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Guanosine-Derived Supramolecular Hydrogels: Recent Developments and Future Opportunities

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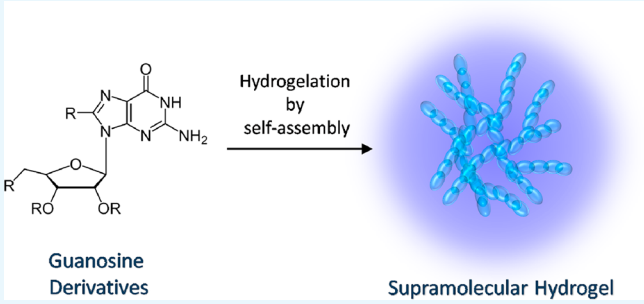
ABSTRACT: Hydrogels are attractive materials for designing sensors, catalysts, scaffolds for tissue engineering, stimuli responsive soft materials, and controlled-release drug delivery systems. In recent years, self-assembly of guanosine and its derivatives has received immense interests for devising programmable supramolecular biomaterials including hydrogels. This perspective highlights some of the history and the recent developments of guanosine-based supramolecular hydrogels and their applications. Future prospects and scope of the guanosine-based hydrogels have also been discussed.



1. INTRODUCTION

Hydrogels are cross-linked networks of hydrophilic polymer chains capable of imbibing large amount of water.[1−10] The supramolecular hydrogels, formed by low-molecular-weight gelators have gained tremendous interest due to their profound implications in tissue engineering, controlled release of bioactive substances, sensing, catalysis, targeted drug delivery, and in optoelectronics.[1−10] Low-molecular-weight gelators assemble via noncovalent interactions like $\pi-\pi$ interactions, hydrogen bonding, and charge interactions into various entangled networks such as fibers, tapes, tubes, helices, etc.[1−10] The properties of the hydrogels can be tuned by changing the external stimuli, such as pH, temperature, ionic strength, or variation in concentration of their components. Several natural products like amino acids, peptides,[7,11−13] fatty acids,[14−16] sugars,[5] and nucleobases, nucleosides, and nucleotides,[17,18] have been used as ideal building blocks for supramolecular gels. In an early report, a nucleobase analogue lithium urate was used as an efficient low-molecular-weight hydrogelator.[19] Since then, nucleobases have been functionalized and derivatized by several groups to explore their gelation abilities.[20] Guanosine **1**, a natural nucleoside, is an important low-molecular-weight building block for supramolecular hydrogels due to its unique self-assembly properties. This nucleoside containing the natural nucleobase purine provides multiple edges for hydrogen-bonding interactions. The self-complementary hydrogen-bonding donors (N1 amide and N2 amino) and acceptors (N7, N3 and O6) enable guanosine and its derivatives to self-assemble into dimers, ribbons, sheets, or macrocycles via noncanonical base pairing.[21−29] Most of the guanosine-based hydrogels are based on the supramolecular assembly of macrocyclic G-quartet units. This macrocyclic structure generates a central cavity where four carbonyl oxygens (O6) provide potential sites for cation coordination (typically Na^+, K^+),[21−29] thus providing cation-induced stability to the columnar aggregates of G-quartets that immobilize significant amount of water to form hydrogel (Figure 1). The G-quartet motif is the basic building block of biologically relevant DNA[30] and RNA[31] G-quadruplexes present in the telomeres, promoter regions as well as the untranslated regions of mRNAs of several proto-oncogenes.[32−34]

In addition, the biocompatible and biodegradable properties of guanosine **1** and its derivatives provide a diverse toolbox in biomedicinal research, particularly in the field of intracellular delivery of drug molecules. More importantly, the ease of synthetic derivatization of guanosine enables tuning the functionality and variability of guanosine-derived supramolecular hydrogels.

2. MECHANICAL INSIGHTS AND CHARACTERIZATION OF GUANOSINE-BASED HYDROGELS

The hydrogelation of guanosine is a multistep hierarchical nucleation process that drives sol-to-gel transitions. The gelation procedure involves heating a solution of guanosine or its derivatives to dissolve the gelator and subsequent cooling of the homogeneous solution to form a metastable state that does not free flow, generating self-supported hydrogel. In this heating-and-cooling process, guanosine bases can associate through Hoogsteen type hydrogen bonding to form square planar aromatic G-quartet structures that stack upon one another and grow into G-wires. The physical cross-linking, branching, and lateral aggregation of G-wires drive the gelation process. The gel network can be easily broken down by disrupting the supramolecular assemblies using appropriate external stimuli. Owing to this reversible nature, guanosine-based hydrogels have been considered as stimuli responsive "smart" biomaterials.

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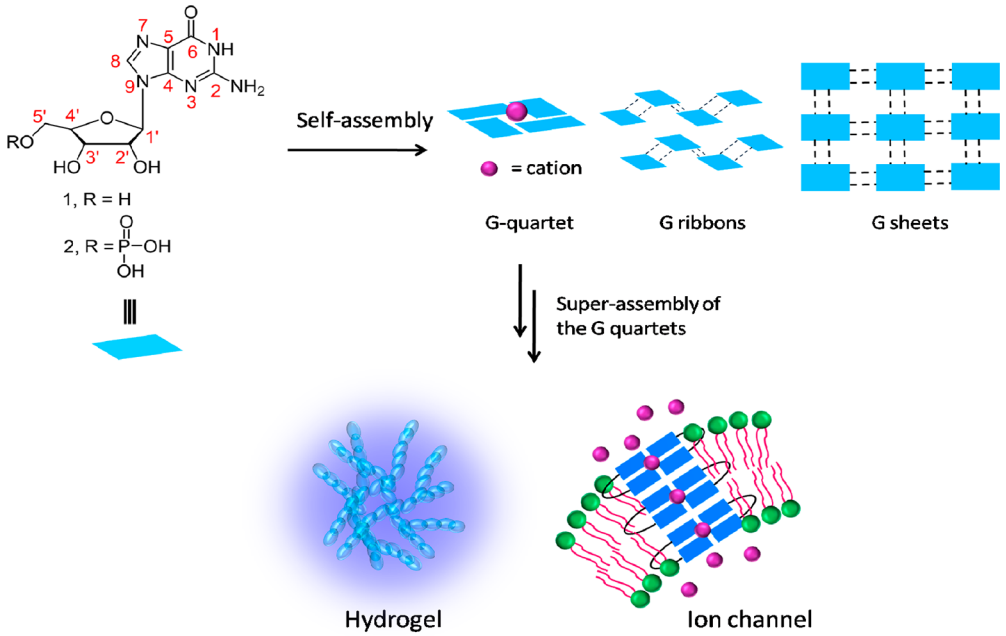

Figure 1. Schematic illustration of hierarchical assemblies formed by guanosine derivatives.

