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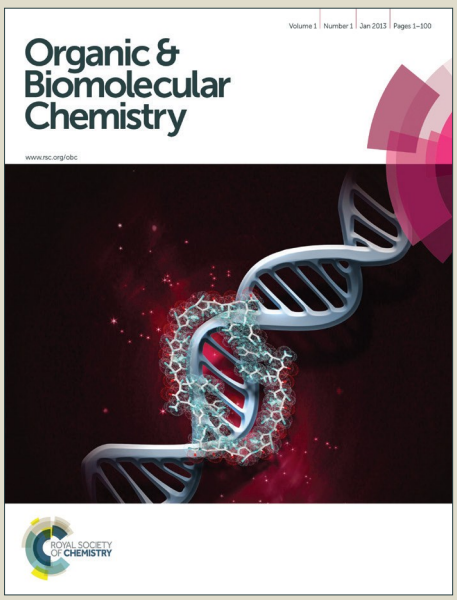

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Guanine-quartet derived functional architectures

Jyotirmayee Dash,*[a] and Puja Saha[a]

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This perspective is intended to light upon the recent developments in the design and construction of functional materials such as supramolecular hydrogels and ion channels using guanine motif as a self-assembling building block.

Introduction

Self-assembly has imparted life in non-living molecules, where biomolecules self-assemble into versatile polymeric structures with diverse and important functions in living systems.[1] For instance, the nucleotides form functional nucleic acids DNA and RNA. The nucleic acids exhibit structural and conformational diversity as the nucleobases recognize through specific H-bonding such as adenine combines with thymine (or uracil) and guanine combines with cytosine in a Watson-crick hydrogen bonding manner.[2] In addition to the conventional duplex structure, guanine rich DNA sequences can adopt four stranded higher order structures, called G-quadruplexes (**Fig. 1a**).[3] G-quadruplex structures are known to form in the regions of biological significance, such as human telomeres[4] and oncogene promoters.[5] It has been shown that G-quadruplexes present in the promoters (such as *c-MYC*, VEGF, *K-RAS*, *BCL-2*, *c-KIT* etc.) can regulate expression of various genes and those present in the human chromosome ends can maintain the telomere length and hence the aging.[6] Therefore, DNA G-quadruplexes have recently emerged as potential new class of targets for the development of anticancer drugs.[3,6] G-quadruplex motifs are also prevalent in RNAs and play key regulatory roles in regulating pre-mRNA processing and mRNA translation.[7]

The G-quadruplexes consist of guanine-quartet (G-quartet, also known as G-tetrad)[8] as the basic building block, a square-planar arrangement of four guanine motifs connected through hydrogen bonds between complementary Watson–Crick and Hoogsteenedges of neighbouring guanines (**Fig. 1b**). G-quadruplex structures are generated by a core of two or more π–π stacked G-quartets (**Fig. 1a**) and further stabilized by monovalent cations (typically Na^+, K^+) that occupy the central cavities between the stacks.[6] G-quadruplexes can be formed intramolecularly with one G-rich strand or intermolecularly with two or four strands. The intramolecular G-quadruplexes are comparatively stable and highly polymorphic leading to varied biological roles.[6] Given the potential role of G-quadruplexes in regulating gene expression and telomerase activity, several small molecule ligands have been designed and synthesised over the past decade that could open up a new avenue for the discovery of novel anticancer agents. Therefore, a variety of natural and synthetic compounds with the ability to bind and stabilize the G-quadruplex structures have been developed.[3a,6] Furthermore, the creative assembly of G-quadruplex through supramolecular organization of guanosine subunits has fashioned a plethora of complex nanostructures with precisely controlled size, shape and spatial functionalization.[9]

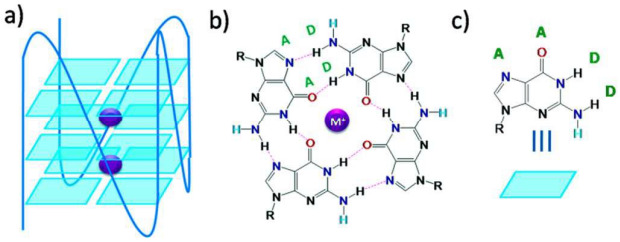

Figure 1. a) G-quadruplex, b) G-quartet. c) Guanine motif.

On the other hand, guanine derivatives can mimic G-quartet structures that subsequently self-assemble to construct synthetic G-quadruplexes.[3,10] Over the years, the Gottarelli, Spada and Davis groups have significantly contributed to the supramolecular self-assembly of guanosine derivatives.[10] Guanine derivatives are able to form a variety of stable and ordered assemblies in water as well as in organic solvents in the presence of alkali-metal cations.[11] The supramolecular architectures formed in water are mainly of G-quartet based assemblies; whereas the assemblies resemble ribbons, sheets and helical architectures in organic solvents.[10h] Self-assembly of guanine derivatives has been used a strategy

[a] Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata-700032, India. Email: ocjd@iacs.res.in

for developing useful systems such as selective metal ion binder,[12a,b] water templated ion pair receptor,[12c] molecular electronic devices,[12d-f] dendrimers,[12g] organogels,[12h-j] hydrogels,[13-25] ion transporters,[26-30] etc. In this perspective, we will describe recent developments in G-quartet based functional bio-materials such as hydrogels and ion-channels.

