Supramolecular Chemistry

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Triggering of Guanosine Self-Assembly by Light**

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Controlling a function at the molecular level by means of external stimuli is one of the key requirements in the development of "smart" materials, and light is a very appealing trigger because of its ready availability, easy manipulation, and noninvasive character.[1] In particular, self-assembly processes that can be controlled by photochemical stimuli are an actively pursued research field and one ultimate goal in supramolecular chemistry.[2]

In recent years, lipophilic guanine derivatives (lipoGs) have received increasing attention because of their rich supramolecular behavior.[3,4] Most of the supramolecular architectures obtained from lipoGs and so far reported in the literature require the presence of a cation (usually an alkali-metal cation, but also an alkaline-earth or lanthanide cation) that stabilizes the G-quartet-based assemblies through dipole–ion interactions (Figure 1a). However, even in the absence of metal cations suitable lipoGs are able to undergo extensive self-assembly mediated by H-bonding between guanine bases, thus leading to the formation of ribbonlike architectures (e.g., Figure 1b).

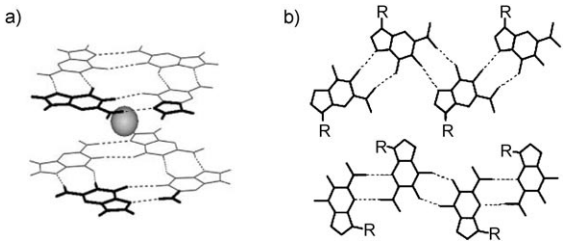
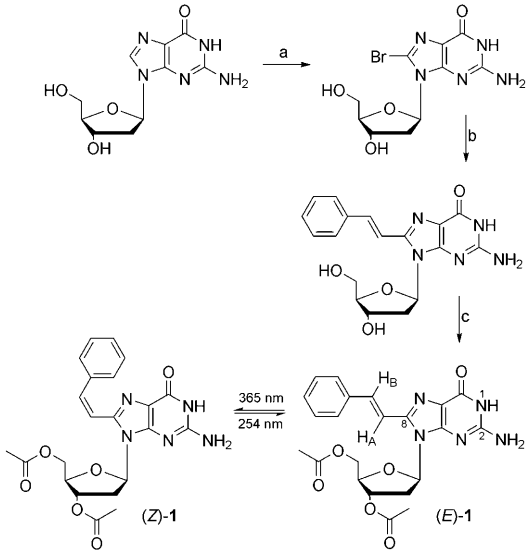


Figure 1. a) D_4-symmetric octamer and b) ribbonlike architectures.

We have already demonstrated the chemically driven switching between different supramolecular motifs for lipoGs both in solution[5] and at the solid/liquid interface.[6] Herein, we report the photocontrolled self-assembly of a modified guanosine nucleobase. Compound (*E*)-**1** (Scheme 1) in the presence of a measured amount of KI self-assembles into a D_4-symmetric complex consisting of two stacked G-quartets. Photoisomerization to the *Z* isomer determines the decomposition of the octameric complex, which is re-formed when



Scheme 1. Synthesis of (*E*)-**1**. a) NBS; b) *trans*-2-phenylvinylboronic acid, Na_2CO_3, TPPTS, $Pd(OAc)_2$; c) acetic anhydride, DMAP. NBS = *N*-bromosuccinimide, TPPTS = tris(3-sulfophenyl)phosphine trisodium salt, DMAP = 4-dimethylaminopyridine.

the molecule is reverted to the *E* isomer by either thermal or photochemical back isomerization.

Following our experience with photoswitchable systems,[2f,7] for the introduction of photochemical control over guanosine self-assembly our first approach was to introduce an azobenzene moiety in the 8-position of the guanine base. We expected that, if the photoactive moiety were placed close to the sites of base recognition, the geometrical changes associated with photoisomerization of the azo chromophore would have resulted in strong effects over guanine self-assembly. Unfortunately, the compounds obtained did not show the desired supramolecular behavior. While this work was in progress, interesting results were reported by Ogasawara and Maeda[8] for oligonucleotides containing a modified guanosine, in which an arylvinyl moiety had been introduced at the 8-position. We therefore turned our attention to the 8-styrylguanine moiety as the photoswitching unit.