The gelation mechanisms and properties of the guanosine-based hydrogels have been established by various characterization techniques. NMR[35−50] spectroscopy, electrospray ionization mass spectrometry (ESI-MS),[35,45] matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) mass spectrometry,[39,49] and IR spectroscopy[37,47−50] have been widely used for structure elucidation and identification of the supramolecular assemblies present in the guanosine hydrogel. The NMR spectroscopy has been used to predict the structural properties of the constituents and the resulting aggregates involved in gel formation. In the solution-phase ^{1}H NMR, the gelators, which take part in the formation of gel fibers, cannot be detected because of line broadening and loss of spectral resolution. This principle has been used to determine the relative content of gelators in the gel network.[35−50] Variable temperature NMR (VT-NMR) experiments have been used to study the thermal responsiveness of the self-assembled fibers.[43,49,51] An upfield shift in peak positions and decrease in integral values of the peaks, as gelation proceeds with decrease in temperature (from melting temperature of gel to room temperature) have been observed in VT-NMR analysis of the guanosine gel samples.[49,51] The magic-angle-spinning (MAS) NMR has been used to identify the component crucial for gelation as well as provide information about the stacking interaction of G-quartets in the gel network.[43,52] Diffusion ordered NMR spectroscopy (DOSY) is used to characterize gelators of various sizes based on their self-diffusion coefficients (D_t).[43] ^{1}H double-quantum MAS spectroscopy is a useful technique to distinguish between G-ribbons and G-quartet in the supramolecular assemblies of guanosine.[43] Other techniques like solid-phase NMR and two-dimensional NMR spectroscopy have also been used for structure elucidation of various guanosine gels. Solid-state magic-angle-spinning (MAS) ^{11}B NMR spectroscopy confirms the presence of borate diesters in the guanosine borate hydrogels, as reported by Davis group.[43] ESI-MS and MALDI-TOF further confirm the components present in the gel network. IR spectroscopy gives an insight into the presence of functional groups in the gel network.

Several other techniques have also been used to characterize the supramolecular architecture within the gel system. The X-ray techniques reveal the structural motifs and physical properties of the supramolecular architectures in the guanosine gels. Small-angle X-ray scattering (SAXS) is used to determine the length of the structures in the nanometer to micrometer range and indicates the repeat distances of the gel fibers.[41,43,53] Small-angle neutron scattering (SANS) also characterizes the shape, size, and dimensions of the gel fibers.[39,43,53] SANS and SAXS data from various reports on guanosine-derived gels suggest that the average dimension of the guanosine gel fibers is in the nanometer range and highly dependent on the dimensions of the component guanosine units. For instance, whereas the gel fibers in the binary hydrogel derived from 2′,3′,5′-tri-*O*-acetylguanosine and guanosine have a radius of 1.47 nm and a length of 32 nm,[39] the guanosine borate hydrogel fibers are 2.15 nm in radius and 46 nm in length.[43] It has also been inferred from the SANS studies that the core of the fibers is comprised of the G-quartets formed by the guanine bases and the shell region is comprised of the ribose units.[43] The size distribution profile of the supramolecular gels and the thickness of the gel fibers can also be studied using dynamic light scattering measurements.[44,51] Powder X-ray diffraction (PXRD) studies have been used to confirm the $\pi-\pi$ stacking interactions between the successive G-quartet stacks within the guanosine hydrogel.[46,49−51] The PXRD analysis of the dry guanosine hydrogels shows a broad peak at 26.8°, which corresponds to the distance between two adjacent vertical G-quartet stacks (d = 0.33 nm). The presence of G-quartet stacks in the gel fibers is also evident from the UV−vis absorption spectroscopy.[41]

Circular dichroism (CD) spectroscopy provides key insights into the stereostructure of the supramolecular assembly of the gelator molecules.[40−46,48−50,52] Positive peaks at 254 and 295 nm and negative peaks at 236 and 270 nm in the CD spectrum indicate both head-to-tail and head-to-head stacking of the G-

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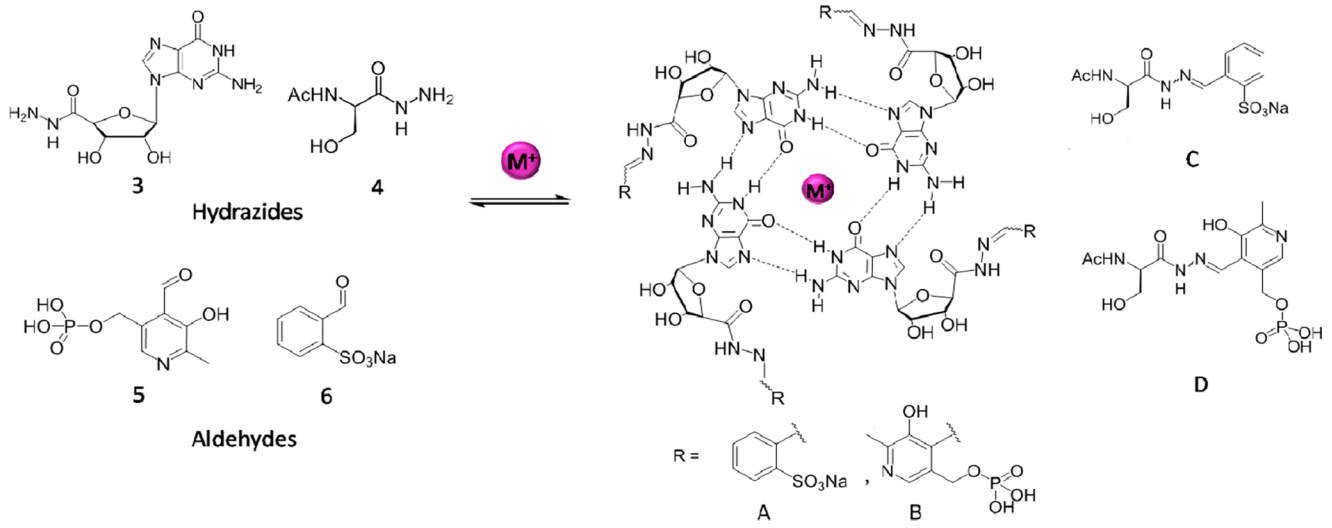

Figure 2. Dynamic combinatorial library consisting of guanosine-derived acylhydrazones.

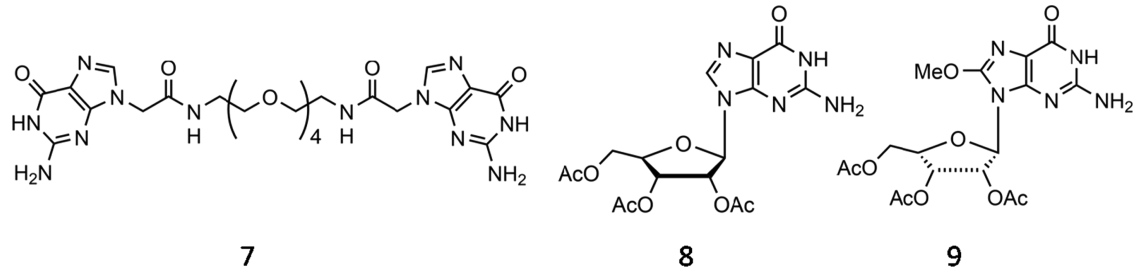

Figure 3. Guanosine derivatives (**7**–**9**) used for the preparation of stable hydrogels.

