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SUPPORTING INFORMATION

A $G_4 \cdot K^+$ Hydrogel that Self-Destructs

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General Experimental: NMR spectra were recorded on Bruker DRX-400, Bruker DRX-500, or Bruker AVIII-600 spectrometers. Chemical shifts are reported in ppm relative to the residual solvent peak. Deuterated solvents were purchased from Cambridge Isotope Labs. Mass spectrometry experiments were performed on a JEOL AccuTOF-CS Spectrometer. CD Spectroscopy was performed on a Jasco J-810 spectopolarimeter. Rehological data was collected with an AR2000 stress-controlled rheometer from TA instruments. Chemicals and solvents were purchased from Acros, Aldrich, Alfa Aesar, Fisher, and Santa Cruz Biotechnology.

General Gel Preparation Procedure: The desired amount of 5′-IG **2** was weighed into a vial, and the appropriate amounts of $KB(OH)_4$ stock solution and water were added. The vial was physically shaken and sonicated for ~1 minute. The mixture was placed in a water bath and heated to the desired temperature (90 °C unless otherwise noted) at a rate of ~5 °C/min. The vial was then removed from the bath and was allowed to cool at room temperature (20 °C). Unless otherwise noted gels were formed at a 5′-IG **2** concentration of 50 mM and a 1:2 ratio of 5′-IG **2**:$KB(OH)_4$. G **1** gels were formed at a 1:0.5 ratio of G **1** to $KB(OH)_4$.[1–3]

2D NMR – HSQC and COSY procedures: 50 mM 5′-IG **2** gels were formed following the general 5′-IG **2** gel procedure. Two samples were made; one in 90% H_2O:10% D_2O and one in D2O. NMR experiments were run at 25 °C (32 scans, 1.5 second delay). Upon examination of the HSQC it was evident there were two 5′ signals. One, corresponding to 5′-IG **2** at low ppm values (yellow box), and a second with two separate H's (green box), which we would assign as 5′-*c*G **3** using the COSY spectrum. Since experiments were performed on gels NMR signals correspond

to the borate esters of 5′-IG **2** and 5′-*c*G **3**. Note that 5′-*c*G **3** is a known compound, and our spectra match literature values with slight differences due to different solvents (d-6 DMSO in the literature) and borate esters.[4]

