, V.; Hobley, G.; Rivera, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 10403–10405. (b) Gonzalez-Rodriguez, D.; van Dongen, J. L. J.; Lutz, M.; Spek, A. L.; Schenning, A. P. H. J.; Meijer, E. W. *Nat. Chem.* **2009**, *1*, 151–155.

[12] The [2 + 2] cycloaddition in solution is not usually the favoured dissipative process after photoexcitation (heat dissipation, *trans*−*cis* isomerization, and emission being usually favoured). And while still relatively rare, relative to examples [2 + 2] cycloaddition reactions can occur in crystalline environments: (a) Bhogala, B.; Captain, B.; Parthasarathy, A.; Ramamurthy, V. *J. Am. Chem. Soc.* **2010**, *132*, 13434–13442. (b) MacGillivray, L. R.; Papaefstathiou, G. S.; Friscić, T.; Hamilton, T. D.; Bucar, D.-K.; Chu, Q.; Varshney, D. B.; Georgiev, I. G. *Acc. Chem. Res.* **2008**, *41*, 280–291. (c) Yang, S.-Y.; Naumov, P. e.; Fukuzumi, S. *J. Am. Chem. Soc.* **2009**, *131*, 7247–7249.

[13] (a) Ushakov, E. N.; Vedernikov, A. I.; Alfimov, M. V.; Gromov, S. P. *Photochem. Photobiol. Sci.* **2011**, *10*, 15–18. (b) Svoboda, J.; König, B. *Chem. Rev.* **2006**, *106*, 5413–5430. (c) Mizoguchi, J.-i.; Kawanami, Y.; Wada, T.; Kodama, K.; Anzai, K.; Yanagi, T.; Inoue, Y. *Org. Lett.* **2006**, *8*, 6051–6054. (d) Iwaura, R.; Shimizu, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4601–4604.

[14] Although the double bonds in **1** could be positioned in a relative geometry that would lead to the α-truxilate, analysis of the resulting mixed octamer of $\mathbf{1}_4\mathbf{2}_4$ made with it revealed many detrimental interactions that would prevent its formation. McClenaghan, N. D.; Bassani, D. M. *Int. J. Photoenergy* **2004**, *6*, 185–192.

[15] The peak at m/z = 3471 could correspond to $[\mathbf{1}_{16}\bullet 3K]^{3+}$ or $[\mathbf{1}_8\mathbf{2}_4\bullet 3K]^{3+}$ (Figure S20), which leaves open the possibility that the latter (a mixed dodecamer) could form at least in the gas phase as well as in small amounts in solution.

[16] Furlan, R. L. E.; Otto, S.; Sanders, J. K. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4801–4804.

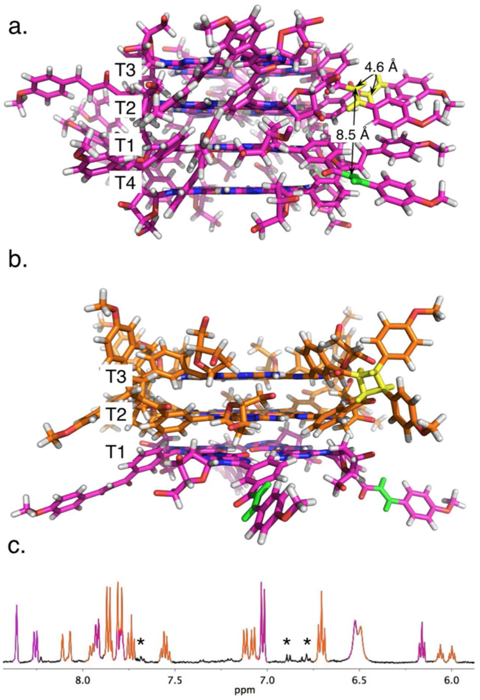

Figure 3. Molecular models of (a) $\mathbf{1}_{16}$ and (b) $\mathbf{1}_4\mathbf{2}_4$ showing the spatial proximity of the reactive double bonds and the resulting cyclobutyl moiety, respectively (both highlighted in yellow). Adjacent double bonds from T1 are highlighted in green, and due to their large separation the dimerization occurs exclusively between T2/T3 or T1/T4. (c) ^{1}H NMR (500 MHz, DMSO-d_6, 298 K) of $\mathbf{1}_4\mathbf{2}_4$ sample. DMSO-d_6 effectively disrupts the assembly, allowing characterization of both **1** (magenta) and **2** (orange) as monomers. Peaks marked with asterisks correspond to *cis*-**1** (~4%).

in the constituent subunits in $\mathbf{1}_4\mathbf{2}_4$ but also the spatial distribution of such subunits, where tetramers $\mathbf{1}_4$ and $\mathbf{2}_4$ self-sort[17] at opposite sides of the supramolecule. The resulting symmetry can only result from a mixed assembly with a Janus type configuration (Figure 3b).[18]

In summary, the phenomenon described here goes as follows: (1) irradiation of monomer **1** leads to isomerization to *cis*-**1**; (2) irradiation of $\mathbf{1}_{16}$ leads to a [2 + 2] photocycloaddition of two subunits of **1** to form a covalent dimer **2**; (3) the dimer still preserves some of the information for assembling, but it cannot self-assemble by itself into a well-defined discrete supramolecule. Instead, it self-sorts with subunits of **1** to form a heteromeric octamer $\mathbf{1}_4\mathbf{2}_4$; (4) formation of **2** does not abolish all assemblies because, although a homomeric assembly of dimer **2** is not viable, in combination with **1** the resulting system can fulfill a larger number of noncovalent interactions (e.g., hydrogen bonds, $\pi-\pi$ interactions), which would otherwise go unmet. The resulting heteromeric SGQ is structurally anisotropic along the assembly's main (C_4) axis (i.e., a Janus type supramolecule). The *4*T-SGQ $\mathbf{1}_{16}$ is, to the best of our knowledge, the first example of a precise photoresponsive supramolecular assembly able to shift to an alternative precise supramolecule ($\mathbf{1}_4\mathbf{2}_4$). The synthesis of related derivatives containing functional elements (e.g., fluorophores, dendrons) will provide a platform for the development of molecularly precise multifunctional supramolecules for a wide variety of applications.

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Supporting Information Available. Experimental details, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] (a) Safont-Sempere, M. M.; Fernández, G.; Würthner, F. *Chem. Rev.* **2011**, *111*, 5784–5814. (b) Wu, A.; Isaacs, L. *J. Am. Chem. Soc.* **2003**, *125*, 4831–4835.

[18] In principle, an assembly having twice as many tetrads (i.e., six) may show similar NMR and MS spectra. This possibility was discarded on the basis of the evidence provided in previous studies by our group where we have shown that 8ArG derivatives cannot form assemblies with more than four tetrads. This is because the enhanced repulsive interactions (steric, electronic) for stacking five or more tetrads are not sufficiently compensated by attractive noncovalent interactions. For relevant information see refs 6c, 6d, 7, and 11a.

The authors declare no competing financial interest.