quartets in the gel fibers. Parallel and antiparallel arrangements of the G-quartets in the gel fibers induced by the stabilizing cation can also be monitored using the CD spectroscopy.[49,52] Whereas CD spectroscopy throws light upon the orientation of the G-quartet stacks within the gel framework, several microscopic techniques have been used to visualize the microscopic structures of the self-assembled systems. Scanning electron microscopy, atomic force microscopy (AFM), and transmission electron microscopy (TEM) have been used to investigate the morphology of the gel sample.[35−56] The microscopic images of these hydrogels reveal that the gel matrix is composed of a highly entangled three-dimensional network of ribbon- or fiberlike structures of variable width and length. A change in the appearance of these fibers on changing the stabilizing cation or the guanosine derivative can also be monitored by these techniques. For instance, it has been recently reported by our group that whereas the AFM image of the guanosine−phenylboronic acid hydrogel stabilized by K^+ ions exhibits an entangled network of knotted fibers, the guanosine−phenylboronic acid hydrogel stabilized by Pb^{2+} ions displays comparatively straight fibers that were not very interlinked.[49] Confocal laser scanning microscopy is also helpful for imaging the incorporation of dyes into fibrous gel network.[51]

Differential scanning calorimetry (DSC)[39,49,51] and thermogravimetric analysis (TGA)[49] indicate the thermal stabilities of the hydrogels. The DSC studies determine the gelation temperature (T_{gel}), whereas the TGA studies provide the thermal degradation profile of the hydrogels. T_{gel} for various reported guanosine hydrogels vary within 50−80 °C and stronger gels show a higher T_{gel} compared to the weaker gels. Rheological experiments reveal the strength of the hydrogel in the presence of stress and strain.[39−41] The strength of the guanosine gels are measured by monitoring their storage (G') and loss (G'') moduli under varying conditions like shear stress, shear strain, and frequency.

3. CATION-STABILIZED GUANOSINE HYDROGELS

In 1910, Bang et al. reported that concentrated 5′-guanosine monophosphate (5′-GMP) **2** solution in water formed gelatinous aggregates.[57] After a few decades, Gellert et al. in 1962 discovered that the G-quartet (G4) is the basic structural unit of these hydrogel fibers.[58] These findings established that guanosine derivatives can drive hydrogelation through the stacking assembly of tetrameric G4 units in the presence of a stabilizing cations. Numerous studies have shown the role of cations and pH in the stabilization of guanosine hydrogels.

Sreenivasachary and Lehn used dynamic combinatorial chemistry to construct thermodynamically stable G-quartet hydrogels (Figure 2).[35] A dynamic combinatorial library consisting of hydrazides and aldehydes yielded the most stable acylhydrazone hydrogel in the presence of cations by selecting the optimum aldehyde component **5** and guanosine hydrazide **3**. The guanosine-5′-hydrazide hydrogel network was found to be capable of incorporating and releasing biologically active and volatile molecules,[36,37] such as acyclovir, vitamin C, vancomycin, fragrant aldehydes, and ketones via reversible acylhydrazone bond formation. Thus, this hydrogel system may find useful applications in developing drug delivery vehicles as well as in fragrance-releasing commercial gels. Lehn's group also reported a dynamic hydrogel system using a guanine dimer **7** that could undergo cyclic sol−gel transitions on reversible

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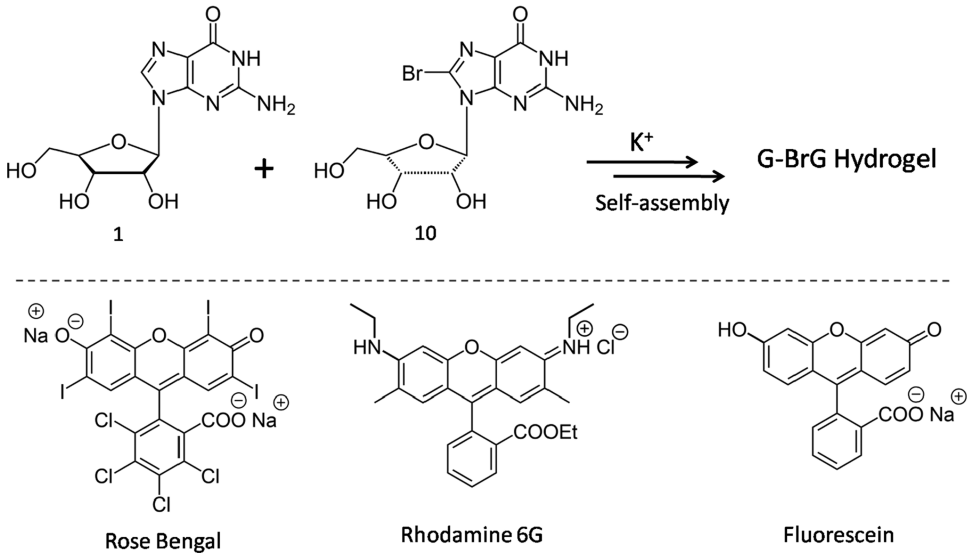

Figure 4. Formation of G−BrG binary hydrogel that exhibits birefringent properties in the presence of dyes.

uptake and release of K^+ ions.[38] The bis-guanine gelator **7** formed stable gels in the presence of K^+ ions (Figure 3). The gel-to-sol transition was achieved by addition of a cryptand that could pull out K^+ from the G-quartet hydrogel network. Upon protonation, the cryptand released K^+ ions, enabling the regeneration of gel. This dynamic gel−sol interconversion demonstrated the effective role of K^+ ions in stabilizing G-quartet formation in the gel network, and it also indicated the stimuli-responsive nature of the guanosine hydrogelation systems.

However, low shelf-life due to precipitation of gel components and requirement of high concentration of stabilizing cations were found to be the major drawbacks of most of the guanosine-derived hydrogels. To overcome these limitations and to form stable gels with modulable properties, two-component (binary) gel systems were developed. In the binary gel systems, the use of two different guanosine derivatives increased the gel stability by hindering the crystallization of gel components.

The McGown group reported a two-component hydrogel system using hydrophobic guanosine **1** (gelator) and hydrophilic 5′-GMP **2** (nongelator) in the presence of K^+ ions.[54] They highlighted that the greater solubility of 5′-GMP (in water) over guanosine **1** was the prime factor for gelation. Depending on the ratio of the two components in the gel medium, the gel exhibited thermoassociative and thermodissociative behavior. To further enhance the stability and biocompatibility of the gels, the Rowan group used a combination of guanosine **1** and its acetyl derivative 2′,3′,5′-tri-*O*-acetylguanosine **8** to prepare clear hydrogels with a longer shelf-life (Figure 3).[39,53] They have further reported that the use of 8-methoxy-2′,3′,5′-tri-*O*-acetylguanosine **9** as the other component along with guanosine **1** formed hydrogels at lower salt concentrations, establishing the fact that guanosine in its syn conformation as in **9** was more prone to self-assembly (Figure 3).[40] In addition, these guanosine-based gels were able to sustain cell growth and proliferation without inducing significant apoptosis, suggesting their promising applications in tissue engineering and tissue scaffolding. The same group further reported that guanosine-derived polymers can be used to improve the mechanical properties of the supramolecular hydrogels.[55]

During the same time, our group reported that guanosine **1** and 8-bromoguanosine **10** can form a binary hydrogel system (G−BrG hydrogel) within a wide range of their ratio compositions (Figure 4).[51] Significantly, a binary mixture of **1** and **10** formed stable and transparent hydrogels, whereas the individual components form weak and unstable hydrogels. A VT-NMR study of the hydrogel showed that **10** was a better gelator compared to **1**. The resulting hydrogel itself did not show any birefringence but exhibited a birefringence in the presence of dyes; thus the gel system might find potential applications in optical devices and biomolecular imaging. Furthermore, organic dyes like rose bengal, rhodamine 6G, and fluorescein were efficiently diffused into the binary gel network through noncovalent stacking interactions. Moreover, the hydrogel system was able to release dyes in a controlled manner from the gel network. Such guanosine-based hydrogels can be used for dye removal as well as in drug delivery applications, as these gels can reversibly incorporate aromatic small molecules. Self-assembly of guanosine and deoxyguanosine has also been reported to form stable hydrogels with self-healing properties.[56] Although various binary guanosine hydrogels have been designed to form stable and biocompatible hydrogels, little attention has been focused on their practical applications.