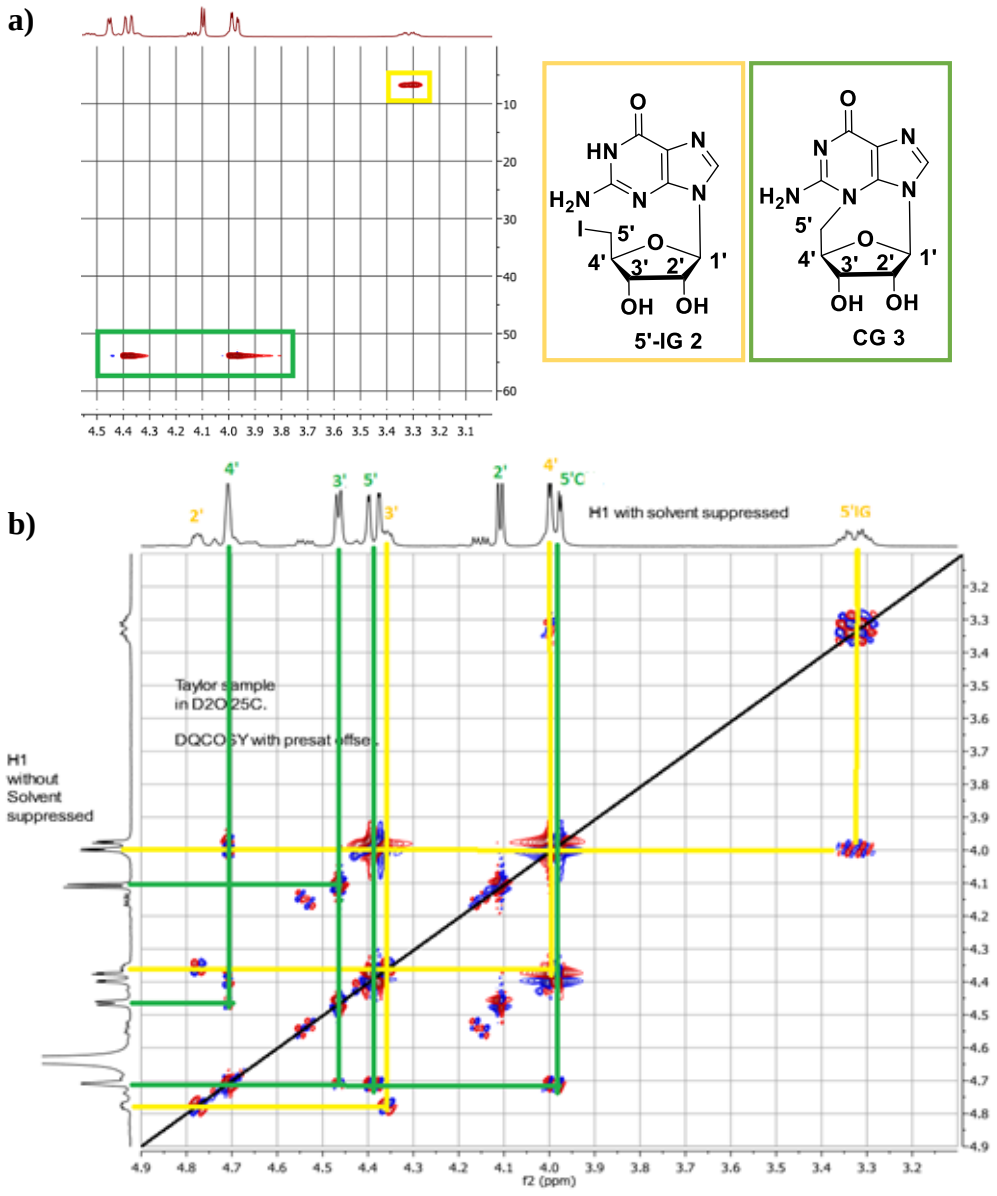

Figure S1: The HSQC spectrum (a) indicates two different species from the 5′-signals (yellow and green boxes). COSY (b) was used to assign the peaks to 5′-IG **2** (yellow labels) and 5′-*c*G **3** (green labels).

Mass Spectrometry Procedure: 50 mM 5′-IG **2** gels were formed following the general 5′-IG **2** gel procedure. The gel was then diluted with water and sonicated until the system was no longer a gel and could be injected into the JEOL AccuTOF-CS Spectrometer.

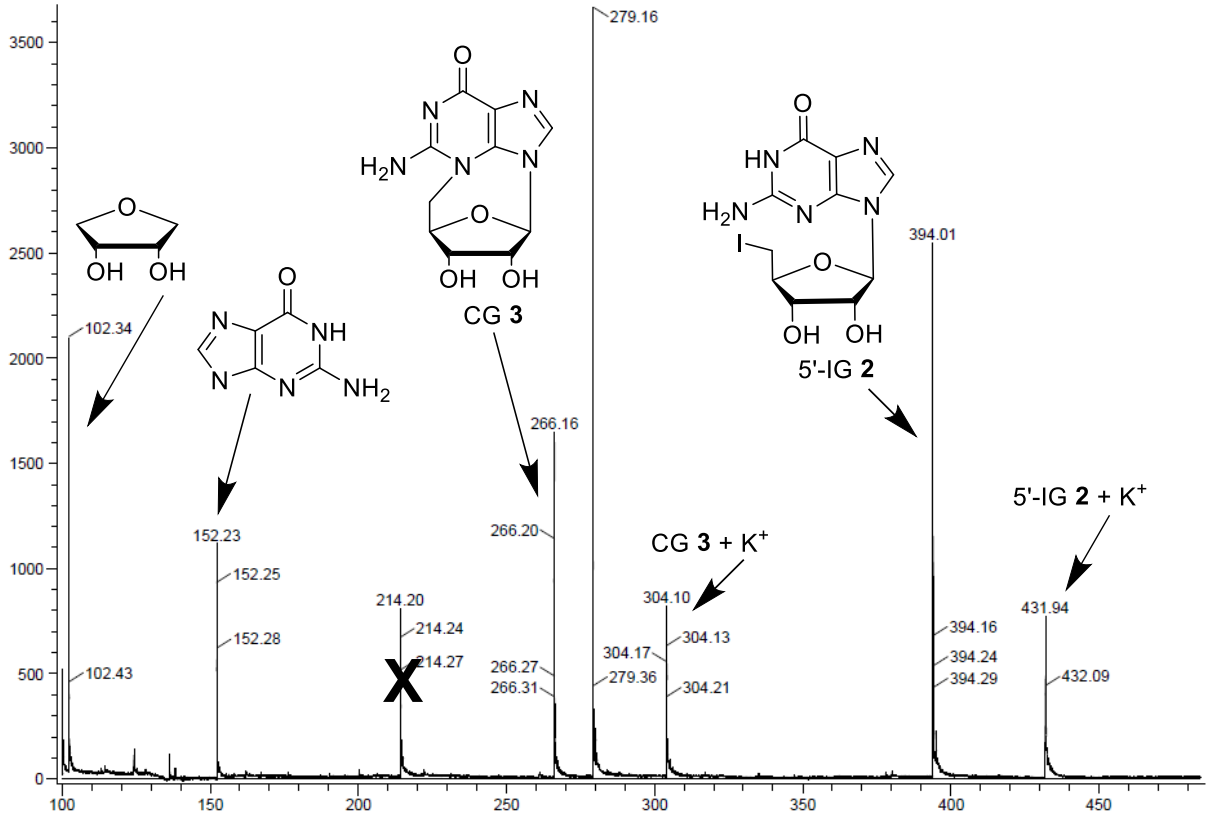

Figure S2: Mass spectra of a 50 mM 5′-IG **2** gel. Peaks are labeled with their corresponding species. The peak at 214 m/z is a contaminant in the mass spectrometer.

