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Songjun Xiao and Jeffery T. Davis*

A $G_4•K^+$ hydrogel made from 5′-hydrazinoguanosine and KCl reacts with α,β-unsaturated carbonyls of different electrophilicities (acrolein, methyl vinyl ketone and methyl acrylate) in water and the gas phase to form cyclic adducts. This aza-Michael addition/cyclization domino reaction by the 5′-hydrazino $G_4•K^+$ hydrogel has promise for environmental remediation of toxic α,β-unsaturated carbonyls from water and the atmosphere.

Supramolecular hydrogels are made from low-molecular-weight compounds and held together by non-covalent bonds.[1] One application of supramolecular hydrogels is environmental remediation of ions, dyes and pollutants.[2] Using an "off-the-shelf" or "easy-to-make" compound to prepare self-assembled gels that can remove contaminants has potential for water purification. DNA hydrogels can bind metal ions and dyes, but the cost of DNA synthesis makes such hydrogels prohibitive for large-scale.[3] One solution is to use hydrogels made from nucleosides or nucleotides.[4] Such materials retain many of DNA's molecular recognition properties while being easier and cheaper to make. We have used hydrogels made from guanosine (G **1**) to absorb dyes and aldehydes from water.[5]

A century after their discovery,[6] G gels are undergoing a resurgence due to their ease of preparation, biocompatibility and applications.[7,8] The basis for most G gels is the G_4-quartet, a macrocycle templated by K^+.[9] The G_4-quartets stack to form entangled nanowires that give a matrix that immobilizes water. As shown in **Fig. 1**, we describe a $G_4•K^+$ hydrogel that contains bisnucleophilic 5′-hydrazines (G **3**) for covalent capture and remediation of α,β-unsaturated carbonyls (α,β-UCs).

Electrophilic α,β-UCs, pervasive due to both natural and industrial processes, pose a threat to our health and environment. Acrolein (AC), methyl vinyl ketone (MVK) and methyl acrylate (MA), all important commodity chemicals, are also cytotoxic. These α,β-UCs with two reactive ends, a Michael acceptor and carbonyl, are potent electrophiles that trap nucleophiles in proteins and nucleic acids, thus damaging living organisms.[10] Although resins containing alkylhydrazines have been used for solid-phase synthesis of hydrazones and scavenging of aromatic aldehydes,[11,12] and resins with the less nucleophilic sulfonylhydrazides have been developed for scavenging AC,[13] there have not been, to our knowledge, reports of soft materials that can react with and absorb α,β-UCs from solution or the atmosphere. One could imagine formulating a gel into thin films that would filter volatile α,β-UCs from the air that we breath or make flexible membranes to remove α,β-UCs from the water that we drink.

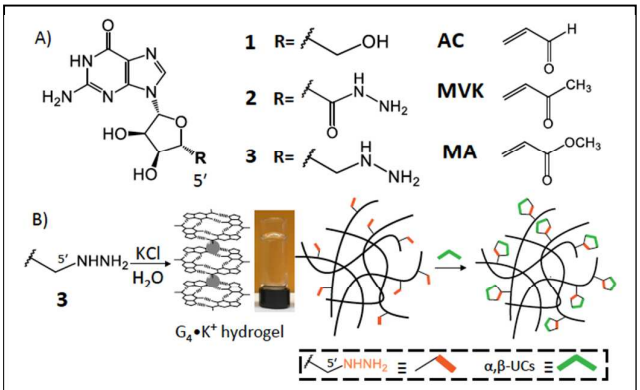

Fig. 1. A) Nucleosides **1**-**3** used to make $G_4•K^+$ hydrogels and α,β-UCs (acrolein-**AC**, methyl vinyl ketone-**MVK** and methyl acrylate-**MA**) targeted for remediation. B) A $G_4•K^+$ hydrogel made from hydrazine **3** reacts with α,β-UCs to give cyclic adducts, enabling removal of these toxins from water and atmosphere.