Mann and co-workers reported that a silver (Ag) ion mediated 5′-GMP **2** gel could be finely tuned by modulating the 5′-GMP-to-Ag molar ratios.[41] This Ag/5′-GMP gel system could be used as molecular sensors, as the fibrillar network of this hydrogel was capable of binding cationic dyes such as methylene blue and Hoechst-33258. It was also reported that the protein molecules such as cytochrome C could be immobilized within the Ag/5′-GMP hydrogels without any loss of enzymatic activity. This work demonstrated that small-molecule drugs and protein molecules can be incorporated within the gel network.

Recently, our group reported that carbon dots (G-dots) derived from $Na_2$5′-GMP could form a fluorescent hydrogel system.[42] These nanosized G-dots were prepared from $Na_2$5′-GMP under microwave irradiation and exhibited photo-

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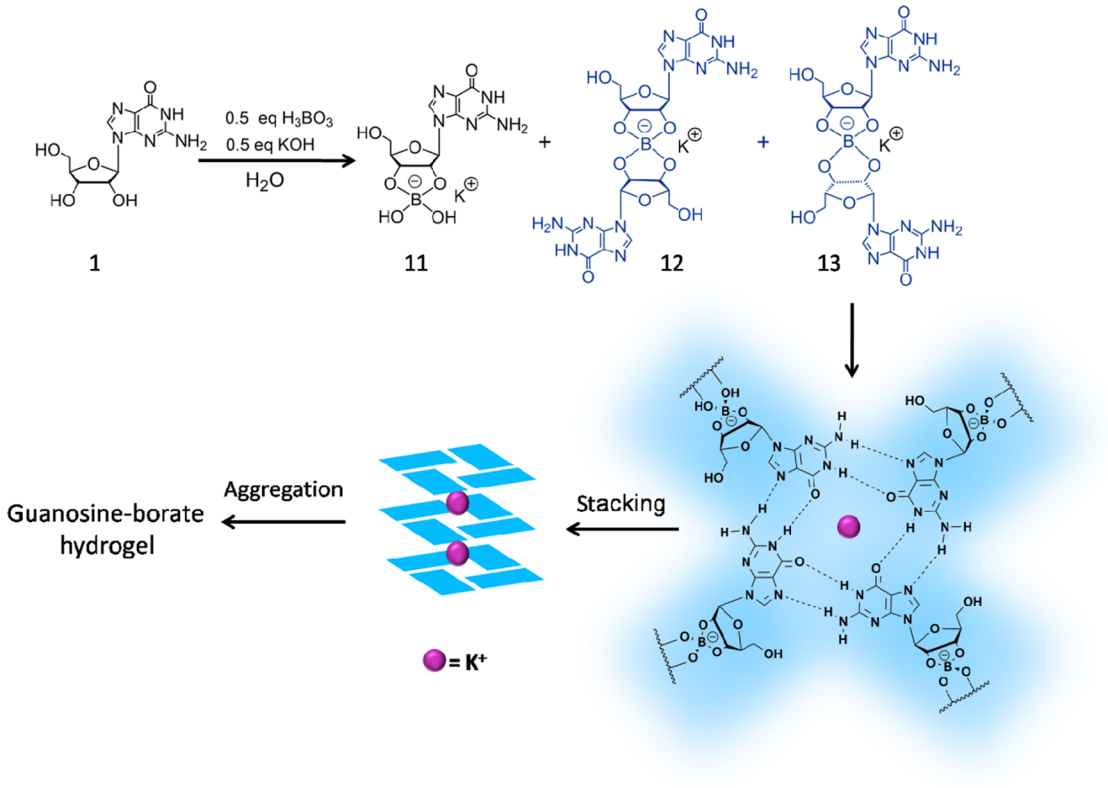

Figure 5. Formation of guanosine borate hydrogel.

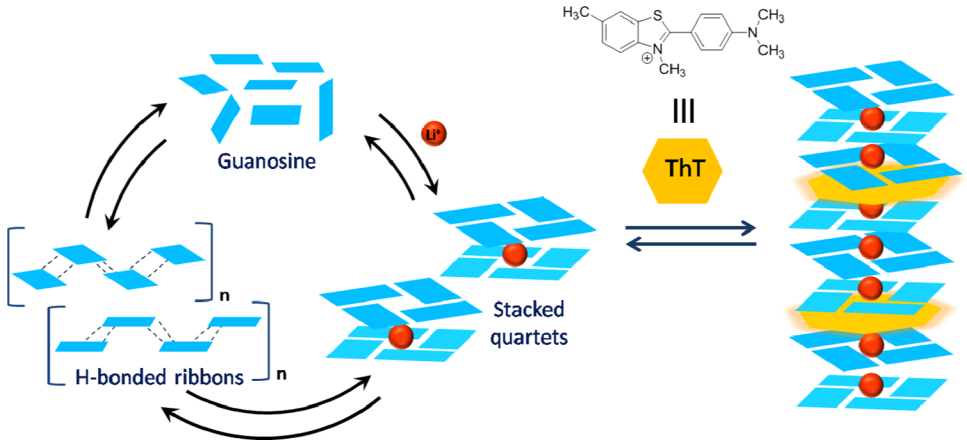

Figure 6. Schematic representation of thioflavin T (ThT) acting as a molecular chaperone for stabilizing the Li^+ gel.

luminescent properties. A detailed characterization using various spectroscopic techniques showed that the G-dots were composed of 5′-GMP-polymers of variable length. Interestingly, the G-dots could utilize the self-assembly property of 5′-GMP to form fluorescent hydrogels without any externally added monopositive cations. The TEM analysis of the dispersed hydrogel showed the presence of fibrillar structures in the G-dot hydrogel. This example illustrated that guanosine-derived nanomaterials can undergo super-assembly to form fluorescent hydrogels that may find prospective applications in biomedical engineering.