Derivative (*E*)-**1** was obtained in three steps from natural guanosine (Scheme 1). Bromination at the 8-position with NBS followed by Suzuki coupling with 2-phenylvinylboronic acid and esterification of the hydroxy functions with acetic anhydride afforded (*E*)-**1** in a 48% overall yield as the pure isomer.

Compound (*E*)-**1** dissolves readily in MeCN. The ^{1}H NMR spectrum of (*E*)-**1** (Figure 2a) in CD_3CN (5 mM) shows sharp signals, which suggests that extensive self-assembly to form ribbonlike aggregates does not occur under these conditions.[9] This finding is supported by

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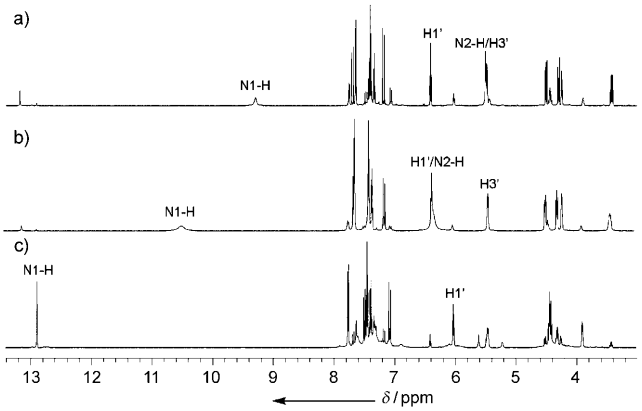

Figure 2. ^{1}H NMR spectra for a) a 5 mM solution of (*E*)-**1** in CD_3CN, b) a 30 mM solution of (*E*)-**1** in CD_3CN, and c) a 5 mM solution of (*E*)-**1**/KI in CD_3CN.

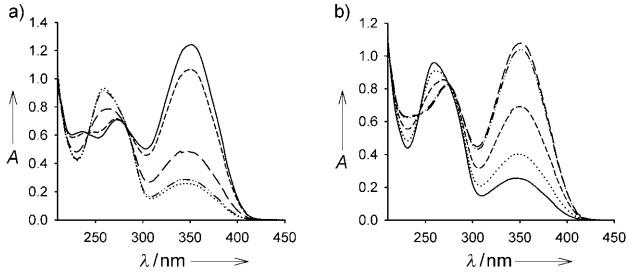

Figure 3. a) Absorption spectra for photoisomerization of (*E*)-**1** (5 mM in MeCN) upon irradiation at 365 nm; initial spectrum (——) and spectra recorded after 2 (-----), 6 (– – –), 22 (–•–•), and 28 min (•••••). b) Absorption spectra for photoisomerization of (*Z*)-**1** upon irradiation at 254 nm; initial spectrum (——) and spectra recorded after 3 (•••••), 7 (-----), 20 (–•–•), and 30 min (– – –).

NOESY spectra, which show no cross peak attributable to intermolecular correlations. Extensive self-assembly takes place upon increasing the concentration above 20 mM: the imino N1-H and amino N2-H protons, which resonate at $\delta =$ 9.30 and 5.50 ppm, respectively, in 5 mM solution, shift downfield to $\delta = 10.47$ and 6.33 ppm in a 30 mM solution (Figure 2b). This indicates progressive involvement of these groups in H-bonding. Accordingly, the NOESY spectrum now clearly shows an intermolecular correlation between the N2-H and H1′ of adjacent guanosine moieties. Interestingly, these spectra (see the Supporting Information) indicate a conformational change around the glycosidic bond as a function of concentration. In diluted samples (below 5 mM), a cross peak correlating H1′ and H_A suggests a *syn* conformation around the glycosidic bond, but at higher concentrations (20 mM and above) this cross peak is no longer apparent. The presence of an intermolecular peak relating the N2-H and H1′ of adjacent guanosine units indicates that a ribbonlike architecture is present and the *anti* conformation is now predominant.