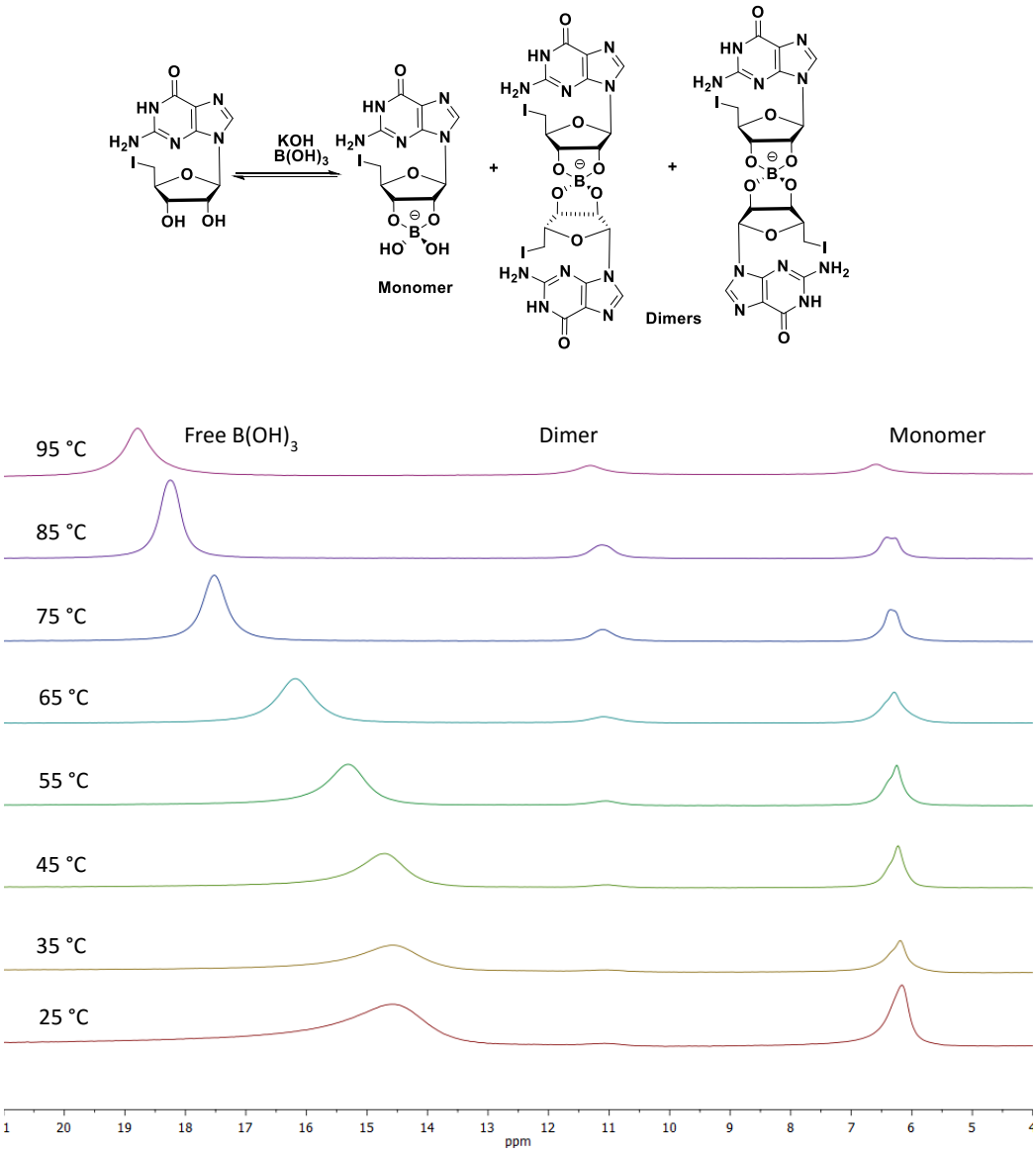

Figure S3: Top: The possible borate ester species present in the 5′-IG **2** gel system. Bottom: Variable temperature ^{11}B NMR spectra; experiment were performed on 50 mM 5′-IG **2** gels. Peaks are assigned based on literature precident.[1]