4. ANION-STABILIZED GUANOSINE HYDROGELS

Recently, the Davis group developed an elegant approach for the synthesis of a novel guanosine hydrogel system stabilized by borate anion (Figure 5).[43,52] On reaction with boric acid (H_3BO_3) in the presence of KOH, guanosine **1** formed covalent borate monoester **11** and diastereomeric diesters (**12** and **13**). These borate esters self-assembled in the presence of K^+ ions to form hydrogels that were found to be more stable than previously reported binary gel analogues. This study elucidated the application of the 2′ and 3′ hydroxyl groups of guanosine's ribose moiety for the modulation of the self-assembly of stacked G4s. The columnar G4 stacks laterally associated to form cation templated entangled fibers. The borate anions solubilize guanosine and stabilize the gel at physiological salt concentration, whereas the K^+ ions stabilized the G-quartet as well as the anionic borate diesters, making it suitable for biological applications. Various techniques such as PXRD, SANS, and rheology were employed to characterize the hydrogels. The VT-NMR studies showed that the gels formed in the presence of K^+ ions were stronger than those formed in

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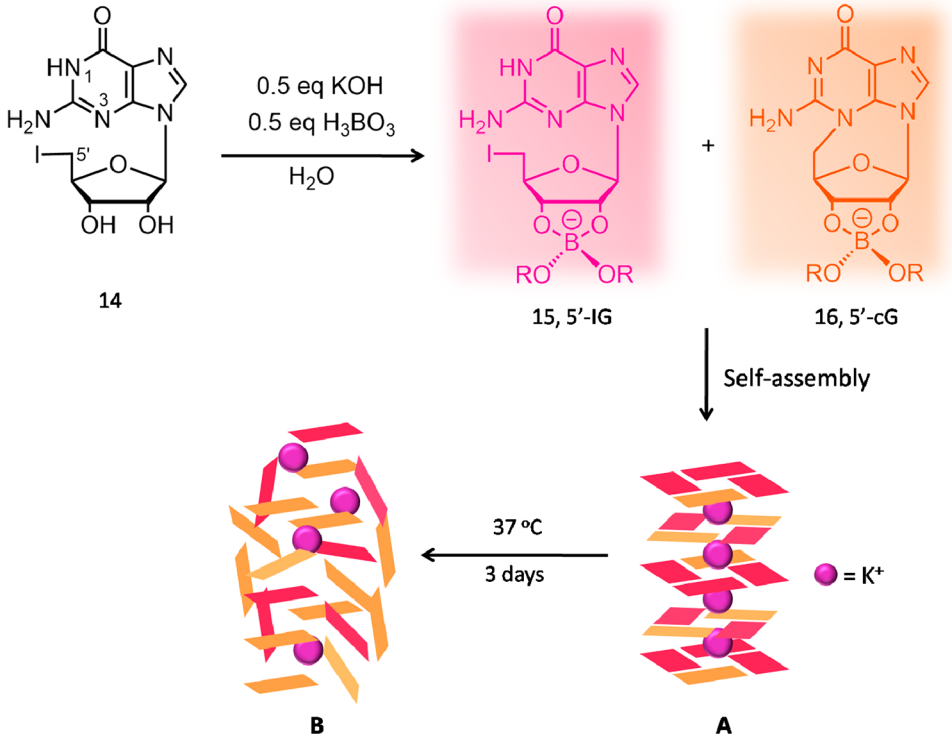

Figure 7. Hydrogel undergoing self destruction via an in situ chemical reaction.

the presence of other cations (Na^+, Li^+, Rb^+, Cs^+, etc.). These results suggested that the physical properties of guanosine borate hydrogels can be modulated by varying the borate salt.

Significantly, the anionic hydrogel could selectively incorporate nucleosides via exchange reactions of boron-diol covalent bonds and hydrogen bonding. The gel could also incorporate G-quadruplex DNA interacting dyes by using both electrostatic and stacking interactions. The G-quadruplex-binding molecules are mostly planar aromatic small molecules that readily stack upon the G4 units.[59] These small molecules are considered as potential anticancer drugs that act by telomere maintenance[60] and regulation of oncogene expression.[61] The G-quadruplex interacting dyes methylene blue and thioflavin T (ThT) were shown to bind to the gel network. The nonfluorescent ThT dye displayed enhanced fluorescence upon interaction with the G4 units of the hydrogel. These properties make the hydrogel system attractive for the delivery of quadruplex targeting anticancer drugs.

They further demonstrated that weak guanosine borate hydrogels formed in the presence of Li^+ ions could be strengthened by using a G-quadruplex interacting small molecule dye, ThT (Figure 6).[44] In the presence of Li^+ ions, guanosine tended to form ribbonlike aggregates and generate weak gel. ThT stabilized the stacking interaction of Li^+-stabilized G4s and made the gel more strong. ^1H NMR spectroscopy in liquid state showed that ThT could speed up the self-assembly process of the Li^+ gel.

They further established that not only ThT but also other planar aromatic molecules like thiazole orange, methylene blue, crystal violet, methylene violet, etc. were capable of stiffening the weak Li^+ hydrogel. The rheological studies of Li^+ gels in the presence of different cationic dyes showed that crystal violet was found to be more effective in stabilizing the gel network. These observations suggested that G-quadruplex binding ligands could be utilized as molecular chaperones facilitating the formation of long-lived G-quartet-based hydrogel assembly. This study revealed that ligand or additives could modulate the structure and properties of supramolecular gels. It has also opened up a new strategy for the identification of high-affinity DNA G-quadruplex binding ligands by using Li^+-ion-stabilized guanosine borate hydrogels.

Davis's group also demonstrated a self-destructive hydrogel system by using 5′-deoxy-5′-iodoguanosine **14** with a good leaving group like iodide at 5′ position as the gelator.[45] Iodoguanosine **14** upon heating at 90 °C in the presence of boric acid and KOH for a few seconds formed a self-supporting transparent hydrogel due to the formation of the borate ester **15**. However, on prolonged heating, no gelation was observed as compound **15** was converted to cycloguanosine borate ester **16** by intramolecular cyclization. The cyclization occurred via displacement of 5′-iodide by guanosine N3 and deprotonation of N1H. The cycloguanosine borate ester **16** lacked the N1 H-bonding donor and was thus incompatible for inclusion in a G-quartet, disassembling the gel network. Moreover, most of the iodoguanosine borate ester **15** was converted to cycloguanosine borate ester **16** after 72 h at 37 °C, destructing the gel into a viscous liquid (Figure 7). This example demonstrated that the gel's own component could self-destruct the gel through in situ chemical reaction in a time- and temperature-dependent manner. The authors subsequently established that this self-destructive gel system can incorporate guanosine-derived anti-human immunodeficiency virus drugs acyclovir and ganciclovir. This iodoguanosine borate hydrogel showed higher incorporation and enhanced drug release properties compared to the previously reported cation-stabilized guanosine hydrogel system.[36,37] This work gave a new dimension in designing biocompatible guanosine hydrogel systems for drug-delivery applications.