Guanine derived hydrogels: Hydrogel technology offers a promising platform in a wide range of clinical applications such as tissue engineering, cellular immobilization, separation of bio-molecules and controlled release of bioactive substances as well as targeted drug delivery.[31] In particular; much emphasis has been given on supramolecular hydrogels with biocompatible and biodegradable molecules as the principal components.[32] Supramolecular hydrogels involve non-covalent interactions such as H-bonding, π-π stacking, van der Waals forces and hydrophobic interactions. Guanine, being a natural nucleobase, is undoubtedly an important building block for making supramolecular hydrogels.[33] The origin of guanine hydrogels can be traced back to 1910, when Bang reported that 5′-guanosine monophosphate (5′-GMP) **1** forms gelatinous aggregates at higher concentrations (**Fig. 3**).[34] In 1962 Gellert *et. al.* found that the gel network contains macrocyclic G-quartet building blocks.[8] The unusual ability of guanine derivatives to form planar G-quartet structures by means of Hoogsteen type hydrogen bonding and subsequent assembly into columnar aggregates by π-π stacking, offers the possibility of generating tunable three-dimensional highly cross-linking fibrillar network.[13-25] This type of fibrous network is able to entrap large amount of water that leads to the formation of self-standing and self-supporting hydrogels (**Fig. 2**). Moreover, the gelation property can be tuned by external stimuli like pH, temperature, constituents and ions.

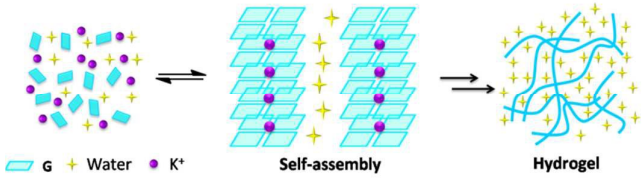

Figure 2. Schematic representation of entrapment of water by the ordered self-assembly of guanosines. The formation of entangled fibrous network gives rise to self-supporting hydrogels.

Lehn and Sreenivasachary employed Dynamic Covalent Chemistry (DCC)[35] to construct thermodynamically stable dynamic G-quartet hydrogels.[13] They reported a Dynamic Combinatorial Library (DCL) consisting of guanosine hydrazide **2** (**Fig. 3**) and various aldehydes that can undergo a reversible acylhydrazone formation reaction. The resulting DCL of G-quartet acylhydrazones provide the most stable hydrogels in the presence of cations by selecting the optimal aldehyde component.[14] They have further demonstrated that guanosine-5′-hydrazide **2** hydrogel network is capable of releasing biologically interesting molecules, such as acyclovir, vitamin C, and vancomycin.[15] The Lehn group also developed a dynamic hydrogel system using a ditopic guanine derivative **3** that can undergo cyclic sol-gel transition, driven by reversible uptake and release of K^+ ion.[16] The bis-guanine **3** forms stable gels in the presence of K^+ ions. A cryptand (an ionophore) pulls out K^+ from the G-quartet hydrogel network and transforms it into soluble polymeric fibres. Upon protonation, the cryptand releases K^+ and regenerates the gel. The cyclic conversion of cryptand into protonated and deprotonated form triggers the dynamic gel-sol inter-conversion over multiple cycles by simply controlling the incorporation of K^+ ion into G-quartet.

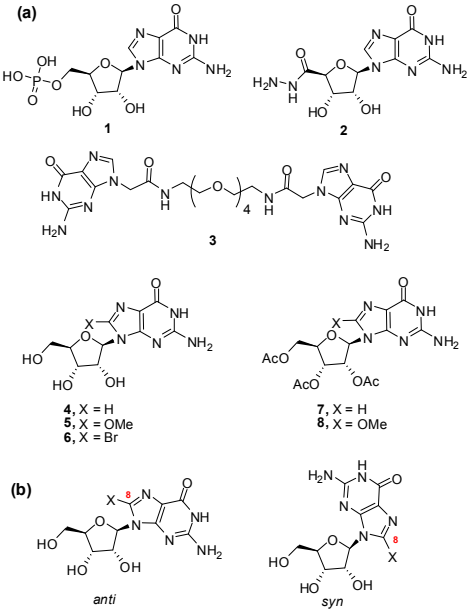

Figure 3. (a) Guanine derivatives used for the preparation of hydrogels. (b) *Anti* and *syn* conformations of guanosine.

Gelation occurs through the formation of the G-quartet and its subsequent self-assembly into columnar stacks (**Fig. 2**).[17] The hydrogels are typically obtained at low temperature and acidic pH. The requirement of high salt concentrations and specific pH values for gelation hamper the potential applications of guanosine gels for *in vivo* applications. Furthermore, the gels have poor lifetime stability as they collapse due to crystallization of guanosine in aqueous KCl solutions.

