

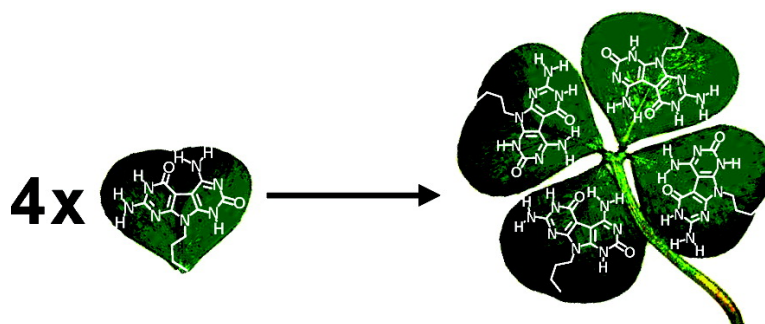
Communication

**G^AC Quartet # A DNA-Inspired Janus-GC Heterocycle:
Synthesis, Structural Analysis, and Self-Organization**

Ali Asadi, Brian O. Patrick, and David M. Perrin

J. Am. Chem. Soc., **2008**, 130 (39), 12860-12861 • DOI: 10.1021/ja8047128 • Publication Date (Web): 04 September 2008

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G^ΔC Quartet — A DNA-Inspired Janus-GC Heterocycle: Synthesis, Structural Analysis, and Self-Organization

Ali Asadi, Brian O. Patrick, and David M. Perrin*

Chemistry Department, University of British Columbia, 2036 Main Mall, Vancouver, B.C., V6T-1Z1, Canada

Received June 19, 2008; E-mail: dperrin@chem.ubc.ca

Hydrogen bonding is largely responsible for the characteristic features of life and plays an essential role in storage, replication, and transcription of genetic information. In addition, H-bonding has been widely used to enable the self-organization of properly encoded, one or two-component self-complementary molecules into a series of supramolecular architectures including linear structures, ribbons, crinkled tapes, cyclic rosettes, or three-dimensional arrays.^{1–3} In G-quartets the tetrameric unit is formed by four guanine nucleotides and enhanced by various cations.^{4,5} Similarly, folic acid and pterin, which resemble guanine, form tetramers closely related to G-quartets.^{6–9} A wide variety of hexameric rosettes have been obtained from two-component self-complementary H-bonding motifs (e.g., cyanuric acid and melamine).^{10–12} Nevertheless, the formation of the cyclic arrays in most of the aforementioned examples depends on additional factors such as metal ion (K⁺, Sr²⁺) binding, peripheral crowding, or covalent preorganization. There are far fewer examples of using one-component self-complementary motifs (i.e., Janus type molecules^{13–15} and Tectons^{16–18}), in which proper hydrogen bonding itself is sufficient to unambiguously govern the structural outcome of the self-organization. Several studies have exploited the strong H-bonding interaction of guanine and cytosine to create self-complementary heterocycles that condense into trimeric and hexameric rosettes architectures.^{19–31} In particular, Mascali and Fenniri have pioneered the synthesis of G^ΔC heterocycles that form well-ordered hexameric rosettes representing prototypical nanotubes. Inspired by their reports, we now report the synthesis, structural analysis, and self-organization of a tetrameric Janus type DNA base hybrid: G^ΔC **1** (Figure 1). As with both their G^ΔC bases and ours, and unlike guanine/pterin systems, no metal cation induces association since the lone pair of the oxygen is sandwiched between two H-bonds leaving no site for metal chelation.

This self-complementary G^ΔC heterocycle orients the H-bonding faces of both guanine (ADD) and cytosine (DAA) on a 90° angle dictated by the central pyrrol bond angles that specify a tetrameric rosette containing 12 hydrogen bonds. This is the first case of a self-complementary G^ΔC heterocycle where hydrogen bonding induces a tetrameric rosette. As G^ΔC **1** was heretofore unknown, its synthesis is briefly described in Scheme 1.