Next, they developed a binary hydrogel composed of 8-aminoguanosine **17** and guanosine **1**, stabilized by binary

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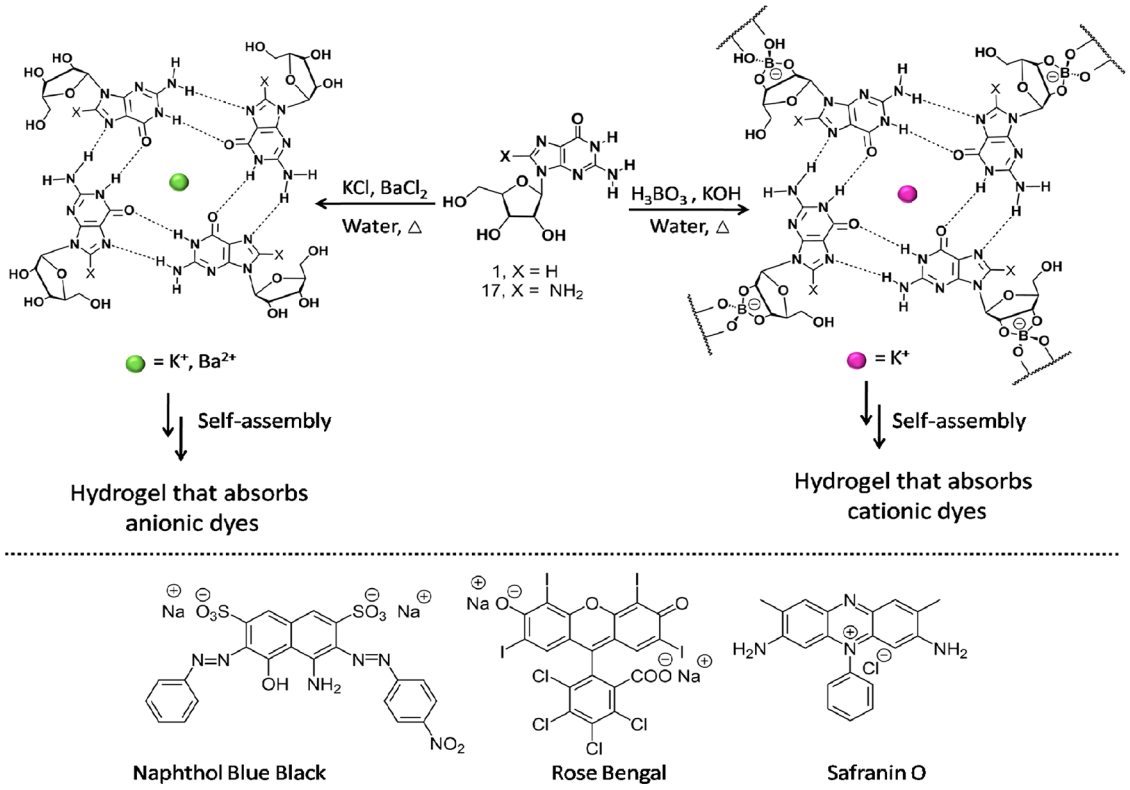

Figure 8. Binary hydrogel derived from guanosine and amino guansoine.

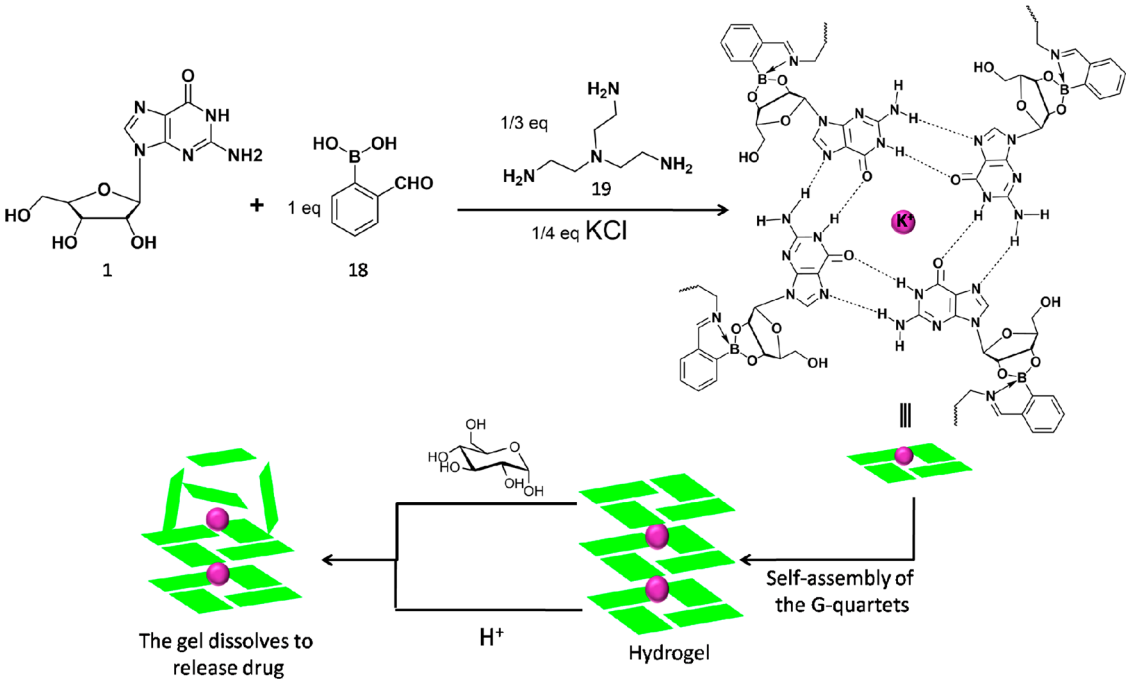

Figure 9. G-quartet hydrogels composed of guanosine, boronic acid, and tris(2-aminoethyl)amine exhibiting a zero order drug release in response to stimuli like glucose and acid.

cations (Figure 8).[46] They presumed that the 8-amino group of **17** on protonation in the aqueous gel medium would provide a cationic gel network suitable for anionic dye absorption. To increase the positive charge density in the hydrogel matrix and enhance its efficiency of absorbing anionic dyes, divalent cations such as (Ba^{2+}, Sr^{2+}, and Pb^{2+}) were used as stabilizing cations. It was observed that the binary gel stabilized by Ba^{2+} was comparatively stronger and exhibited a greater absorption of the anionic dyes compared to the K^{+}-stabilized gel. The Ba^{2+}-stabilized hydrogel exhibited a selective absorption of the anionic dyes naphthol blue black and rose bengal over the cationic dye safranin O. These results demonstrated that guanosine-derived gels can be modulated to absorb both

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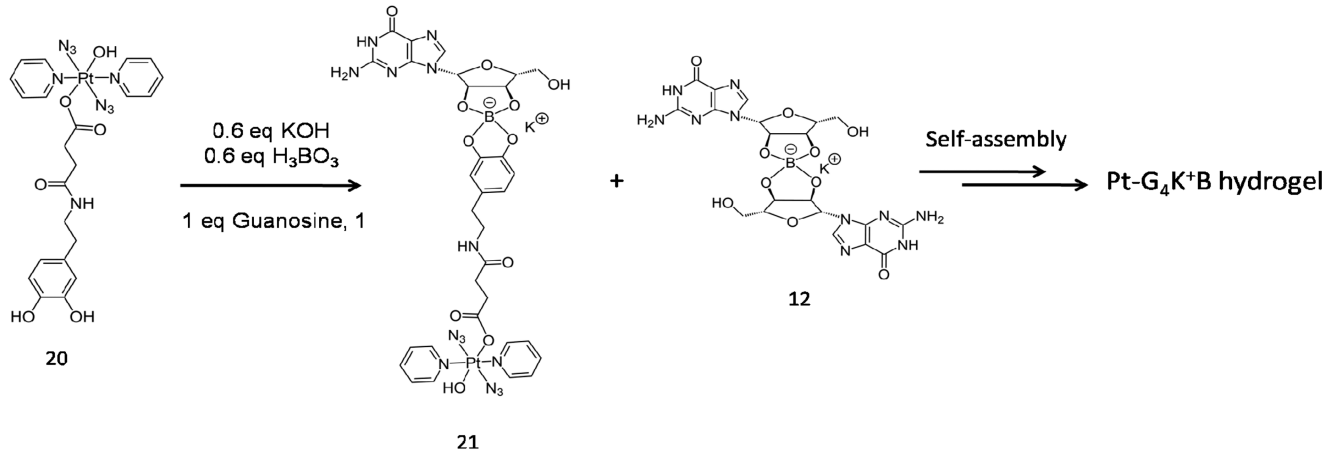

Figure 10. Borate hydrogel incorporating a photoactivatable dopamine-conjugated platinum(IV) anticancer complex.

