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COMMUNICATION

Crystal structures of 8-arylethynyl substituted guanosine derivatives: are hydrogen-bonded ribbons a surprise?†

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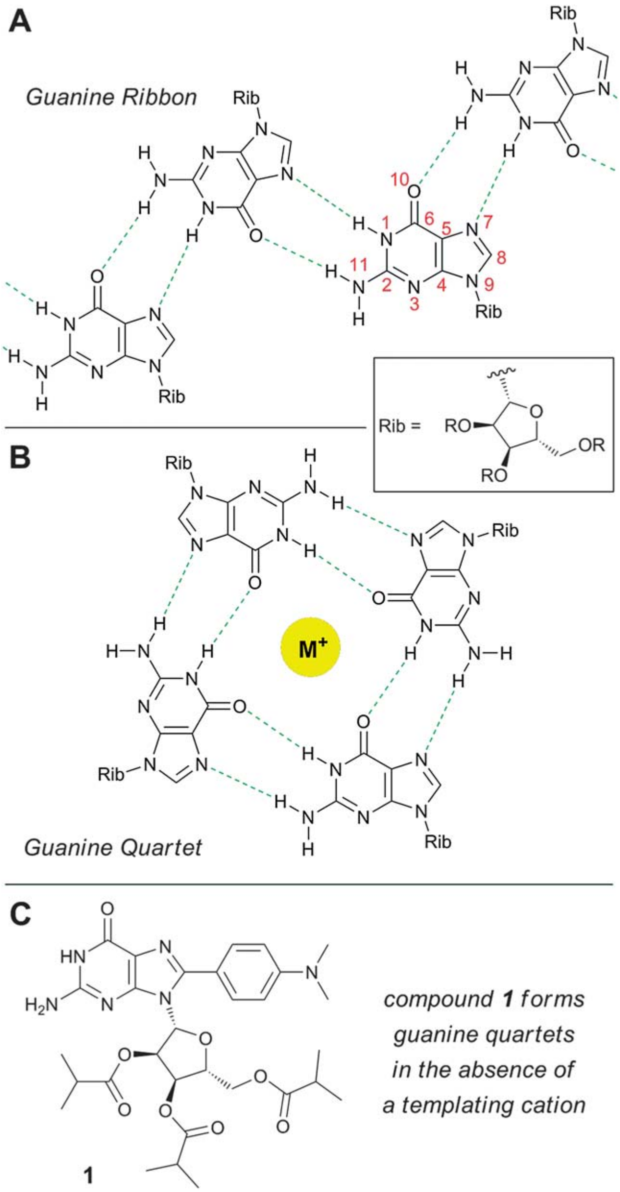
Crystal structures of two 8-arylethynyl substituted guanosines reveal twisted hydrogen-bonded ribbon superstructures, contrasting a previous report of guanine quartet formation from 8-aryl derivatives. The structural switch is attributed to the stabilization of the ribbon through intermolecular [π···π] stacking between the optimally positioned electron-poor arylethynyl substituents and electron-rich guanine nuclei.

Naturally occurring DNA and RNA nucleobases, as well as their synthetic derivatives, are commonly used motifs in supramolecular chemistry[1] on account of their low cost and well-established propensity for intermolecular association through hydrogen bonding and [π···π] stacking. In addition, ribose- and deoxyribose-substituted nucleobases—known respectively as nucleosides and deoxynucleosides—are readily available chiral (and enantiopure) building blocks.

Among the five nucleobases, guanine has the most diverse supramolecular chemistry, as it can self-assemble into discrete dimers and tetramers, or extended ribbon- and helix-shaped structures.[2] The most common mode of guanine self-assembly is an infinite *guanine ribbon*, stabilized by pairs of [C6–O10···H–N11] and [N7···H–N1] hydrogen bonds (Scheme 1A). Alternatively, discrete *guanine quartets*[3] (Scheme 1B) can be formed when four guanine nuclei organize into a cyclic tetramer through four [C6–O10···H–N1] and four [N7···H–N11] hydrogen bonds. Guanine quartets' symmetry, convergent geometry, and ability to complex cations make it a versatile and often used component of functional supramolecular assemblies,[2] including ion transporters,[4] gelators,[5] liquid crystals,[6] drug-delivery vehicles,[7] and DNA-based molecular machines.[8]

What determines whether a given guanine derivative will assemble into a ribbon or a quartet superstructure? Traditionally, guanine quartets were favoured only in the presence of a templating metal cation (*e.g.* K^+) that would be pseudo-chelated by the four carbonyl oxygens of the quartet structure. However, in a seminal 2000 report, Sessler and coworkers[9] challenged this view by demonstrating that compound **1** (Scheme 1C) forms a quartet superstructure without



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Scheme 1 Guanine derivatives can assemble into infinite guanine ribbons (A) or discrete guanine quartets (B). The latter superstructure is typically templated by a metal cation; compound **1** (C), however, forms guanine quartet superstructures without a templating cation.