The McGown, Rowan and Dash groups have reported two-component hydrogel systems to improve the stability of guanosine derived hydrogels.[18-22] McGown and co-workers have developed two-component hydrogels formed by mixtures of hydrophobic guanosine **4** and hydrophilic 5′-GMP **1** in the presence of K^+ ions.[18] The nucleotide 5′-GMP is highly soluble at neutral pH (pH = 7) and it does not form a gel, while guanosine is insoluble to form a stable gel even in the presence of high salt concentrations. They have proposed that 5′-GMP helps to solubilise insoluble guanosine and the insolubility of guanosine promotes gelation of 5′-GMP at lower concentrations. This binary system can form stable gels over a

temperature range that can be tuned by varying the relative proportions of guanosine and 5'-GMP in the mixture.

Rowan and co-workers have subsequently developed guanosine derived gels by mixing a guanosine-derived non-gelator 2',3',5'-tri-O-acetylguanosine **7** (**Fig. 3**) with guanosine **4** in potassium chloride solution to maintain heterogeneity that disfavour crystallization.[19] The resulting hydrogels are transparent and stable for a longer period. The physico-mechanical and morphological properties of guanosine based hydrogels could be significantly controlled by changing the ratio of gel components. For example, atomic force microscopy (AFM) and small-angle neutron scattering (SANS) measurements revealed that the length and thickness of gel fibres can be manipulated by varying the content of **7**.[20]

Generally, guanosine exists in the *anti*-conformation but adopts the *syn*-conformation in self-assembly to form a G-quartet (**Fig. 3b**).[36] Rowan group reported that 8-substituted guanosine derivatives predominantly exist as the *syn*-conformation and therefore, they are more prone to self-assemble and form gels at biologically relevant low salt concentrations.[21] They have reported that 8-methoxy guanosine derivative **8** forms stable gels at low gelator concentrations in saline solutions (0.5 wt%) and in cell media. The gelator **8** is non-toxic to cells and suitable for tissue engineering. The gel properties of **8** can be easily tuned by forming co-gels with **7**. Recently, the Rowan group has established that guanosine derived polymers can be used as cross-linking units to enhance the mechanical properties of the this low molecular weight gelator **8** in a concentration dependent manner.[21b]

Our group reported a two-component guanosine hydrogel system comprising of guanosine (**4**) and 8-bromoguanosine (**6**) with potassium as the stabilizing cation. Both **4** and **6** can independently form hydrogels, however both the gels are unstable as they crystallize.[22] However, the mixtures of **4** and **6** are able to form self-standing transparent and stable hydrogels within a wide range of their ratio compositions. VT-NMR spectroscopy revealed that **6** is a comparatively better gelator than **4**. The gel formation could be initiated by columnar stacking of hybrid G-quartets and subsequent lateral association of the columnar stacks into interconnected gel network. The composition-dependent evolution of the gel nanostructures has been studied using TEM and AFM experiments (**Fig. 4**). This two component gel system can be used for diffusion and controlled release of dyes like rhodamine-6-G, fluorescein and rose bengal, suggesting its bio-medical applications. It is noteworthy that the gel itself does not show any birefringence but it exhibits birefringence in the presence of dyes. These stable and transparent guanosine-bromoguanosine hydrogels are expected to have potential applications in optical devices and biomolecular imaging. Recently self-assembly of guanosine and deoxy-guanosine has been reported to form stable hydrogels with self-healing properties.[23]

Dash *et al* has demonstrated that silver ion-mediated self-assembly of 5'-GMP (**1**) can be used to generate a supramolecular hydrogel system.[24] The physico-mechanical property of the Ag-GMP gel can be finely tuned by modulating the GMP:Ag molar ratios. Additionally, the system presents potential applications in the development of molecular sensors as the fibrilar network of Ag-GMP is capable of binding cationic dyes such as methylene blue and Hoechst-33258. Protein molecule such as cytochrome c can be immobilized within the Ag-GMP hydrogels without loss of enzymatic activity.

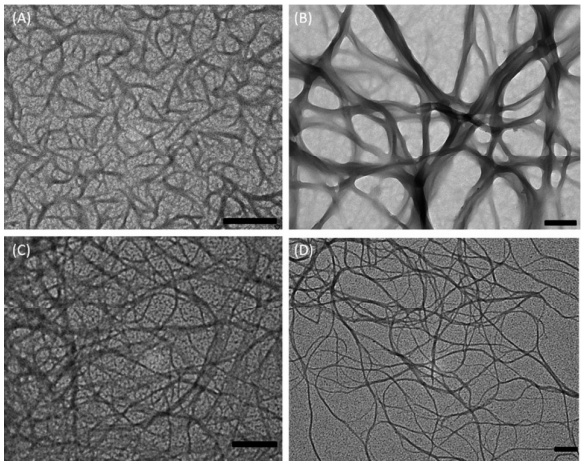

Figure 4. TEM image of hydrogels of (A) G, (B) BrG, (C) G.BrG [1:1] and (D) G.BrG [1:2]; scale bar: 200 nm (Adapted from reference 22).