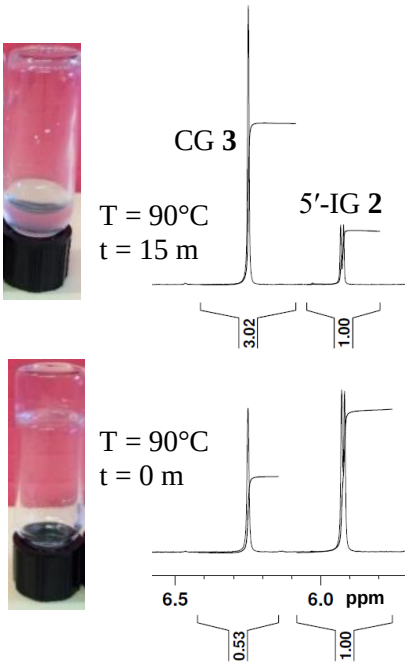

Figure S4: ^{1}H NMR experiments on the dissociated gel systems formed with different heating times show that 5′-IG **2** is the gelator. Spectra show the H1′ region. The gel (bottom) is roughly 65% 5′-IG **2** and 35%5′- *c*G **3**. The viscous solution (top) contains far more 5′-*c*G **3** (75%) than 5′-IG **2** (25%).

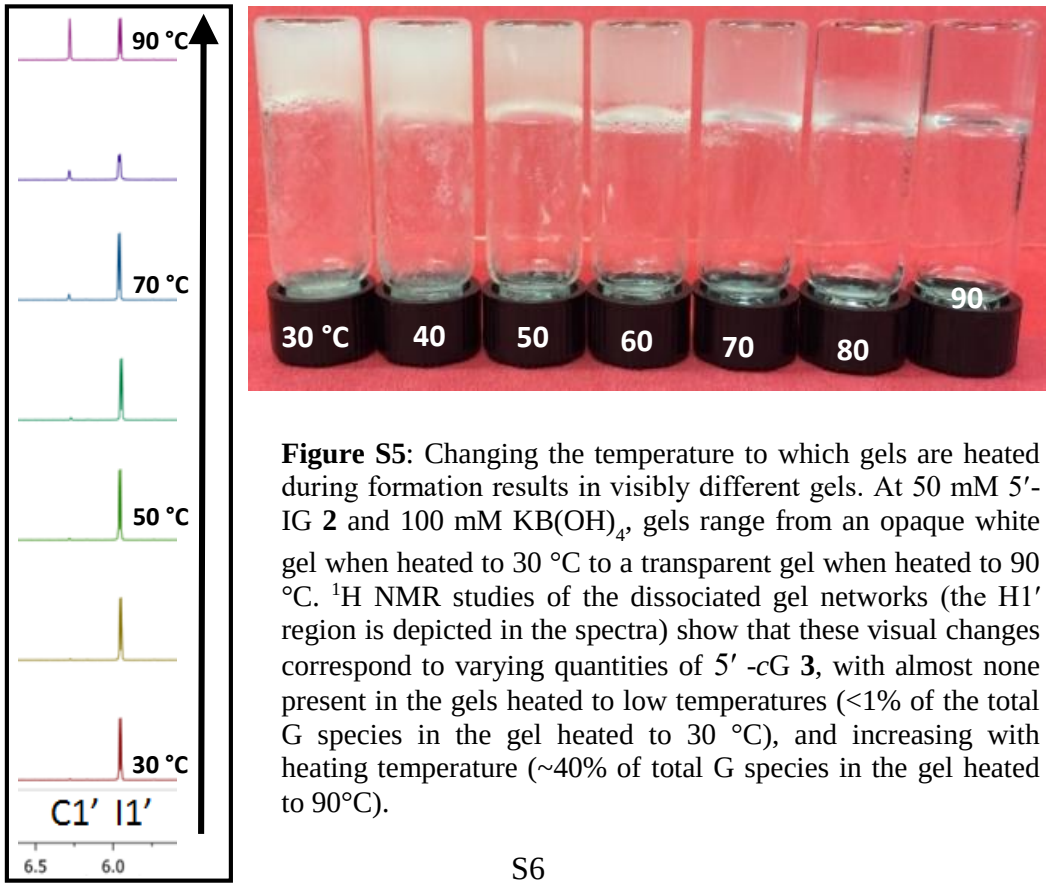

Figure S5: Changing the temperature to which gels are heated during formation results in visibly different gels. At 50 mM 5′-IG **2** and 100 mM $KB(OH)_4$, gels range from an opaque white gel when heated to 30 °C to a transparent gel when heated to 90 °C. ^{1}H NMR studies of the dissociated gel networks (the H1′ region is depicted in the spectra) show that these visual changes correspond to varying quantities of 5′ -*c*G **3**, with almost none present in the gels heated to low temperatures (<1% of the total G species in the gel heated to 30 °C), and increasing with heating temperature (~40% of total G species in the gel heated to 90°C).