Our initial design involved synthesizing a $G_4•K^+$ hydrogel from a G analog **3** with a bisnucleophilic hydrazine at its 5′-position. The hydrazine group, known for effective conjugation of aldehydes and ketones near neutral pH,[14] should "cap" both ends of α,β-UCs inside the gel matrix to give cycloadducts (**Fig. 1 and 2**),[15] resulting in extraction of these volatile α,β-UCs from water or air While alkylhydrazine polymers are known, they are typically used to couple with aldehyde-containing polymers to generate hydrogels

Department of Chemistry & Biochemistry, University of Maryland College Park, MD 20742, USA. E-mail: jdavis@umd.edu
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with hydrazone cross-links.[16] To our knowledge, there have been no reported hydrogels, either supramolecular or polymeric, that contain nucleophilic alkylhydrazines. This is also the first report of a hydrogel designed to target α,β-UCs. We chose a supramolecular G_4-quartet hydrogel for covalent capture of α,β-UCs because: 1) we have experience with G_4-quartet gels;[4a,5] 2) synthesis of gelator **3** from G **1** is easy;[17] 3) the gel is stimuli-responsive, and its stability and mechanical properties can be modulated by K^+ concentration, temperature and pH;[5b] 4) the gel can be disassembled after covalent modification by α,β-UCs, enabling characterization of products **4-6** and 5) G_4-quartet gels are often biocompatible,[4a,8] which may enable use of this hydrazine gel for remediation of α,β-UCs in damaged tissue.[18,19] While we chose the G_4-quartet gel to showcase remediation of α,β-UCs, alkylhydrazines can be made from 1° alcohols, so this approach should be useful with other gels, be they supramolecular, polymeric or double-network materials.

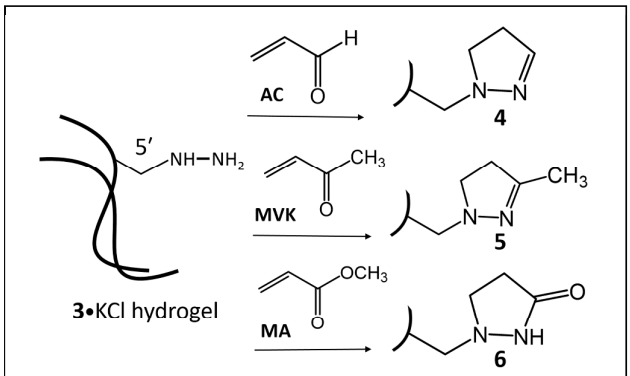

Fig. 2. Bisnucleophilic hydrazine **3**, in the $G_4•K^+$ hydrogel, traps α,β-UCs of varying electrophilicity to form cyclic adducts **4**-**6**.

Sreenivasachary and Lehn published seminal studies on the gelator 5′-hydrazidoguanosine (**2**), which forms $G_4•K^+$ hydrogels that react with aromatic aldehydes to give acylhydrazones.[20] Intrigued by the potential to use such hydrogels containing nucleophilic sidechains to scavenge toxic aldehydes we developed a related G_4•KCl hydrogel with a more basic and nucleophilic sidechain than the hydrazide in **2**. We recently used $G_4•K^+$ hydrogels containing 5′-deoxy-5′-hydrazinoguanosine **3**[17] to react with and remove propionaldehyde from water.[5b] Since both nitrogen atoms in the $–NHNH_2$ hydrazine are nucleophilic, we reasoned that a hydrogel made from **3** would be ideal for remediation of α,β-UCs, since tandem aza-Michael addition and cyclization with AC/MVK should form pyrazolines (**Fig. 2**).[15] We also expected that tandem aza-Michael addition/transacylation between a gel containing hydrazine **3** and the α,β-unsaturated ester MA would work, since tandem aza-Michael addition/cyclization proceeds in reaction of methyl hydrazine and ethyl acrylate.[21] We show that the G_4•KCl hydrogel made from hydrazine **3** covalently traps AC, MVK, and the less reactive MA, removing all 3 α,β-UCs from the gas phase and from water solution.