Another fascinating G-quartet derived supramolecular hydrogel system has recently been developed by the Davis group by mixing guanosine **4** with 0.5 equiv of $KB(OH)_4$ (**Fig. 5**).[25] The borate anions solubilise **4** and react with it to form covalent borate monoester and diastereomeric borate diesters **9** and **10**. These diesters (**9** and **10**) self-assemble in the presence of K^+ to give stable hydrogels. The resulting guanosine–borate hydrogel system binds cationic dye methylene blue and selectively incorporates nucleosides. This gel system might be useful in generating sensors and drug delivery systems.

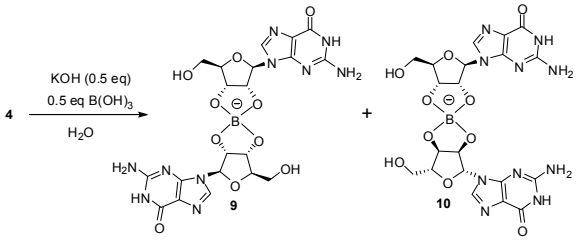

Figure 5. Formation of diastereomeric borate diesters.

These studies demonstrate that the guanine derived hydrogels can be used for versatile applications. However, so far only a few guanine derivatives (**Fig. 3**) have been used to prepare hydrogels. The scope of the guanine-based gelators should be expanded for specific applications such as drug delivery, tissue engineering and nanoscale devices. Furthermore, the gel elasticity and long-term stability should

be improved by incorporating suitable co-gelators or developing multi-component hydrogel-constructs.

Guanosine derived ion-channels: Biological ion channels, primarily constitutive of transmembrane proteins, regulate osmosis and transportation of ionic and non-ionic substances.[37] The structural aspects of ion channels have been mimicked to devise functional materials with wide application as drug delivery systems, antimicrobial agents and biosensors.[38] Artificial ion channels have been made from peptides, proteins and DNA structures. There are several naturally occurring and a growing number of unnatural small molecules that show ion channel activity.[38] Despite continuous progress in developing synthetic ion channels, the fundamental problems like simple synthetic access, modulation of pore size and ion selectivity, voltage and ligand gating, as well as channel blockage by specific inhibitory compounds, need to be addressed.

The Hoogsteen hydrogen bonded macrocyclic G-quartet has drawn attention in devising supramolecular ion channels across lipid bilayers. The Davis group have reported a synthetic unimolecular G-quadruplex that transports Na^+ across a phospholipid bilayer.[26] The unimolecular G-quadruplex was obtained via olefin metathesis based post-modification of the artificial G-quadruplex that was assembled from the lipophilic guanosine **11** containing terminal alkene groups (**Fig. 6a**). In the same year, Matile and Kato groups reported that a folate dendrimer **12** could induce long-lived single-channel currents after insertion in lipid bilayers.[27] Folic acid contains similar H-bonding motif as in guanine and the dendrimer **12** can self-assemble to form π-stacked rosettes with ionophoric properties (**Fig. 6b**). Recently Simeone *et al.* reported synthesis of a variety of amphiphilic guanosine derivatives that exhibit ion transportation properties.[12i]

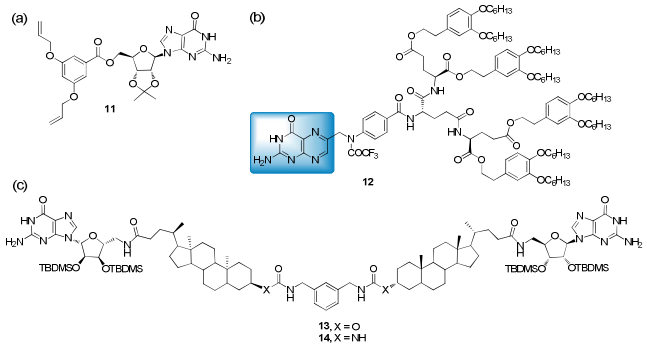

Figure 6. (a) *Meta*-substituted allyl ethers containing guanosine derivative; (b) A folate dendrimer and(c) Ditopic guanosine-sterol conjugates.

Davis and co-workers reported the ability of ditopic guanosine–bile acid conjugates **13** and **14** to form ion channels across a phospholipid membrane (**Fig. 6**).[28,29] Previously the Lehn[16] and Barboiu[39] groups have shown that ditopic guanosine derivatives can self-assemble in the presence of potassium ions to create functional supramolecular materials. The nucleoside-sterol conjugates are composed of two guanosine groups connected by bis-lithocholate linkers (**Fig. 6c**), which upon G-quartet formation and subsequent stacking interaction form ion channels with large, stable and functional pores in the membrane. The existence of these prototypes suggests the potential for guanosine derivatives to perform ion channel-like functions in the membrane.