The CD spectrum of (*E*)-**1** in MeCN at 5 mM concentration (see the Supporting Information) shows only a weak (negative) signal. The profile is almost superimposable on the CD spectrum of (*E*)-**1** in MeOH, a competing solvent for hydrogen bonding, thus suggesting the presence of a disaggregate form of (*E*)-**1**. Upon irradiation of this MeCN solution at 365 nm, (*E*)-**1** isomerizes to the *Z* form and a *Z* photostationary state (*Z*-PSS, $Z = 85\%$) is reached in 28 min, as estimated from UV/Vis spectroscopy by spectral subtraction[10] (Figure 3). The process is perfectly reversible: the *Z* isomer reverts back to the *E* form either by irradiation at 254 nm (30 min) or thermally in the dark (150 min).

When a weighed amount of KI (0.125 mol per mol of guanine, that is, 1/8) is added to a MeCN solution of (*E*)-**1**, the ^{1}H NMR and CD spectra change dramatically, as expected when the formation of stacked G-quartets templated by the cation occurs. In particular, in the ^{1}H NMR spectrum (Figure 2c) the imino proton shifts downfield more than $\delta =$ 3 ppm while the H1′ signal moves upfield by $\delta = 0.4$ ppm and the amino signal becomes unobservably broad at room temperature. No doubling of signals appears in the ^{1}H NMR spectrum: this suggests the formation of an octameric species composed of two stacked G-quartets arranged in a D_4 symmetry. NOESY spectra show a correlation between H1′ and H_A for both diluted and concentrated samples, which implies that in the octameric supramolecular complex all of the guanosine units adopt a *syn* conformation around the glycosidic bond, regardless of concentration.

In the CD spectrum (Figure 4a) of the (*E*)-**1**/KI octameric complex, a positive band at 255 nm and a very strong, positive band at 350 nm can be observed. Although no detailed

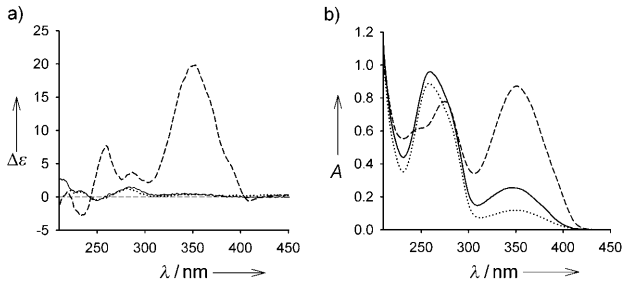

Figure 4. a) CD and b) UV/Vis spectra of a 5 mM solution of (*E*)-**1**/KI (-----), of **1**/KI at the *Z*-PSS (•••••), and of **1** at the *Z*-PSS (——) in MeCN.

information on the electronic transitions are available so far for the 8-styrylguanine chromophore, the spectral changes observed upon addition of potassium ion closely resemble those reported for other unmodified lipophilic guanosines.[3a,b,d] The strong increase of the CD signal associated with the formation of the (*E*)-**1**/K^+ aggregate can analogously be attributed to interchromophore couplings taking place in the stacked complex. When samples of the (*E*)-**1**/K^+ octameric complex are irradiated at 365 nm, photoconversion to the *Z* isomer takes place and the *Z*-PSS is reached in 30 min for a 5 mM sample. The photoisomerization has a dramatic effect on the assembled species. The CD spectrum of the solution of **1**/KI recorded at the *Z*-PSS shows very weak signals: this spectrum is practically superimposable on the CD spectrum of (*Z*)-**1** prior to KI addition and it is similar to that of uncomplexed (*E*)-**1**.

A comparison of the CD and UV spectra for (*E*)-**1** before and after K^+ extraction points to the conclusion that the intensity of the CD signal is mainly attributable to interchromophoric interactions. In particular, the *E* form before K^+ complexation shows a weak CD spectrum, in spite of the strong absorbance in the corresponding UV spectrum. Accordingly, the weak CD signal shown by the system at the *Z*-PPS results from the disaggregation of the stacked supramolecular complex and is not directly related to the lower molar absorptivity of the *Z* isomer. The disappearance of the strong CD bands at 255 and 350 nm is evidence of decomposition of the complex: stacked G-quartets no longer exist in solution.