Commercially available **2** (2-amino-6-chloro-4-hydroxypyrimidine) was refluxed in aqueous *n*-butyl amine to give the diaminopyrimidine **3** in 90% yield. Condensation of **3** with 2-chloro-3-oxo-propionitrile^{25,26} in aqueous solution provided **4**: butylated 7-cyano-7-deazaguanine, which was protected in refluxing neat isobutyric anhydride to obtain **5** in 90% yield. After testing several different nitration conditions, treatment with ammonium nitrate and trifluoroacetic anhydride in CH₂Cl₂ at room temperature afforded **6** in 93% yield.²⁷ Catalytic hydrogenation of the nitro group using Pd/C in methanol gave **7** in near quantitative yield. A single crystal of deprotected **7** was grown in DMF and diffracted to verify the regiochemical orientation of the –NH₂ and –CN groups (Support-

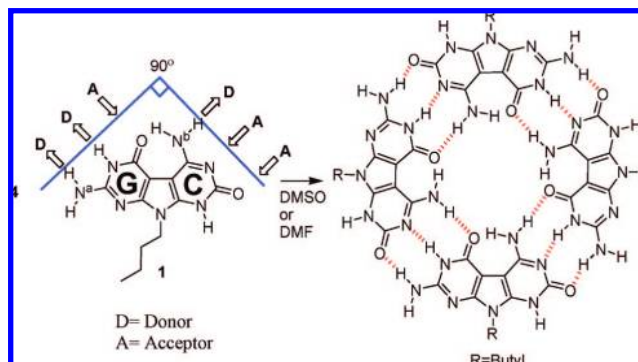
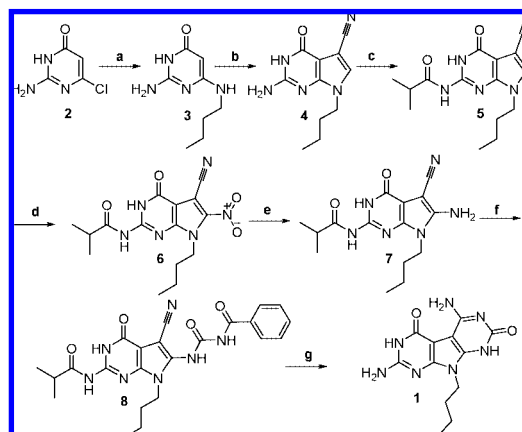


Figure 1. G^ΔC **1** and the corresponding tetrameric rosette structure.

Scheme 1. Synthesis of G^ΔC **1**^a



^a (a) *n*-Butyl amine, water, reflux, 5 h, 90%; (b) 2-chloro-3-oxo-propionitrile, sodium acetate, water, 80°C, 75%; (c) isobutyric anhydride, reflux, 2 h, 90%; (d) ammonium nitrate, TFAA, CH₂Cl₂, rt, 8 h, 93%; (e) H₂ 1 atm, 10%-Pd/C, MeOH, rt, 2 h, 97%; (f) benzoyl isocyanate, pyridine, CH₂Cl₂, rt, 1 h, 93%; (g) sodium hydride, ethanol, toluene, reflux, 15 h, 89%.

ing Information, SI). Ultimately, treatment of **7** with benzoyl isocyanate^{28,29} in the presence of pyridine/CH₂Cl₂ provided the desired benzoyl urea **8** in excellent yields. Treatment of **8** with NaH in refluxing toluene/ethanol cleanly removed the benzoyl and isobutyryl groups and concomitantly induced annulation of the cytosine face to complete the synthesis of G^ΔC **1** in excellent yield. A single crystal of **1** was obtained as a formate salt by diffusing dioxane into a solution of formic acid (99%) (Figure 2).