We envisaged developing an ion channel platform using a modular synthetic approach based on Cu(I) catalysed azide and alkyne cycloaddition involving lipophilic guanosine azide and guanosine alkyne building blocks. The diguanosine derivatives would form membrane-spanning pores that would establish some structure-activity relationships of the guanosine-based ion channels through covalent tethering of a variety of linkers between two guanosine units. As a proof of the principle, we synthesized four diguanosine derivatives (**Fig. 7**) that involve click reaction between i) guanosine derived azide building block **15** and dialkyne linkers (**17, 18**) and ii) guanosine derived alkyne building block **16** and diazide linkers (**19, 20**).[30]

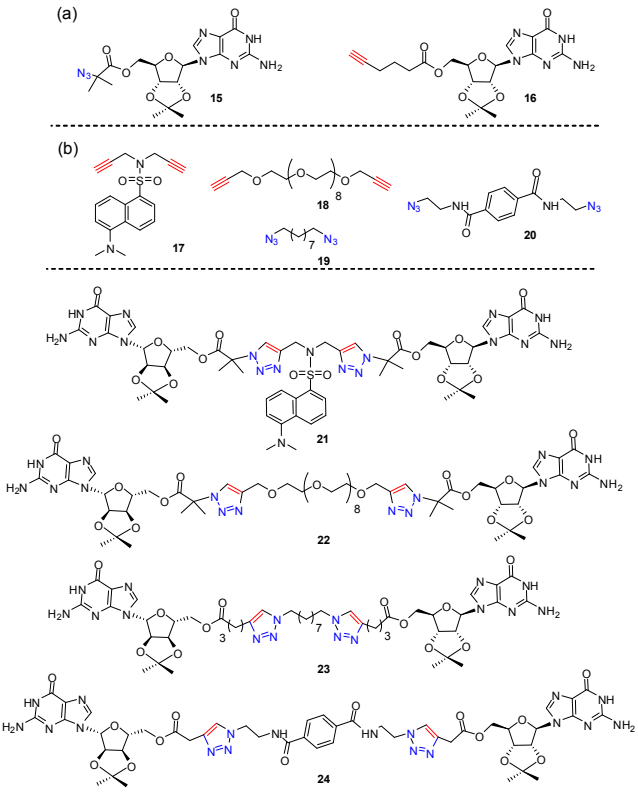

Figure 7. (a) Azido and alkyne functionalized guanosine derivatives, (b) dialkyne and diazide linkers (c) Bis-triazolyl diguanosine derivatives.

The azido functionalized guanosine **15** is reacted with fluorescent dansyl **17** and amphiphilic polyethylene glycol (PEG) **18** dialkyne linkers to afford diguanosine derivatives **21** and **22** in high yields (**Fig. 7b**). The reaction of alkyne functionalized guanosine **16** with the diazide linkers **19** and **20**

provides diguanosine derivatives (**23, 24**) containing lipophilic alkyl group and phenylene dicarboxamide, respectively.

Single channel analysis using voltage-clamp experiments revealed that all the four diguanosine derivatives **21-24** form ion channels in K^+ buffer across the planar bilayer. The PEG formed ~ 50% channels with conductance values of 2-5 nS (life time of 5 seconds) and ~ 20% channels with conductance values of 1-2 nS. The channels formed by diguanosine derivatives **23** and **24** showed well-defined currents with conductance values of 1-2 nS. The fluorescent dansyl guanosine derivative **21** showed nearly 60% channels with conductance values of < 0.1 nS and 36.1% of the channels with conductance values of 0.1-0.5 nS. These results indicate that the conductance values and the pore size can be modulated by varying the clickable linker between the two guanosine units.

Moreover, the PEG linked diguanosine derivative **22** does not exhibit any appreciable conductance in $MgCl_2$ and $CaCl_2$ containing buffers while it shows well defined currents for monovalent cations Na^+ (1-5 nS conductance values), K^+ (2-5 nS) and Cs^+ (1-2 nS). These results are suggestive of the presence of G-quartet assembly in the bilayer, as G-quartet is known to be stabilized by monovalent cations. The diguanosine derivatives self-assemble into 'barrel stave' type ion channels in the presence of monovalent ions (**Fig. 8**). We have further shown that the ion channel activity of **22** can be inhibited by the addition of cytosine, which possibly distorts the quartet assembly in the membrane (**Fig. 9**).

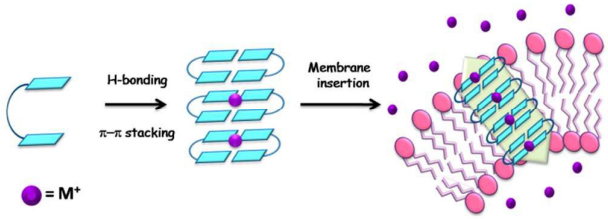

Figure 8. Self-assembly of diguanosine derivative through H-bonding and π-π stacking interactions to generate barrel-stave type ion channels across lipid bilayer.

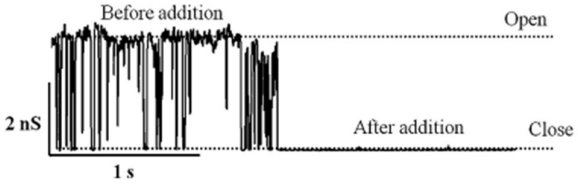

Figure 9. Formation and inhibition of ion channel formed from **22** (Adapted from reference 30).