We have shown that hydrazine **3** and KCl form robust $G_4•K^+$ hydrogels that are stable when suspended in KCl solution.[5b] We expected that this G_4•KCl hydrogel made from hydrazine **3** would covalently trap AC, a toxin found in wood smoke, tobacco smoke, generated during cooking, and released into the environment during chemical manufacturing.[10,22] AC, which forms mutagenic DNA adducts and cross-links proteins,[23,24] has been implicated in cancer, atherosclerosis, Alzheimer's and alcoholic liver disease.[22,25] We first tested the ability of the **3**•KCl hydrogel to absorb the volatile AC from the gas phase. We placed an uncapped vial, containing the hydrogel (made from 0.5 mL of water and containing 68 mM of **3** and 34 mM of KCl) inside a larger vial, added 1.0 eq of AC per monomer of **3** to the outer vial and sealed the set-up (**Fig. S1**). After 2 days at RT we lyophilized the gel, dissolved the resulting powder in DMSO-d_6 and analyzed it by NMR and electrospray ionization mass spectrometry (ESI-MS).

The ^{1}H NMR spectrum of the xerogel indicated formation of pyrazoline **4** **(Fig. 3A)**. NMR signals corresponding to hydrazine **3** were gone. The triplet at δ 6.81 (blue dot) is characteristic of a hydrazone CH coupled to adjacent CH_2 protons (inset).[26] The ^{13}C NMR spectrum had 13 peaks, as expected **4** (**Fig. S3**). A ^{1}H-^{13}C HSQC spectrum showed 3 CH_2 groups, one for G 5′-CH_2 and the other 2 signals (δ 2.51 and δ 2.90) arising from the pyrazoline (**Fig. S4**). In the ^{1}H-^{1}H COSY spectrum, the CH_2 signals at δ 2.51 correlated with the triplet at δ 6.81 (blue) and multiplet at δ 2.90 (pink), confirming CH_2-CH_2-CH connectivity in **4** (**Fig. S5**). ESI-MS of the reaction product showed a major peak for **4**•H^+ at m/z=335.98 (**Fig. S6**). We found no evidence that the nucleobase of **3** reacted with AC,[27] indicating that the 5′-hydrazine is a better nucleophile than guanine. This data shows that AC is taken up from the air into the hydrogel via formation of covalent adduct **4**, with an absorption capacity of 1.0 eq of AC per eq of hydrazine **3**. For the G_4•KCl hydrogel made with the less nucleophilic hydrazide **2**, we performed similar gas phase uptake of AC. NMR and ESI-MS showed formation of acyclic acylhydrazones **8** (as *cis*/*trans* isomers) and a trace of cyclic adduct **9** (**Fig. S7-S10**).

Having characterized the reaction between the 5′-hydrazinoguanosine **3** hydrogel and AC absorbed from the gas phase, we next confirmed that this $G_4•K^+$ hydrogel could also remove AC from aqueous solution. For comparison, G_4-quartet hydrogels made from the parent G **1** and $KB(OH)_4$,[28] and from hydrazide G **2** and KCl,[20] were also evaluated for their relative ability to scavenge AC from solution. The hydrogels (2 wt %, 68 mM, 2 eq KCl in 0.5 mL of D_2O) were made with D_2O and then placed into 5 mL of a 155 mM KCl solution (pD 6.3) in D_2O containing AC (3.37 mM). Absorption of AC by the hydrogels over time was quantified by ^{1}H NMR analysis (**Fig. 3B**). After 4 h, the G_4-quartet gel made from hydrazide **2** showed moderate absorption of AC (53 %). Importantly, the $G_4•K^+$ hydrogel made from 5′-hydrazine **3** showed complete absorption (> 99%) of AC after 4 h. ^{1}H NMR of the lyophilized **3**•KCl hydrogel after 4 h of reaction with AC showed separate sets of signals for hydrazine **3** and pyrazoline **4** (in an approximate 1:1 ratio), indicating covalent attachment of AC to hydrazine sidechains in this reactive $G_4•K^+$ hydrogel (**Fig. S11**).