Rheology Procedure: 72 mM 5′-IG **2** and G **1** gels were prepared following the general gel procedures. Experiments were performed on an AR2000 stress-controlled rheometer from TA instruments at 20 °C with a 20 mm diameter parallel plate geometry. The gels were allowed to equilibrate on the plate for 10 minutes. Frequency sweeps were performed at 1% strain.

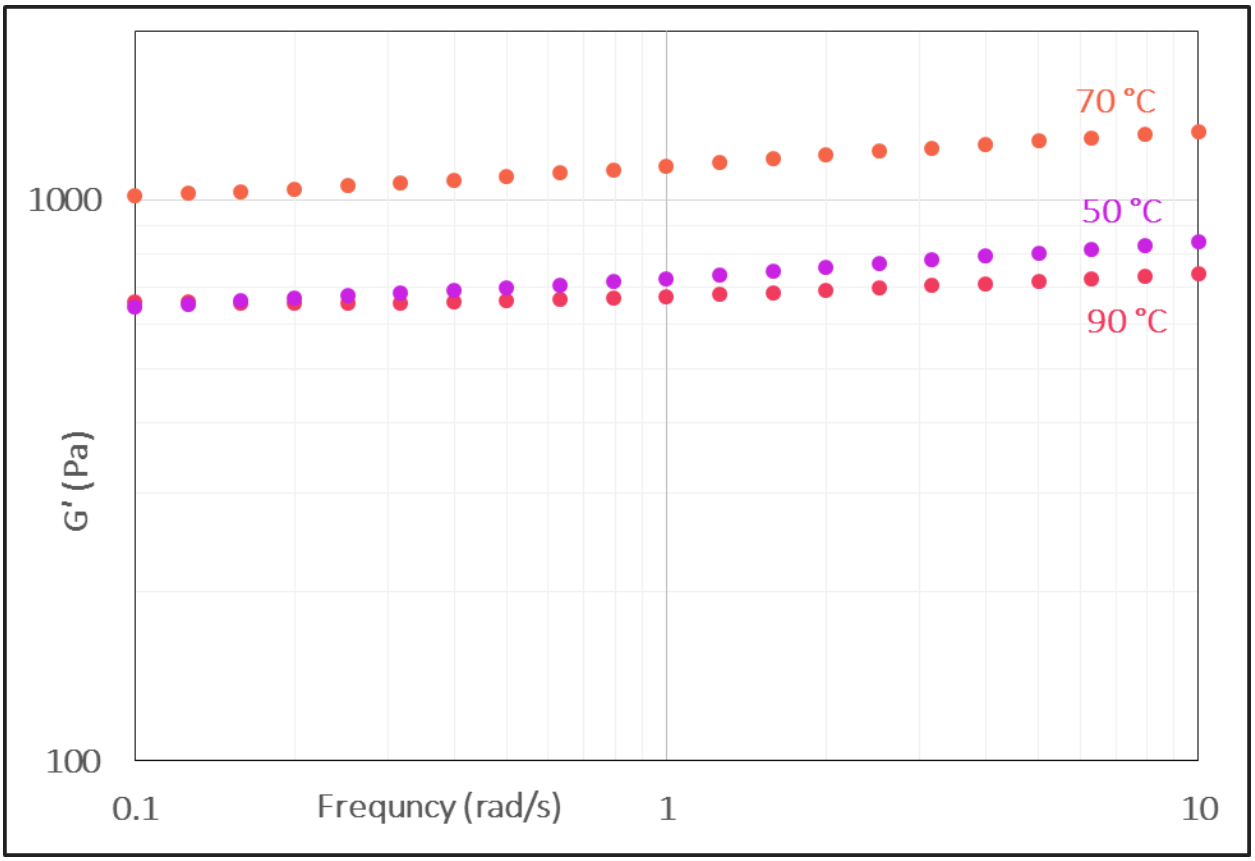

Figure S6: Frequency sweeps of 5′-IG **2** gels formed at different temperatures show the gel formed at 70 °C is much stronger than the gels formed at 50 and 90 °C. The G′ value for the gel formed at 70 °C is ~1000 Pa, whereas the values for the gels formed at 50 and 90 °C are around ~700 Pa.

Circular Dichroism Spectroscopy Procedure: 50 mM 5′-IG **2** or G **1** gels were prepared according to the general gel procedure. The gels were allowed to sit for 1-2 hours before the experiments. Spectra were collected at room temperature in a Hellma 106-QS quartz cell with an optical path length of 0.01 mm. Experiments were performed at 25 °C with a scanning speed of 200 nm/min, response time of 2 sec, and a bandwidth of 1 nm. Each experiment was repeated at least 3 times, and the signals were averaged.