Most synthetic channels have been prepared using multistep linear synthesis with low overall yields. Our results broaden the choice of specific spacer to allow spacer-modulated ions transportation by changing the pore size and conductance. It is noteworthy to mention that the fluorescent labeled guanosine derivatives can be used for the visualisation of synthetic ion channels in the lipid bilayer. Moreover the inhibition of ion channels can enable a new approach to control the flow of ions that can enable preparation of gated ion channels. It can be proposed that synthesis of versatile amphiphilic diguanosine derivatives by varying the length of the linkers may lead to increased diversity in ion channel properties like high conductance values, controlled opening of the functional pores and transportation of larger biomolecules across the liposomes and cell. Inspired from the guanine self-assembly, utilization of other nucleobases in supramolecular chemistry can be used for devising DNA-inspired synthetic ionophores.[40]

Conclusions and Outlook

This perspective highlights recent examples, illustrating the attractive features of guanine derivatives as promising molecular templates in "bottom-up self-assembly" to design functional materials such as hydrogels and ion channels. In these bio-materials, guanine derivatives for their self-complementary hydrogen bonding edges and aromatic surfaces provide programmability to build complex supramolecular structures under appropriate conditions, using multiple non-covalent interactions such as Hoogsteen type H-bonding, metal coordination and π-π stacking.

Although G-quartet hydrogels are known for a very long time, only a few recent studies demonstrate their potential applicability for tissue engineering and devising birefringent materials and sensors. New guanine derived hydrogelators and hybrid multi-component hydrogel-constructs with complex morphologies and tunable properties need to be engineered for the development of drug delivery systems for biomedical applications. Similarly, appropriate design of synthetic ion channels may enable interesting and many untapped opportunities for programming antimicrobials, drug delivery systems, sensors and more. In addition, self-assembly of guanine derivatives connected to nanoparticles[41] is an unexplored area that may provide a platform for constructing functional nanomaterials.

We anticipate that synthetic modifications of guanine derivatives would enable construction of tailor-made bio-inspired supramolecular assemblies of greater flexibility and complexity in both structure and function. And such guanine assemblies have a lot of potential to open up new possibilities of systematic fabrication of diverse architectures and materials that would be useful for future development in supramolecular engineering, biomaterials design, catalysis, sensing, imaging and drug delivery.