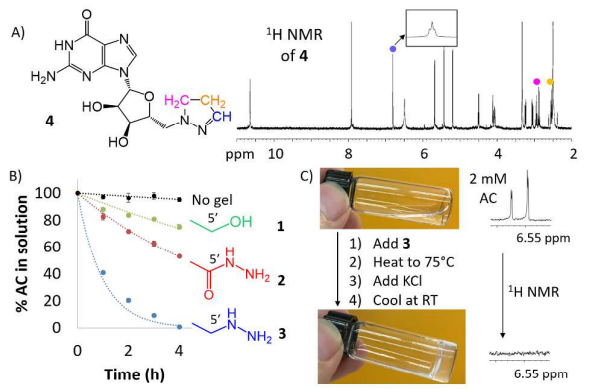

Fig. 3. A) ^{1}H NMR spectrum of pyrazoline **4** formed from **3**•KCl hydrogel and 1.0 eq of **AC** in gas phase set-up. B) % **AC** (3.37 mM) remaining in a 5 mL solution of 155 mM KCl in D_2O, pD 6.3 after addition of hydrogels (0.5 mL, 2 wt % gelator and 136 mM KCl) made from **1-3**. C) Gelation of a 2 mM solution of **AC** in D_2O by adding hydrazine **3** (68 mM) and KCl (136 mM). NMR shows **AC**'s olefinic region before and after hydrogelation.

Figure 3C illustrates how K^+ templated gelation by **3** might be used to effect cleanup of water contaminated by AC. In this experiment, we added hydrazine **3** (68 mM) to a 2 mM solution of AC in 0.5 mL of D_2O to obtain a suspension that was then heated to 75 ^oC to give a clear solution. We then added 2 eq of KCl (136 mM) and let the solution cool to RT. Within 5 min the solution turned into a self-standing hydrogel. Importantly, ^{1}H NMR of this gel showed that all the signals for AC had disappeared, indicating that this α,β-UC had reacted with the 5'-hydrazinoguanosine **3** in the gel matrix. Overall, the data in Fig. 3 shows that G_4•K^+ hydrogels made from hydrazide **2** and, particularly hydrazine **3**, are excellent scavengers for removing the α,β-unsaturated aldehyde AC from water.

We next determined whether G_4•K^+ hydrogels made from hydrazide **2** and hydrazine **3** could scavenge MVK, an α,β-UC enone less electrophilic than aldehyde AC.[29] MVK, a valuable commodity chemical, is also a potent DNA alkylating agent, powerful lachrymator and neurotoxin.[30] In a gas phase absorption experiment involving hydrazine **3** and MVK, NMR and ESI-MS analyses of the xerogel after reaction showed 1:1 adduct formation between **3** and MVK to give pyrazoline **5** in quantitative yield (**Fig. S12A**). Absorption experiments from aqueous solution (155 mM KCl) showed that reaction of MVK was significantly faster with the hydrogel made from hydrazine **3** as compared to the gel containing hydrazide **2** (**Fig. S12B**). Absorption of MVK from water by gels made from hydrazine **3** and hydrazide **2** to give the respective products, pyrazoline **5** and acyclic hydrazide, were confirmed by NMR and ESI-MS analysis (**Fig. S13-19).** The comparative data in **Fig. S12** shows that the G_4-quartet hydrogel made from hydrazine **3** (2 wt %, 68 mM) and KCl (136 mM) is an excellent material for remediation of the neurotoxic MVK, scavenging over 90 % of a 3.37 mM solution in 4 h at RT.