To characterize properties of self-association, compound **1** was examined by electrospray ionization mass spectrometry (ESI-MS), variable temperature ¹H NMR spectroscopy, and diffusion-ordered spectroscopy (DOSY) (see SI). ESI-MS analysis of **1** showed two major peaks for the monomer and dimer and a peak of lower intensity for the quartet consistent with tetrameric association of

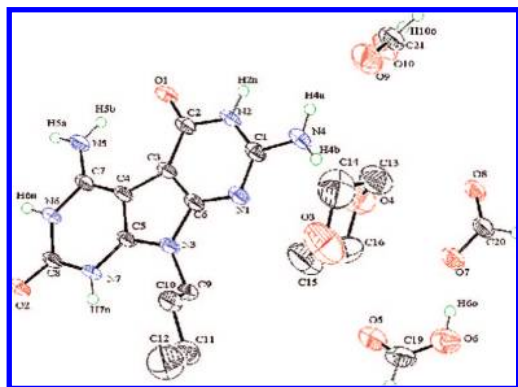


Figure 2. ORTEP view of the X-ray crystal structure of **1** as the formate salt grown in the presence of dioxane.

1. There was no detectable peak for the trimer or for any other higher ordered aggregates.

Williams *et al.*³⁰ used variable-temperature ¹H NMR to show that the two amino groups within a G–C base pair rotate at two different rates. Only at very low temperature is rotation so retarded that the exocyclic –NH₂ protons of a G–C base pair reveal four distinct ¹H-resonances. We performed variable-temperature ¹H NMR from 25 to –70 °C on a solution of **1** in *d*₆-DMSO/CDCl₃ (1–3 mM) to verify H-bonding between the two faces of **1**. At higher temperatures, H₂N^a of the G-face rotates rapidly on the NMR time scale and both protons appear as a single broad coalesced resonance at 6.3 ppm. At –65 °C they resolve as two distinct resonances at 5.75 and 7.3 ppm. In contrast, the amino protons of the H₂N^b of the C-face appear as a very broad, almost undetectable resonance (6.75–7.65 ppm), which at –10 °C rapidly splits into two well-resolved resonances at approximately 6.8 and 7.5 ppm. At –65 °C the NH₂ protons present as four distinct resonances. The observation of new peaks at very low temperature is consistent with a G–C pairing scheme and suggests formation of a quartet rosette in the solution phase.

Self-association of **1** was initially investigated using 2D-NOESY (see SI). Nevertheless to correlate the NOESY data with tetramerization in solution, we opted to investigate self-association and size determination of the quartet ensemble with pulse field-gradient (PFG) NMR spectroscopy.^{31,32} Diffusion measurements of **1** were carried out in a coaxial NMR tube under identical conditions of concentration and temperature (to diminish the effect of convection) in the presence of equimolar concentrations of carbazole, which was chosen as a standard because of its similar geometry to **1**. The results are summarized in Table 1 (see SI for details). The results of diffusion coefficient analysis are in very good agreement with the results obtained from the ESI-MS and validate the presence of a tetrameric rosette in *d*₆-DMSO. Furthermore, this work highlights the utility of DOSY-NMR for characterizing the stoichiometry of noncovalently associated macromolecules.

In summary, the salient points of this work are as follows: The synthesis of a heretofore unknown self-complementary G/C heterocycle has been fully disclosed for the first time. The central pyrrol ring arrays the self-complementary DDA-AAD faces at precisely 90° which programs self-assembly into H-bonded tetrameric structures. These tetrameric structures are inferred from gas-phase data as well as VT and DOSY NMR experiments that provide conclusive evidence of this interaction in solution.

The self-organization of **1** and its potential for formation of functional higher order systems such as organic nanotubes and discotic liquid crystalline mesophases via π -stacking of quartets will be reported in due time. A noteworthy application of **1**, and homopolymers thereof based on DNA and PNA, will be in the sequence specific recognition of GC-rich sequences in RNA and DNA. Such work is currently under investigation.

Acknowledgment. The authors thank Prof. Marco Ciufolini for helpful discussions and Dr. Nick Burlinson and Mr. Mehran Nikan for helpful advice on advanced NMR techniques. A.A. received a Gladys Estella Laird fellowship, and D.M.P. received a Senior Scholar Award of the Michael Smith Foundation for Health Research in B.C. This work was supported by NSERC Operating funds, and equipment was provided by the CFI.

Supporting Information Available: ¹H and ¹³C NMR spectra, DOSY data, and CIF files of the X-ray structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA8047128