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References

1 (a) J.-M. Lehn, *Science*, 2002, **295**, 2400; (b) G. M. Whitesides and B. Grzybowski, *Science*, 2002, **295**, 2418.
2 J. D. Watson and F. H. C. Crick, *Nature*, 1953, **171**, 737.
3 S. Neidle and S. Balasubramanian, Quadruplex Nucleic Acids., RSC, Cambridge, UK, 2006.
4 A. M. Zahler, J. R. Williamson, T. R. Cech and D. M. Prescott, *Nature*, 1991, **350**, 718.
5 V. S. Chambers, G. Marsico, J. M. Boutell, M. Di Antonio, G. P. Smith and S. Balasubramanian, *Nat. Biotechnol*., 2015, **33**, 877.
6 For reviews see: (a) Y. Qin and L. H. Hurley, *Biochimie,* 2008, **90**, 1149; (b) S. Balasubramanian, L. H. Hurley and S. Neidle, *Nat. Rev. Drug Discovery,* 2011, **10**, 261; (c) D. Monchaud and M. -P. Teulade-Fichou, *Org. Biomol. Chem.,* 2008, **6**, 627; (d) A. De Cian, L. Lacroix, C. Douarre, N, Temime-Smaali, C. Trentesaux, J.-F.Riou c, J.-L. Mergny, *Biochimie*. 2008, **90**, 131; (e) G. W. Collie and G. N. Parkinson, *Chem. Soc. Rev.,* 2011, **40**, 5867; (f) S. A. Ohnmacht and S. Neidle, *Bioorg. Med. Chem. Lett.,* 2014, **24**, 2602; (g) P. Murat and S. Balasubramanian, *Curr. Opin. Genet. Dev.* 2014, **25**, 22.
7 A. Bugaut and S. Balasubramanian, *Nucleic Acids Res.,* 2012, **40**, 4727.
8 M. Gellert, M. Lipsett and D. Davies, *Proc. Natl. Acad. Sci. USA.*, 1962, **48**, 2013.
9 (a) J. Choi and T. Majima, *Chem. Soc. Rev.,* 2011, **40**, 5893; (b) L. A. Yatsunyk, O. Mendoza and J. L. Mergny, *Acc. Chem. Res.*, 2014, **47**, 1836; (c) Y. Tang, B. Ge, D. Sen and H.-Z. Yu, *Chem. Soc. Rev.,* 2014, **43**, 518; (d) F. Wang, X. Liu and I. Willner, *Angew. Chem. Int. Ed*., 2015, **54**, 1098.
10 (a) G. Gottarelli, G. P. Spada and A. Garbesi, in *Comprehensive Supramolecular Chemistry – Vol. 9 - Templating, Self-assembly and Self-organisation*, ed. J.-M. Lehn, J.-P. Sauvage, M. W. Hosseini, Pergamon, Oxford, 1996, ch. 13; (b) G. Gottarelli and G. P. Spada, *Chem. Rec.*, 2004, **4**, 39; (c) G. P. Spada and G. Gottarelli, *Synlett*., 2004, **4**, 596; (d) J. T. Davis, *Angew. Chem. Int. Ed.,* 2004, **43**, 668; (e) S. Sivakova and S. J. Rowan, *Chem. Soc. Rev*., 2005, **34**, 9; (f) J. L. Sessler, C. M. Lawrence and J. Jayawickramarajah, *Chem. Soc. Rev*., 2007, **36**, 314. (g) J. T. Davis and G. P. Spada, *Chem. Soc. Rev.*, 2007, **36**, 296; (h) S. Lena, S. Masiero, S. Pieraccini, and G. P. Spada, *Chem. Eur. J.*, 2009, **15**, 7792.
11 (a) G. Gottarelli, S. Masiero, G. P. Spada, *J. Chem. Soc. Chem. Commun.,* 1995, 2555; (b) J. T. Davis, S. Tirumala, J. Jenssen, E. Radler, D. Fabris, *J. Org. Chem.,* 1995, **60**, 4167.
12 (a) M. M. Cai, A. L. Marlow, J. C. Fettinger, D. Fabris, T. J. Haverlock, B. A. Moyer and J. T. Davis, *Angew. Chem. Int. Ed.*, 2000, **39**, 1283; (b) F. W. van Leeuwen, W. Verboom, X. Shi, J. T. Davis and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 2004, **126**, 16575; (c) F. W. Kotch, V. Sidorov, K. Kayser, Y. F. Lam, M. S. Kaucher, H. Li and J. T. Davis, *J. Am. Chem. Soc.*, 2003, **125**, 15140; (d) R. Rinaldi, E. Branca, R. Cingolani, S. Masiero, G. P. Spada and G. Gottarelli, *Appl. Phys. Lett.,* 2001, **78**, 3541; (e) R. Rinaldi, G. Maruccio, A. Biasco, V. Arima, R. Cingolani, T. Giorgi, S. Masiero, G. P. Spada and G. Gottarelli, *Nanotechnology*, 2002, **13**, 398; (f) G. Maruccio, P. Visconti, V. Arima, S. D'Amico, A. Biasco, E. D'Amone, R. Cingolani, R. Rinaldi, S. Masiero, T. Giorgi and G. Gottarelli, *Nano Lett.*, 2003, **3**, 479; (g) J. E. Betancourt, J. M. Rivera, *Org. Lett.*, 2008, **10**, 2287; (h) B. Buchs, W. Fieber, F. Vigouroux-Elie, N. Sreenivasachary, J. M. Lehn and A. Herrmann, *Org. Biomol. Chem.*, 2011, **9**, 2906; (i) L. Simeone, D. Milano, L. De Napoli, C. Irace, A. Di Pascale, M. Boccalon, P. Tecilla, and D. Montesarchio, *Chem.-Eur. J*., 2011, **17**, 13854; (j) T. Giorgi, F. Grepioni, I. Manet, P. Mariani, S. Masiero, E. Mezzina, S. Pieraccini, L. Saturni, G. P. Spada and G. Gottarelli, *Chem.-Eur. J.*, 2002, **8**, 2143.
13 N. Sreenivasachary and J. M. Lehn, *Proc. Natl. Acad. Sci. USA.*, 2005, **102**, 5938.
14 B. Buchs, W. Fieber, F. Vigouroux-Elie, N. Sreenivasachary, J. M. Lehn and A. Herrmann, *Org. Biomol. Chem*., 2011, **9**, 2906.
15 N. Sreenivasachary and J. M. Lehn, *Chem. Asian. J.*, 2008, **3**, 134.
16 A. Ghoussoub and J. M. Lehn, *Chem. Commun.*, 2005, 5763.
17 P. Mariani, F. Ciuchi and L. Saturni, *Biophys. J.*, 1998, **74**, 430.
18 Y. Yu, D. Nakamura, K. DeBoyace, A. W. Neisius and L. B. McGown, *J. Phys. Chem. B.*, 2008, **112**, 1130.
19 L. E. Buerkle, Z. Li, A. M. Jamieson and S. J. Rowan, *Langmuir*, 2009, **25**, 8833.
20 Z. Li, L. E. Buerkle, M. R. Orseno, K. A. Streletzky, S. Seifert, A. M. Jamieson and S. J. Rowan, *Langmuir*, 2010, **26**, 10093.
21 (a) L. E. Buerkle, H. A. von Recum and S. J. Rowan, *Chem. Sci.*, 2012, **3**, 564. b) A. E. Way, A. B. Korpusik, T. B. Dorsey, L. E. Buerkle, H. A. von Recum and S. J. Rowan, *Macromolecules*, 2014, **47**, 1810.
22 R. N. Das, Y. P. Kumar, S. Pagoti, A. J. Patil and J. Dash, *Chem.-Eur. J.*, 2012, **18**, 6008.
23 B. Adhikari, A. Shah and H.-B. Kraatz, *J. Mater. Chem. B*, 2014, **2**, 4802.
24 J. Dash, A. J. Patil, R. N. Das, F. L. Dowdall and S. Mann, *Soft Matter*, 2011, **7**, 8120.
25 (a) G. M. Peters, L. P. Skala, T. N. Plank, B. J. Hyman, G. N. Manjunatha Reddy, A. Marsh, S. P. Brown and J. T. Davis, *J. Am. Chem. Soc.*, 2014, **136**, 12596; (b) G. M. Peters, L. P. Skala, T. N. Plank, H. Oh, G. N. Manjunatha Reddy, A. Marsh, S. P. Brown, S. R. Raghavan and J. T. Davis, *J. Am. Chem. Soc.*, 2015, **137**, 5819.
26 M. S. Kaucher, W. A. Harrell, Jr. and J. T. Davis, *J. Am. Chem. Soc.*, 2006, **128**, 38.
27 N. Sakai, Y. Kamikawa, M. Nishii, T. Matsuoka, T. Kato and S. Matile, *J. Am. Chem. Soc.*, 2006, **128**, 2218.
28 L. Ma, M. Melegari, M. Colombini and J. T. Davis, *J. Am. Chem. Soc.*, 2008, **130**, 2938.
29 L. Ma, W. A. Harrell, Jr. and J. T. Davis, *Org. Lett.*, 2009, **11**, 1599.
30 Y. P. Kumar, R. N. Das, S. Kumar, O. M. Schütte, C. Steinem and J. Dash, *Chem. Eur. J.*, 2014, **20**, 3023.
31 For reviews on applications of supramolecular hydrogels, (a) N. M. Sangeetha and U. Maitra, *Chem. Soc. Rev.*, 2005, **34**, 821; (b) A. R. Hirst, B. Escuder, J. F. Miravet, and D. K. Smith, *Angew. Chem. Int. Ed.*, 2008, **47**, 8002; (c) K. J. Skilling, F. Citossi, T. D. Bradshaw, M. Ashford, B. Kellam and M. Marlow, *Soft Matter*, 2014, **10**, 237; (d) H. K. Lau and K. L. Kiick, *Biomacromolecules*, 2015, **16**, 28.
32 For reviews on supramolecular hydrogels, (a) L. A. Estroff and A. D. Hamilton, *Chem. Soc. Rev.,* 2004, **104**, 1201; (b) J. W. Steed, *Chem. Commun.*, 2011, **47**, 1379; (c) L. E. Buerkle and S. J. Rowan, *Chem. Soc. Rev.* 2012, **41**, 6089; (d) G. Yu, X. Yan, C. Han and F. Huang, *Chem. Soc. Rev.*, 2013, **42**, 6697; (e) S. S. Babu, V. K. Praveen and A. Ajayaghosh, *Chem. Rev*., 2014, **114**, 1973; (f) R. G. Weiss, *J. Am. Chem. Soc*., 2014, **136**, 7519; (g) J. Raeburn, D. J. Adams, *Chem. Commun.* 2014, **51**, 5170.
33 (a) K. Araki and I. Yoshikawa, *Top. Curr. Chem.*, 2005, **256**, 133; (b) X. Du, J. Zhou and B. Xu, *Chem.- Asian J.*, 2014, **9**, 1446.
34 I. Bang, *Biochem. Z.*, 1910, **26**, 293.
35 (a) J. M. Lehn, *Chem. Eur. J.,* 1999, **5**, 2455; (b) J.-M. Lehn and A. V. Eliseev, *Science*, 2001, **291**, 2331; (c) S. Otto, R. L. Furlan and J. K. Sanders, *Curr. Opin. Chem. Biol.*, 2002, **6**, 321; (d) O.