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† Electronic supplementary information (ESI) available: Synthetic procedures and spectral characterization for all new compounds, and CIFs for **3** and **4**. CCDC reference numbers 806420 and 806421. See DOI: 10.1039/c1ce05618b

metal cation assistance. The authors postulated that steric effects were responsible for the switch. The presence of a (4-dimethylamino) phenyl substituent in the 8-position of the guanine ring system distorted the ribose substituent into an unprecedented *syn*-orientation with respect to the guanine (torsion angle of 42.5°),[10] apparently forcing the formation of the quartet.

In this communication, we present the crystal structures of two 8-alkynyl substituted guanine derivatives **3** and **4** (Scheme 2) which organize into highly twisted hydrogen bonded ribbons, despite the presence of a substituent in the 8-position. We explain this return to ribbon superstructures as a consequence of [$\pi\cdots\pi$] interactions between the electron-poor arylethynyl substituents and electron-rich guanine nuclei, which were enabled by the optimal match between the dimensions of **3**/**4** and the pitch of the guanine ribbon.

Within the guanine ring system, carbon C8 represents the only position that can be substituted without disturbing any of the hydrogen-bonding functionalities; sp^2-character of this carbon makes it amenable to transition metal-catalyzed carbon–carbon bond forming reactions. Much recent interest has been devoted to the study of 8-alkynyl substituted guanine derivatives; the electronic properties and rigid geometry of the C≡C triple bond in these compounds make them appealing precursors to fluorescent monitors of DNA conformations,[11] hydrogen-bonded porous materials,[12] organic nanoparticles,[13] and novel supramolecular ensembles.[14] However, little is known about the solid-state organization of this class of modified guanines—a May 2011 search of Cambridge Structural Database (CSD) revealed no reports of guanine derivatives with an alkyne subunit.

Compounds **3** and **4** were synthesized (Scheme 2) by a Sonogashira coupling[15] of 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine (**2**)[16] with 4-ethynylbenzonitrile and 4-ethynylpyridine, respectively. Single crystals of **3** and **4** were formed by layering their $CHCl_3$ solutions (8 mg mL^{-1} for **3**; 4 mg mL^{-1} for **4**) with pentane (**3**) or hexane (**4**). Compounds **3** and **4** crystallize in $P2_12_12_1$ space group, and are almost isostructural. Each compound crystallizes with two disordered molecules of $CHCl_3$ per molecule of guanine derivative.‡

The crystal structure of compound **3** (Fig. 1A) is characterized by the *syn*-conformation of the ribose substituent relative to the guanine nucleus, with a 10.5° torsional angle between the guanine and ribose moieties.[10] The cyano-substituted phenyl ring is disordered over two closely related orientations (only one is shown in Fig. 1A), and the triple bond is slightly bent, with C≡C–C angles ranging between 173.8° and 179.5° (across both orientations). Aryl and guanine moieties are essentially coplanar—interplanar angle is 7.0°. The supramolecular structure of **3** (Fig. 1B) reveals infinite guanine ribbons, wherein each guanine nucleus acts as a hydrogen bond[17] donor in two interactions, and as an acceptor in another two (see caption to Fig. 1 for distances and angles). Hydrogen-bonded guanine ribbons in the superstructure of **3** are twisted, as illustrated in the side-view in Fig. 1C. The angle defined by the planes of adjacent hydrogen-bonded guanine rings is 37.6°, representing the most highly twisted guanine ribbon reported to date.[18] Molecules of **3** reside in two alternating sets of parallel planes and the distance between two adjacent planes in each set is 3.39 Å. This distance is consistent with