^{1}H NMR – Quantification of cyclization and drug release procedures: 50 mM 5′-IG **2** gels were formed following the general 5′-IG **2** gel procedure in 90% H_2O:10% D_2O. For the drug incorporation experiments the solid drug was added to the vial along with the solid 5′-IG **2** in order to afford a final drug concentration of 5mM. When the vials were removed from the heat 0.5 mL of the gel was pipetted into an NMR tube, with deuterated DMSO inside of a capillary tube sealed with parafilm as an internal standard. The gels were allowed to sit for 1 hour before initial experiments were run. Experiments were run at 25 °C with solvent suppression (32 scans) and repeated on at least 3 gel samples. Room temperature samples were allowed to sit at 20 °C; heated samples were submerged in an oil bath at 37 °C for the time indicated. After the scans were run on the samples left sitting for 72 hours, 10 μL of HCl was added to the NMR tube to completely break up any aggregates and determine the total G-derivative or drug concentration. The integration of the DMSO peak was set to 1.00 and the H1′ peaks of the G-derivatives or drugs were used. Experiments were performed 3 times, and data is reported as the average of the experiments. Error bars represent the standard deviation between the 3 trials. The amount of G-derivative or the amount of drug in solution was determined according to the following equation:

$$\%\, drug\ in\ solution = \frac{[target\ at\ desired\ time]}{[target\ after\ HCl\ addition]}$$

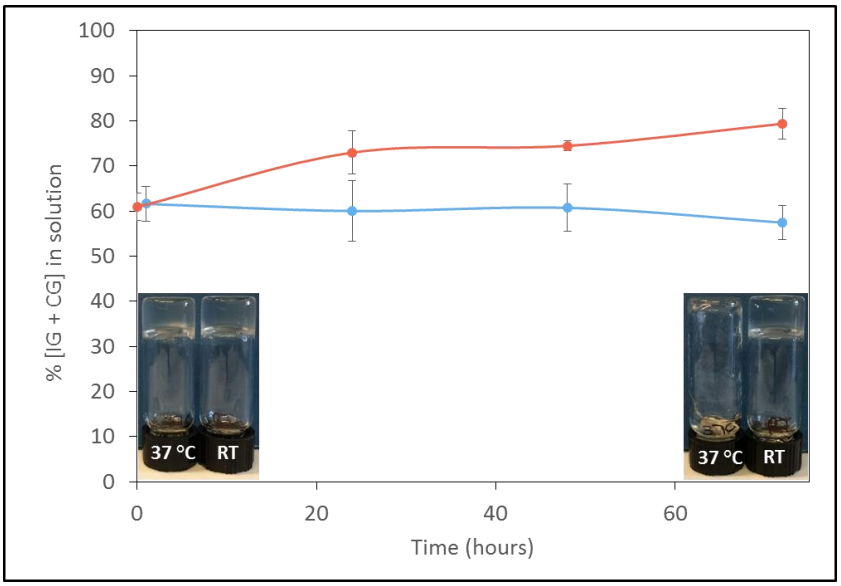

Figure S7: Gels allowed to sit at RT (blue) and 37 °C (orange) were monitored over time. After 72 hours at 37 °C the amount of G species in solution increased and the system was no longer a gel.

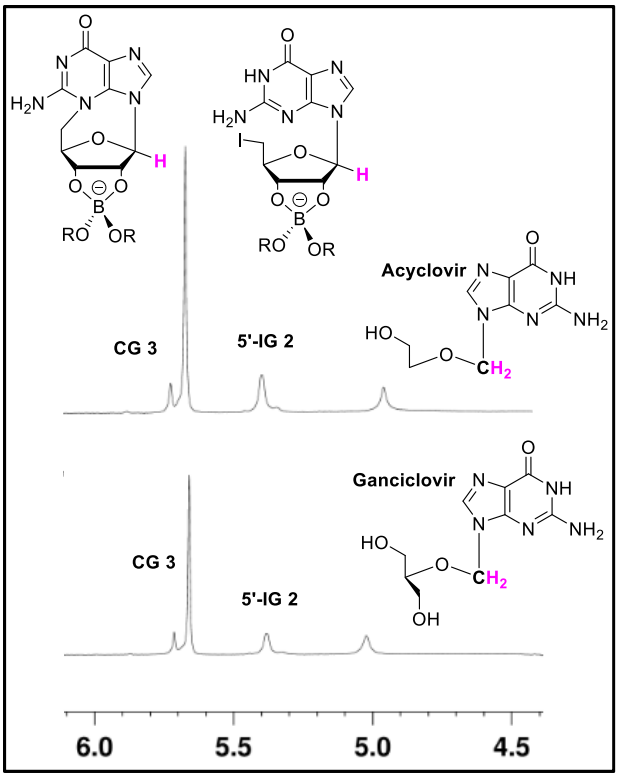

Figure S8: The H1′ (pink on molecules) region of the spectra shows three peaks, one for each species in the sample CG **3**, 5′-IG **2**, and acyclovir (top) or ganciclovir (bottom).