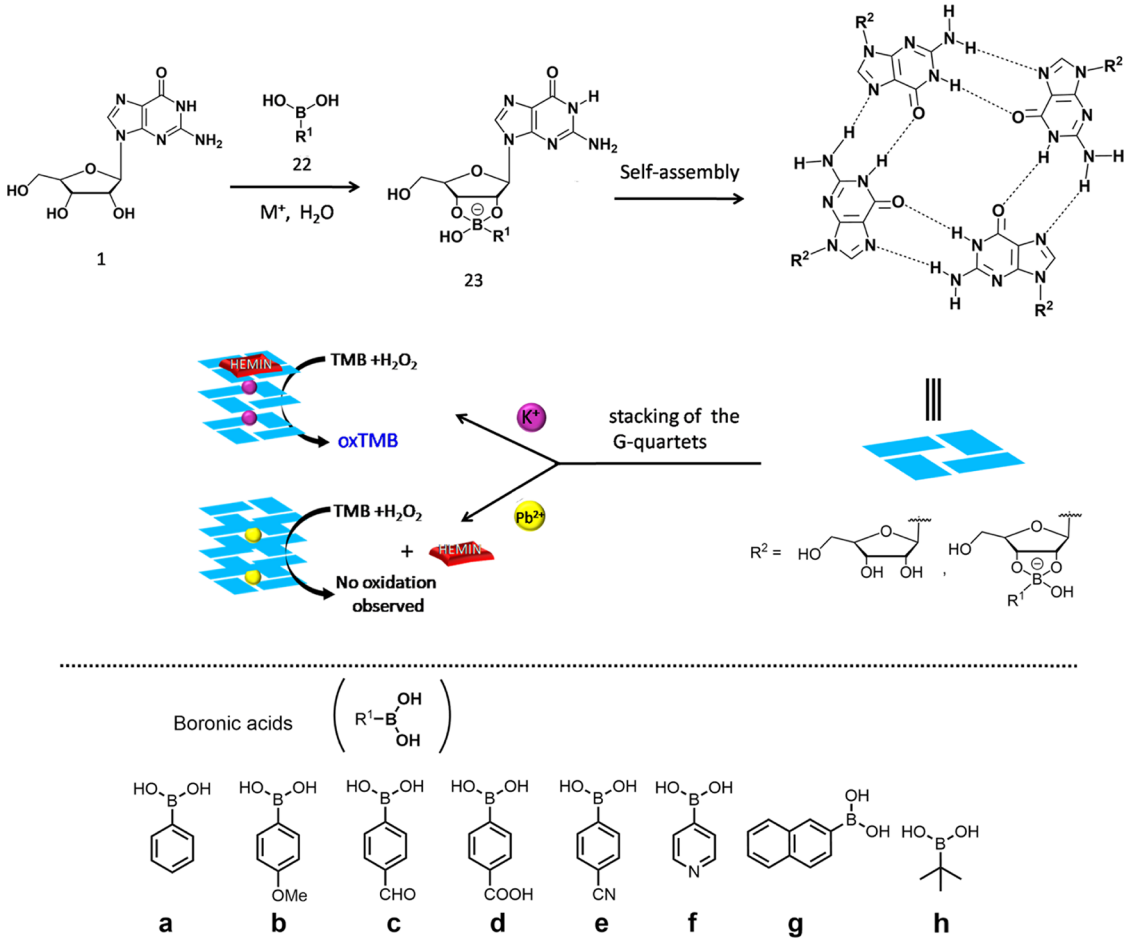

Figure 11. Guanosine-boronate ester hydrogels for sensing and biomolecular logic operations.

cationic[52] and anionic[46] dyes. Thus, guanosine hydrogels can be used for the removal of pollutant dyes from wastewaters.

The versatility of the guanosine boronate ester hydrogel could be utilized for advanced applications. Inspired from the borate ester hydrogels, Shi et al. fabricated a multicomponent stimuli responsive hydrogel system for controlled release of drugs at a constant rate (Figure 9). In this study, the G-quartet hydrogel was prepared from a mixture composed of guanosine **1**, 2-formylphenylboronic acid **18** and tris(2-aminoethyl)amine **19** in the presence of KCl.[47] They proposed that gelation occurred due to the synergistic formation of G-quartet (G4), boronate ester, and iminoboronate linkage. The trifunctional amine **19** could connect adjacent G-quartets via iminoboronate bonds. The iminoboronate bonds in the hydrogel not only strengthened the gel but also made it responsive toward acid and glucose stimuli; a property that was highly useful for controlled release of drugs. The drug release studies were carried out with two model drugs methylene blue and fluorescein isothiocyanate-lysozyme and the release rates were measured using UV−vis and fluorescence spectroscopy. Unlike

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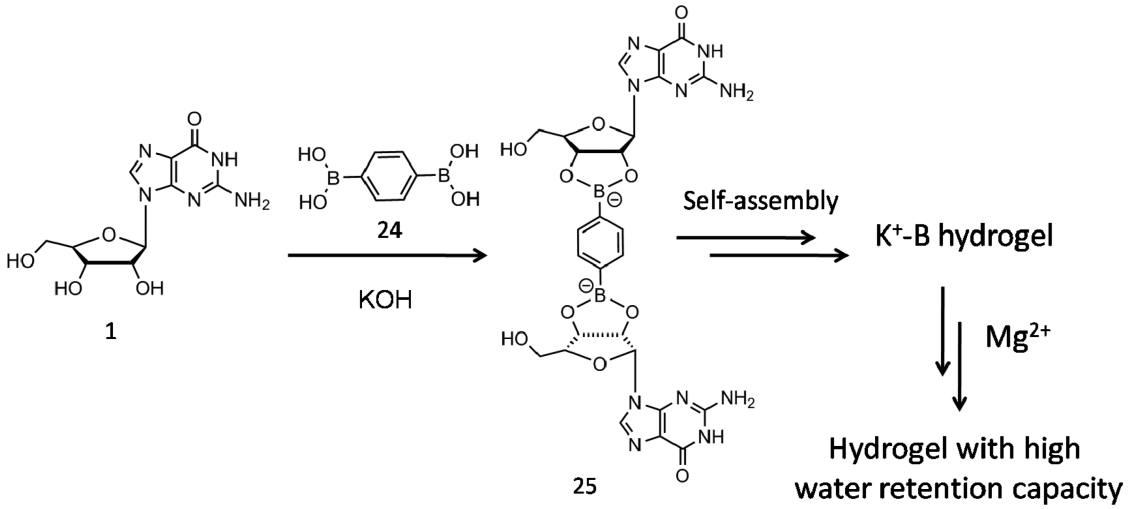

Figure 12. Mg^{2+} cross-linked guanosine bisboronate hydrogel with enhanced water retention property.

other drug delivery systems, where a "fast and then slow" release of drugs is observed, this gel system exhibited a zero order controlled release of drugs in response to stimuli like acid and glucose.