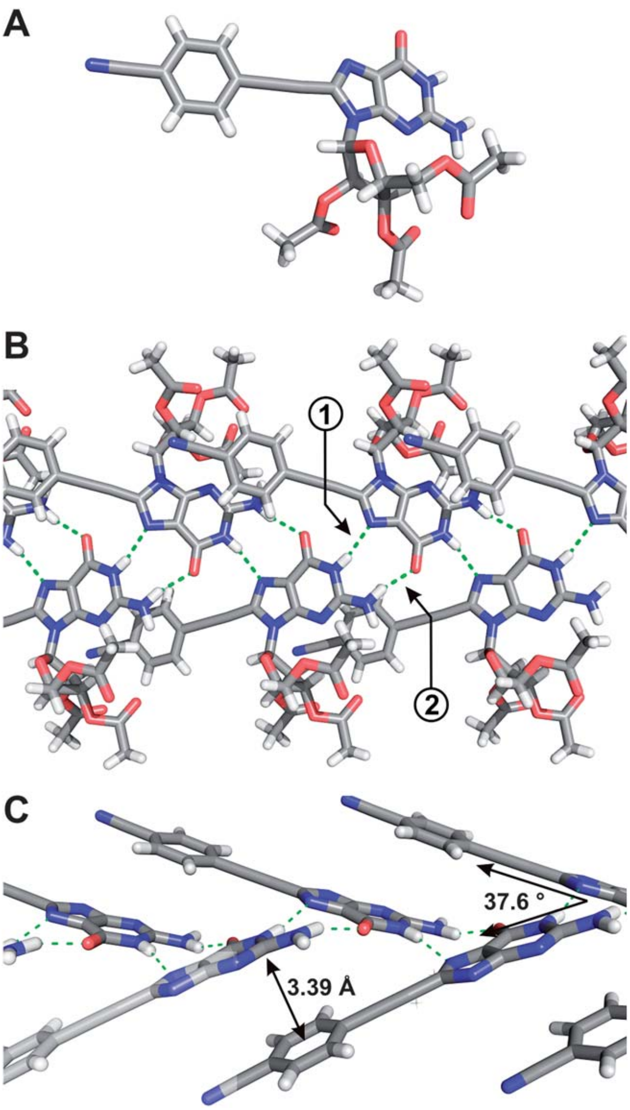
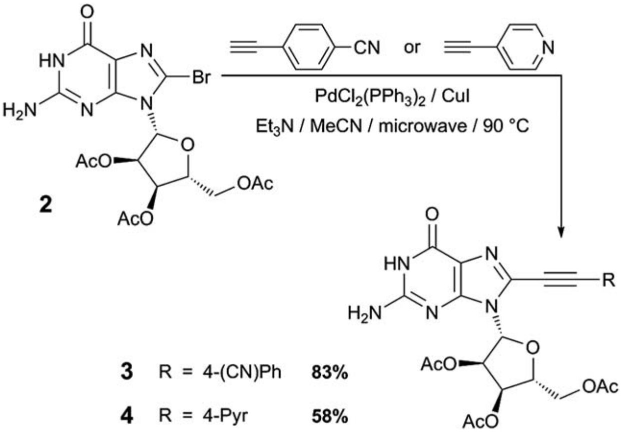


Fig. 1 (A) Crystal structure of **3**. (B) Top view of a twisted hydrogen-bonded guanine ribbon within the superstructure of **3**. Hydrogen bonds are highlighted in green. Contact 1: N···H 2.09 Å, N···N 2.95 Å, N–H···N 167.6°. Contact 2: O···H 1.98 Å, O···N 2.92 Å, N–H···O 161.1°, C=O···H 128.9°. (C) Side view of a twisted guanine ribbon (ribose substituents removed for clarity) highlights the 37.6° angle between the planes of adjacent guanine nuclei, and a 3.39 Å distance between parallel planes, consistent with [$\pi\cdots\pi$] stacking. Disordered solvent ($CHCl_3$) molecules are omitted. C—gray, H—white, N—blue, and O—red.



Scheme 2 Synthesis of alkynylated guanosine derivatives **3** and **4**.

a [π···π] slipped–stacked interaction between the electron-poor 4-cyanophenyl ring and the electron-rich guanine nucleus.[19]

Pyridine derivative **4** is virtually isostructural with **3** (Fig. 2). The molecular structure shows disorder only in the solvent molecules. The triple bond in **4** is slightly bent (C≡C–C angles are 174.7° and 178.7°), pyridine and guanine moieties are at a low 4.0° angle relative to each other, and guanine and ribose are *syn* to each other (torsional angle 7.2°).[10] Just like in the case of **3**, compound **4** organizes into infinite guanine ribbons, stabilized by [N1–H···N7] (2.10 Å) and [N11–H···O10–C6] (2.09 Å) hydrogen bonds. Analogous to **3**, these ribbons are twisted, with adjacent guanine planes defining an angle of 36.3°, and parallel (every other) planes positioned at a distance of 3.23 Å.