SYNTHESIS

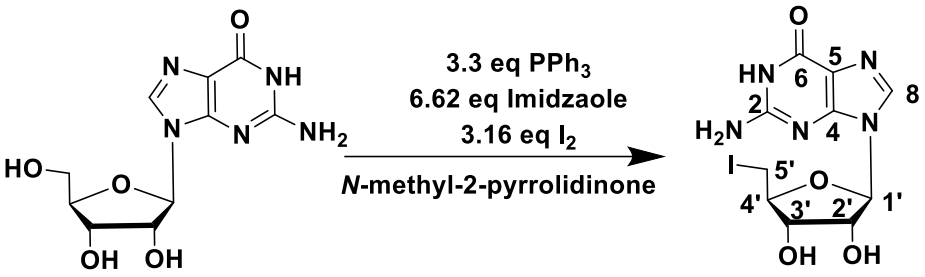

Figure S9: The reaction to synthesize 5'IG-**2** from G **1**.

*5'-deoxy-5'-iodoguanosine (5'-IG **2**):*[5] Guanosine hydrate (2.5 g, 8.33 mmol), triphenylphosphine (7.2 g, 27.5 mmol), and imidazole (3.75 g, 55.2 mmol) were placed in a clean, dry, 250 mL 2-neck round bottom flask with a stir bar and flushed with N_2. N-methyl-2-pyrrolidinone (33.3 mL) was added and the mixture was allowed to stir for 3 minutes. Iodine (6.70 g, 26.3 mmol) was added in 2 batches over the course of 5 minutes. The solution was allowed to stir for 2-3 hours. When ^{1}H NMR of a small aliquot showed complete reaction methylene chloride (333 mL) and water (100 mL) were added. Product was collected via vacuum filtration to afford an off-white powder (up to 2.39 g, 73% yield). ^{1}H NMR (d-6 DMSO) δ: 10.65 (s br, 1H, NH), 7.93 (s, 1H, H8), 6.49 (s br, 2H, NH_2), 5.71 (d, 1H, *J* = 6.4 Hz, H1′), 5.55 (d, 1H, *J* = 6 Hz, OH), 5.39 (d, 1H, *J* = 4.8 Hz, OH), 4.652-4.608 (m, 1H, H2′), 4.079-4.046 (m, 1H, H3′), 3.952-3.912 (m, 1H, H4′), 3.584-3.399 (m, 2H, H5′). ^{13}C NMR (d-6 DMSO) δ: 156.55 (C6), 153.54 (C2), 151.24 (C4), 135.64 (C8), 116.70 (C5), 86.65 (C1′), 83.53 (C4′), 73.02 (C2′), 72.68 (C3′), 7.80 (C5′).