The observation that (*Z*)-**1** does not form (stacked) G-quartets is most likely because in the *Z* form the phenyl group of the styryl unit is twisted[11] with respect to the G-quartet plane. The consequent steric hindrance could force quartets away from van der Waals contact or it could produce a conformational change around the glycosidic bond, which, in turn, would hamper the stacking. Additionally, in the *Z* form the N7 atom is probably shielded by the styryl unit and is no longer available for H-bonding.

Unfortunately, no NMR studies could be carried out on the *Z*-PSS solution: photoisomerization with standard Hg lamps of samples large enough to be suitable for NMR analysis produced substantial amounts of photocycloaddition products, in the time required to attain the *Z*-PSS under these conditions (see the Supporting Information). Hence, direct detailed information on the type and extent of self-assembly undergone by **1** when in the *Z* form in the presence of K^+ could not be obtained. Although the disappearance of the stacked octameric structure is evident from the CD spectrum, the organization of (*Z*)-**1** into other self-assembled species cannot be ruled out.

As stated above, the *Z* form can be converted back to the *E* form either photochemically, by irradiation at 254 nm, or thermally. Retroisomerization to the *E* isomer determines, at the supramolecular level, the re-creation of the octameric complex: the CD spectrum of the solution at this point perfectly overlaps the starting $[(E)\text{-}\mathbf{1}]_8K^+$ trace.

Thus, the G-quartet-based complex can be cyclically assembled and disassembled by light. As shown in Figure 5, the process is perfectly reversible: no change in molar absorptivity was observed for both the *E* and *Z* states after five cycles.

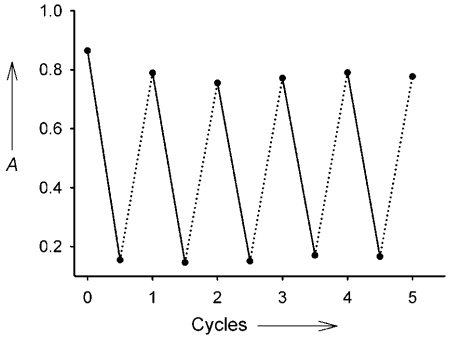

Figure 5. Switching cycles, monitored at 350 nm, between (*E*)-**1**/KI and (*Z*)-**1**/KI by alternate irradiation with light of wavelength 365 nm (for 30 min, ——) and 254 nm (for 28 min, •••••).

In conclusion, by the introduction of a photoactive moiety at C8 in a lipophilic guanosine derivative it is possible to operate photocontrol over the self-assembly of the molecule, such that the existence of G-quartets can be alternately switched on and off (Figure 6).

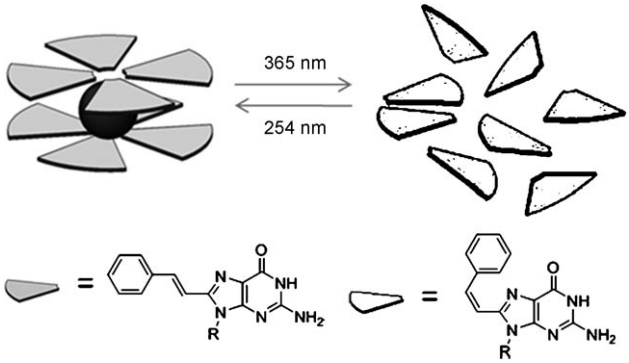

Figure 6. Phototriggering of guanosine self-assembly.

Experimental Section

The photoisomerization of (*E*)-**1** in spectrophotometric-grade acetonitrile was performed at room temperature by irradiating the samples, contained in 0.01 cm quartz cells, with the 150 W xenon lamp of the dichrograph (JASCO J-710). The monochromator of the instrument (slit width 3 mm) was employed to select the UV irradiation wavelengths (365 and 254 nm).

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