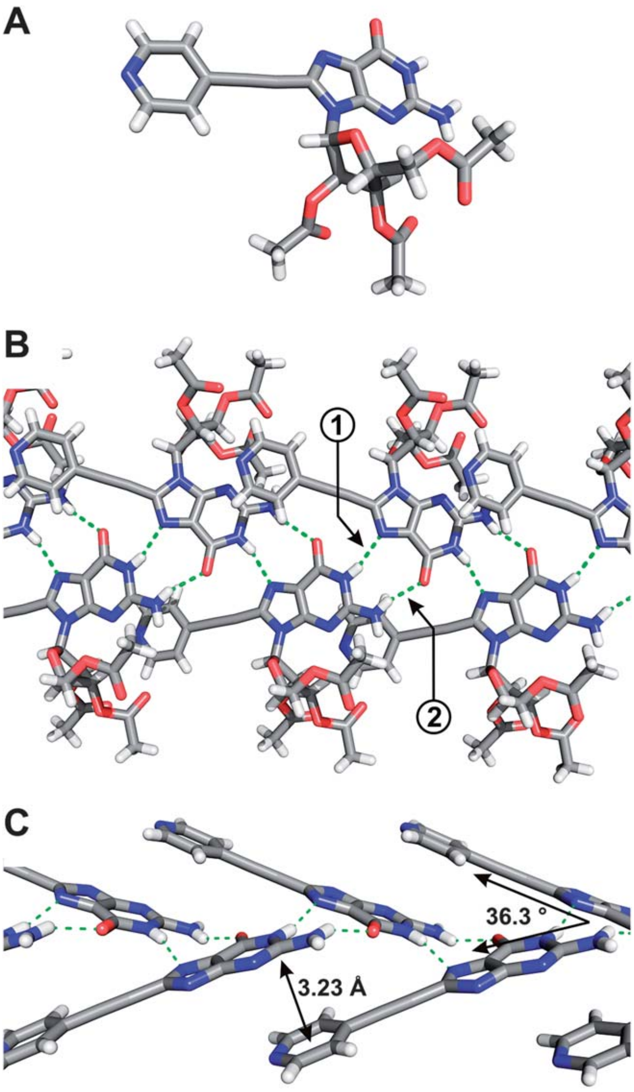


Fig. 2 (A) Crystal structure of **4**. (B) Top view of a twisted hydrogen-bonded guanine ribbon within the superstructure of **4**. Hydrogen bonds are highlighted in green. Contact 1: N···H 2.10 Å, N···N 2.95 Å, N–H···N 164.3°. Contact 2: O···H 2.09 Å, O···N 2.89 Å, N–H···O 153.5°, C=O···H 130.2°. (C) Side view of a twisted guanine ribbon (ribose substituents removed for clarity) highlights the 36.3° angle between the planes of adjacent guanine nuclei, and a 3.23 Å distance between parallel planes, consistent with [π···π] stacking. Disordered solvent ($CHCl_3$) molecules are omitted. C—gray, H—white, N—blue, and O—red.

Given the structural similarity between Sessler's compound **1** and our derivatives **3** and **4**, the difference in their supramolecular organization is unexpected. Since all three systems are characterized by complex substituents in the 8-position and the *syn*-relationship between the ribose and guanine moieties, some more subtle structural variations must be responsible for the switch to ribbon structures in **3** and **4**.[20] We propose that the combination of geometric and electronic factors stabilizes the twisted ribbon superstructure relative to the guanine quartet. Fig. 1 and 2 suggest efficient [π···π] stacking between the alternating guanine nuclei and electron-poor arylethynyl substituents. This is a reasonable proposition for **3** and **4**, since their electron-poor cyanophenyl and pyridyl groups should be electronically complementary to the electron-rich guanine; in **1**, the electronics would be mismatched, since (4-dimethylamino)phenyl substituent would be electron-rich as well. In addition, geometric factors play a role: the ~4 Å long –C≡C– unit in **3** and **4** projects their pendant substituents into an optimal position to stack with the guanine nucleus two sites away in the emerging ribbon superstructure. The shorter linker length in **1** would not have allowed such a match. Finally, the steric bulk of the acyl group on the ribose substituents—acetyl (**3**/**4**) *vs.* isobutyryl (**1**)—might be contributing to the observed absence of [π···π] stacking in **1**, as its (4-dimethylamino)phenyl group effectively gets buried amongst the large isobutyryl groups from the neighboring molecules.[21]