Methyl acrylate (MA), a feedstock for the polymer industry, is cytotoxic and can contribute to health problems.[31] This α,β-UC contains a Michael acceptor and an ester carbonyl, groups that can be also "capped" by the bisnucleophilic hydrazine **3**. Thus, aza-Michael addition followed by intramolecular transacylation should give pyrazolidin-3-one **6** (**Fig. 4A**).[21] The electron-donating oxygen makes MA at least 100-fold less electrophilic than MVK,[29] which makes scavenging MA more challenging than for AC and MVK. As described below, G_4•KCl hydrogels containing bisnucleophilic hydrazine **3** can absorb MA from the atmosphere and solution.

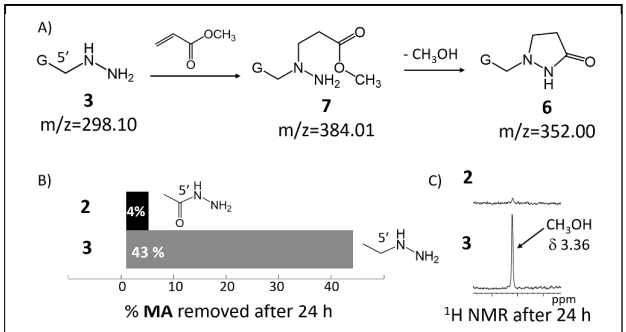

Fig. 4. A) ESI-MS showed the main path for remediation of **MA** by hydrazine **3** hydrogel was formation of aza-Michael adduct **7** (m/z=384.01) followed by transacylation to pyrazolidin-3-one **6** (m/z=352.00). B) % **MA** (3.37 mM) removed after 24 h at RT in a 5 mL solution of 155 mM KCl, pD 6.3 after addition of hydrogels (0.5 mL, 68 mM, 136 mM KCl) made from hydrazide **2** or hydrazine **3**. C) ^{1}H NMR after 24 h shows CH_3OH released by reaction of **MA** with G_4•K^+ hydrogel made from hydrazine **3**.

We began by analyzing for any new adducts formed from gas phase uptake of MA (1 equiv) by G_4•KCl hydrogels containing hydrazide **2** or hydrazine **3** (68 mM and 34 mM KCl). Hydrazide **2** gel did not react with MA under these gas phase conditions, as NMR and ESI-MS of the lyophilized gel showed no new products after 2 days at RT (**Fig. S23-24**). In contrast, the gel made from hydrazine **3** readily absorbed MA from the atmosphere. The ^{1}H NMR of the lyophilized gel after 2 days showed no olefin protons near δ 6.2 ppm, indicating that all the Michael acceptor in MA had reacted. As summarized in **Fig. 4A**, ESI-MS of the lyophilized sample (**Fig. S22**) showed that hydrazine **3** had been converted into two major products, pyrazolidin-3-one **6** (m/z=352.00) formed by tandem Michael addition/cyclization and the acyclic precursor to **6** arising from aza-Michael addition of **3** to the β-carbon of MA (m/z=384.01). In addition to these two major products, there were minor ESI-MS signals for 1:2 adducts wherein both nitrogen atoms in **3** underwent Michael addition with MA (peak B at m/z=470.06 and peak A at m/z= 438.02). Further ESI-MS experiments confirmed that the initial Michael adduct **7** cyclized over time, with loss of CH_3OH, to form the major product **6** (**Fig. S22**). Two important findings came out of these gas-phase uptake experiments: 1) hydrazine **3** is superior to hydrazide **2** for absorption of MA and 2) hydrazine **3** reacts with MA via the Michael addition/cyclization pathway to give pyrazolidin-3-one **6** as the ultimate reaction product.