Venkatesh et al. incorporated a photoactivatable dopamine-conjugated platinum(IV) anticancer complex **20** into borate hydrogels (Figure 10).[48] This hydrogel ($Pt-G_4K^+B$) was prepared from Pt-dopamine conjugate **20**, boric acid, guanosine, and potassium hydroxide in water. Unlike other guanosine borate hydrogels, $Pt-G_4K^+B$ hydrogel was brown in color and exhibited a flakelike morphology. They showed that the hydrogel could induce selective cytotoxicity toward cisplatin-resistant A2780C human ovarian cancer cells over the noncancerous human fibroblast cell line MRC-5 when irradiated under blue light. This strategy designed for the delivery of photoactivatable Pt(IV) anticancer complexes to cancer cells would be highly beneficial for cancer treatment. In addition, the incorporation of the photoactive platinum-based anticancer drugs in the hydrogel network would limit the drug exposure to the external environment and facilitate the slow release of the drug specifically at the target site on exposure to light stimuli. This approach would be helpful for developing a new class of photochemotherapeutic agents with the potential for localized immunogenic treatment of cancers.

Very recently, our group utilized this concept of guanosine boronate ester hydrogels for designing smart versatile materials for sensing and biomolecular logic operations (Figure 11).[49] We used guanosine **1** and boronic acids to prepare hydrogels in the presence of KOH. A variety of aryl, heteroaryl, and aliphatic boronic acids **22a–h** were used to prepare the gels. The detailed characterization of the guanosine–phenylboronic acid hydrogel (G–PhB hydrogel) showed that the gel fibers were composed of G-quartet units resembling the G-quadruplex-like arrangements.[30−34] Although the G-rich sequences were known to fold into G-quadruplexes in the presence of various mono- and divalent cations like Li^+, Na^+, K^+, Cs^+, Ba^{2+}, Zn^{2+}, Mg^{2+}, Pb^{2+}, or Sr^{2+},[62,63] the guanosine–phenylboronic acid (G–PhB) hydrogel is selectively formed in the presence of K^+ and Pb^{2+} ions.

Spectroscopic studies suggested that the conformation of supramolecular assembly of the hydrogel could be altered by changing the stabilizing cation. Interestingly, the K^+-stabilized guanosine–phenylboronic acid (G–PhB) hydrogel on binding with hemin exhibited a DNAzyme-like peroxidase activity,[64−71] promoting the oxidation of 3,3′,5,5′-tetramethylbenzidine in the presence of H_2O_2. This study demonstrated that guanosine-derived hydrogels can mimic enzymatic activity. However, the Pb^{2+}-stabilized G–PhB hydrogel did not show such activity, as the hemin failed to bind the Pb^{2+} gel network. This differential activity was used to efficiently detect nanomolar concentrations of lead ions, thus providing a sensing system for toxic Pb^{2+} ions. Further, an INHIBIT logic gate was developed by monitoring the enzyme-mimicking activity of the hydrogel–hemin complex using K^+ and Pb^{2+} as two inputs. As boronic acids with various functionalities can be introduced into the gel matrix, this approach offered a versatile material platform for generating hydrogels with tunable elastic properties for diverse applications. For instance, drug molecules derivatized with boronic acid functional group could be incorporated into the gel matrix and used for developing the next-generation drug delivery technologies. Moreover, dynamic combinatorial libraries[72−74] can be constructed using guanosine and different boronic acids to generate stable gels for understanding the fundamental aspects of self-organization process.

Another similar artificial enzymatic hydrogel system has been developed by incorporating hemin into G-quartets during the cation-templated self-assembly between guanosine, boric acid, and KOH.[75] The gel system in the presence of the K^+ stabilizing ions bound hemin and showed peroxidase activity, whereas no peroxidase activity was observed in the presence of Pb^{2+} ions. This gel assembly had been utilized to construct two two-input INHIBIT logic gates by employing K^+ and Pb^{2+}, or K^+ and pH as inputs and also provided a sensor for Pb^{2+} ions.

The ditopic phenyl-1,4-diboronic acid has been used to prepare guanosine bis-boronate hydrogels in the presence of cations like K^+ and Ba^{2+}.[50] The G-quartets formed in K^+-stabilized bis-boronate hydrogel could cross-link with Mg^{2+} ions to generate a gel with a high water retention capacity (Figure 12). The diboronic acid as the cross-linker enhanced the swelling property of the gel in the presence of external stabilizing Mg^{2+} cations. These hydrogels, with a high water content was able to sustain cell growth on the surface, showing negligible cell toxicity.

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5. SCOPE AND FUTURE DIRECTIONS

We herein highlight the recent advances in guanosine derivatives with tunable self-assembling abilities that have been explored for developing hydrogels for different applications. This provides new opportunities for engineering more advanced guanosine-derived hydrogelators and hybrid multicomponent hydrogel constructs useful for tissue-engineering and other medicinal applications. However, some fundamental questions still remain to be addressed. For instance, the potential loading capacity and the stability of the incorporated drugs within the gel network are yet to be studied. The guanosine borate hydrogel should be optimized for controlled and more sophisticated responsiveness toward chemical and biological stimuli. Simultaneously, the gel system may need to be further improvised to build self-healing materials by using dynamic and reversible supramolecular interactions. In addition, the hydrogel systems could be useful for hydrophobic drug delivery by incorporating poorly water-soluble drug molecules into the gel network. The hydrogels could be used for the development of novel biomaterials with enzyme-mimicking and catalytic activity. Guanosine-based hydrogels can be exploited for biosensing and bioseparation by linking different enzymes and DNAzymes for enzyme-triggered controllable release of drug molecules at specific sites. Moreover, the guanosine hydrogel can be applied for encapsulation of proteins, peptides, and peptide derivatives that are promising adjuvants; thus, supramolecular hydrogels can be useful for enhancing the potency of vaccines or cancer immunotherapeutics. Moreover, different types of nanomaterials like nanoparticles, nanosheets, nanotubes, and quantum dots can also be incorporated inside the fibrillar matrices of guanosine-based hydrogels to formulate gel nanocomposites that may have widespread applications in catalysis, optoelectronics, and biomedicinal research. The gel nanocomposites can also be prepared with biomaterials such as DNA, proteins, lipids, etc. to develop nanobiocomposites having potential applications in gene therapy and anticancer treatment. Guanosine hydrogel based magnetonanocomposites may be suitable for targeted drug delivery in response to magnet stimuli. Recently, there has been an urgent need to develop efficient antimicrobial agents effective against multidrug-resistant bacteria. Guanosine gel-based nanocomposites composed of different metal ions can provide useful insights into the development of antibacterial hydrogels. Another potential area that needs attention is the development of hydrogel systems made from other nucleosides and different combination of nucleosides by utilizing both canonical and non-canonical base pairing. Because nucleosides are expected to have different coordination abilities with different metal ions, they can be used to generate a wide variety of hydrogels that would find promising applications in therapeutics and medicinal research. The stimuli-controlled self-assembling property of the hydrogel systems could be exploited to provide a platform for devising gel-based biomolecular logic gates. The canonical and noncanonical base-pairing abilities of different nucleosides and in-depth understanding of the underlying principles of their self-assembly processes would pave the way for the construction of advanced functional materials.

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