In summary, we have synthesized two new arylethynyl-substituted guanosine derivatives, whose solid-state structures reveal hydrogen-bonded ribbon superstructures despite the presence of a substituent in the 8-position. These results suggest that the balance between guanine ribbon and quartet superstructures is more subtle than previously thought, with both steric and electronic factors playing a role. Our future work in this area is aimed at synthesizing and crystallizing a series of functionalized guanosine derivatives with minimal structural differences that would help us dissect the steric and electronic effects guiding their self-assembly. Results of these studies will be reported in due course.

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Notes and references

‡ Crystal data for **3**: $C_{27}H_{24}Cl_6N_6O_8$, $M_r = 773.22$, 0.45 × 0.30 × 0.08 mm, orthorhombic, $P2_12_12_1$, $a = 9.726(8)$ Å, $b = 10.525(2)$ Å, $c = 34.007(2)$ Å, $V = 3481.5(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.475$ g cm^{-3}, $\mu = 0.548$ mm^{-1}, $2\theta_{max} = 47.08°$, $T = 223(2)$ K, 15 676 reflections collected, 5190 reflections independent [$R_{int} = 0.062$], 389 parameters, $R_1 = 0.059$, w$R_2 = 0.169$ for reflections with $I > 2\sigma(I)$, and $R_1 = 0.096$, w$R_2 = 0.206$ for all data, GOF = 1.038, max/min residual electron density +0.61/−0.33 e$^-$ Å^{-3}. Crystal data for **4**: $C_{25}H_{24}Cl_6N_6O_8$, $M_r = 749.20$, 0.45 × 0.20 × 0.05 mm, orthorhombic, $P2_12_12_1$, $a = 9.754(1)$ Å, $b = 10.353(1)$ Å, $c = 31.859(3)$ Å, $V = 3217.4(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.547$ g cm^{-3}, $\mu = 0.590$ mm^{-1}, $2\theta_{max} = 47.28°$, $T = 223(2)$ K, 13 581 reflections collected, 4782 reflections independent [$R_{int} = 0.079$], 415 parameters, $R_1 = 0.058$, w$R_2 = 0.124$ for reflections with $I > 2\sigma(I)$, and $R_1 = 0.120$, w$R_2 = 0.169$ for all data, GOF = 1.218, max/min residual electron density +0.44/−0.41 e$^-$ Å^{-3}.

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20 CSD reports ten crystal structures of guanine derivatives with a non-hydrogen substituent in the 8-position (not counting compounds **3** and **4**). Virtually all of these structures feature a *syn*-relationship between the guanine nucleus and the ribose substituent, with torsional angles varying between 2.7 and 53.2°. Despite the structural similarity, this family of crystal structures shows no general pattern of guanine–guanine hydrogen bonding. Nine of the ten reports are structures crystallized from H_2O as the solvent, which significantly disturbs guanine–guanine hydrogen bonding. Structure codes: BEHLIJ, BGUAOS10, BRGUOS, COXNEI, DEMXEY, FUYKEP, IGUANM, MOXFIO, TONBEE, and WISROF.

21 Other, even more subtle, effects cannot be fully excluded. These could include: (a) significantly lower guanine–ribose torsional angles in **3** and **4**, relative to **1** (*i.e.* **3** and **4** are "more *syn*" than **1**); (b) solvent effects (disordered $CHCl_3$ molecules established short contacts with guanine nuclei), or (c) weak [C–H···X] hydrogen bonds established between α-hydrogens on cyanophenyl and pyridyl rings and carbonyl oxygens within ribose acetyl groups (see: G. R. Desiraju and T. Steiner, *The Weak Hydrogen Bond In Structural Chemistry and Biology*, Oxford University Press, Oxford, 1999). We believe that these effects are too small in magnitude to lead to such a pronounced shift in the hydrogen bonding patterns.