MA uptake experiments in aqueous solution (155 mM KCl, pD 6.3) confirmed that the G_4•K^+ hydrogel made using 5′-hydrazine **3** was superior to the hydrazide **2** gel for MA remediation. **Figure 4B** shows that after 24 h much more MA had disappeared from solution when incubated with the 5′-hydrazine **3** gel as compared to incubating with the G_4•K^+ hydrogel made with hydrazide **2**. Importantly, incubation of MA with the hydrogel made from **3** revealed significant formation of an NMR signal at δ 3.36 for MeOH (**Fig. 4C**), indicating that the aza-Michael/cyclization tandem reaction had occurred to give the cyclic product **6**. The G_4•K^+ hydrogel containing 5′-hydrazine **3** is an effective scavenger of the less electrophilic α,β-unsaturated ester MA from solution.

We have shown that a supramolecular G_4•K^+ hydrogel made from 5′-hydrazine **3** can remove the cytotoxic α,β-UCs AC and MVK, and even the less reactive MA, from both the atmosphere and from aqueous solution via formation of cyclic covalent adducts. The enhanced nucleophilicity of the 5′-hydrazino group in **3** (as compared to hydrazide **2**) contributes to the efficiency of aqueous phase remediation of these α,β-UCs. We plan to 1) study whether this G_4•K^+ hydrogel with its 5′-modified sidechain can be used for remediation of other toxic electrophiles of both natural and man-made origin and 2) determine if this and other hydrazine-containing hydrogels can be used for biomedical applications where trapping α,β-UCs would be advantageous for therapeutic benefits.

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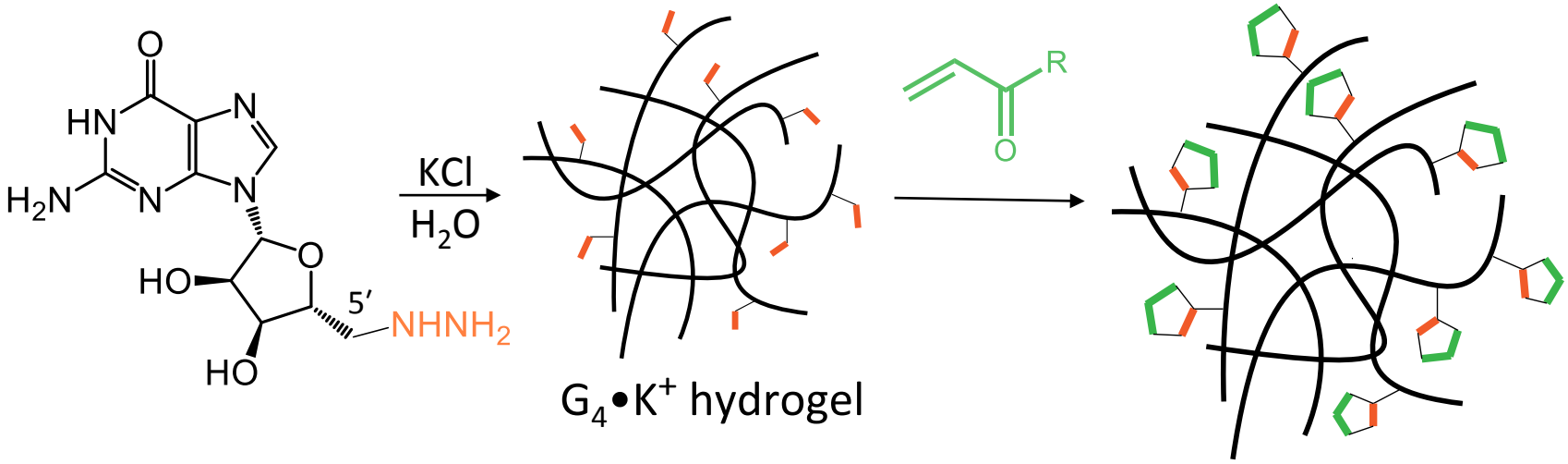
TOC Entry



A G_4•KCl hydrogel with a nucleophilic 5’ sidechain absorbs α,β-unsaturated carbonyls via formation of cyclic adducts.