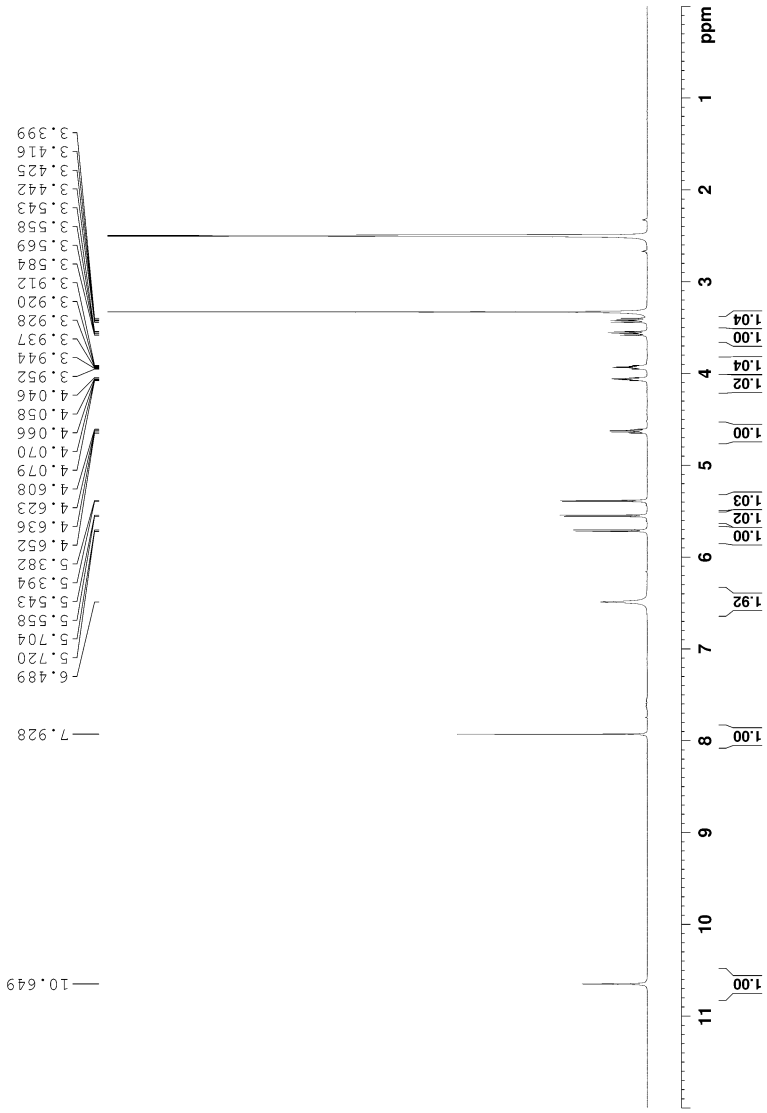

Figure S10: ^{1}H NMR spectrum of synthesized 5'IG-2 in d-6 DMSO.

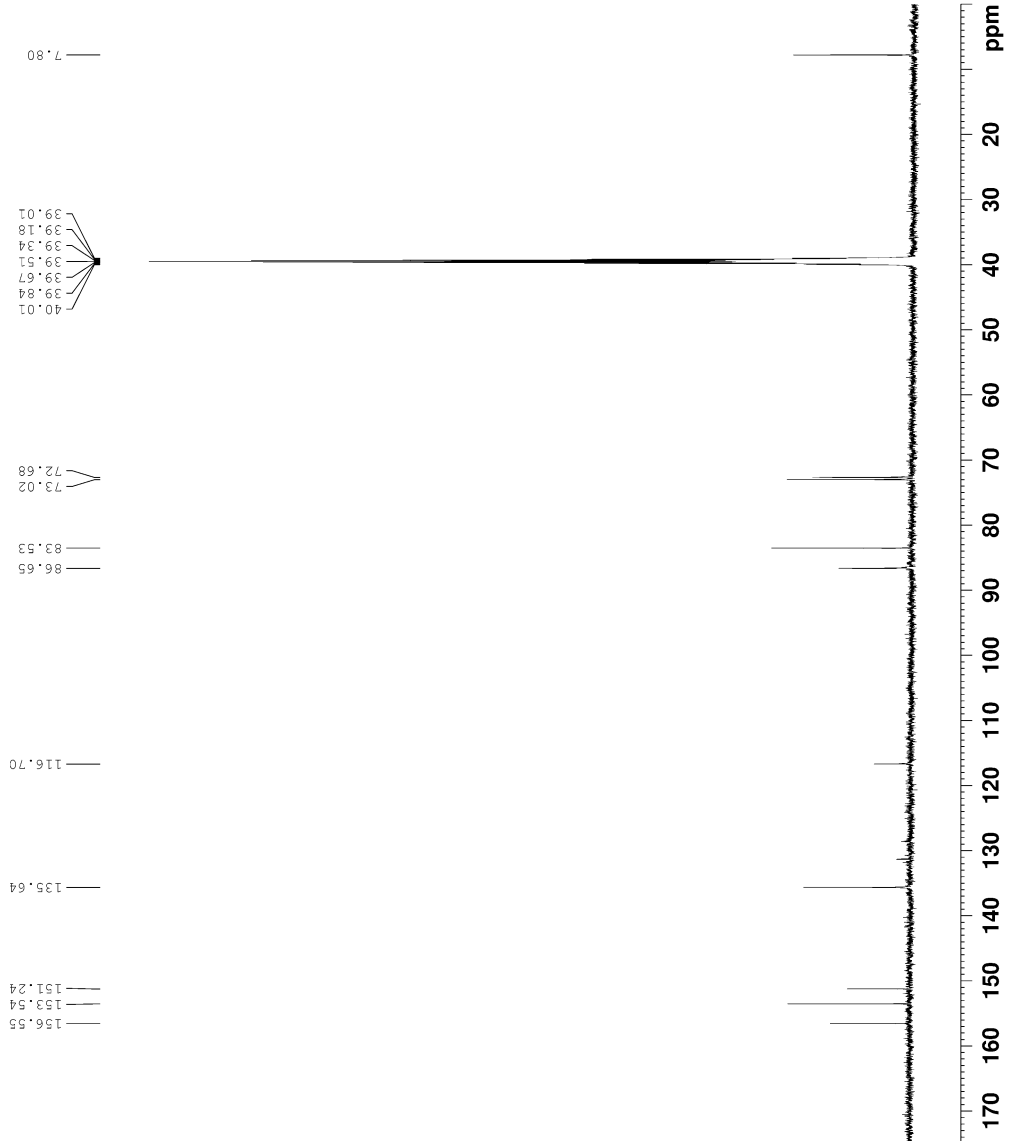

Figure S11: ^{13}C NMR spectrum of synthesized 5'IG-**2** in d-6 DMSO.

References

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