Ramstrom and J. M. Lehn, *Nat. Rev. Drug Discov.*, 2002, **1**, 26; (e) S. Otto, R. L. Furlan and J. K. Sanders, *Drug Discov. Today*, 2002, **7**, 117; (f) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652; (g) J. M. Lehn, *Chem. Soc. Rev.*, 2007, **36**, 151; (h) R. F. Ludlow and S. Otto, *Chem. Soc. Rev.*, 2008, **37**, 101.

36 R. Stolarski, L. Dudycz and D. Shugar, *Eur. J. Biochem.*, 1980, **108**, 111.

37 B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter, *Molecular Biology of the Cell*, 5th ed., Garland Science: New York, 2007. (b) B. Hille, *Ion Channels of Excitable Membranes*; Sinauer Associates: Sunderland, MA, 2001.

38 For reviews see: (a) A. L. Sisson, M. R. Shah, S. Bhosale and S. Matile, *Chem. Soc. Rev.*, 2006, **35**, 1269.; (b) G. W. Gokel and I. A. Carasel, *Chem. Soc. Rev.*, 2007, **36**, 378; (c) J. K. W. Chui, and T. M. Fyles, *Chem. Soc. Rev.*, 2012, **41**, 148. (d) G. W. Gokel and S. Negin, *Acc. Chem. Res.*, 2013**, 46**, 2824; (e) H. Itoh and M. Inoue, *Acc. Chem. Res.*, 2013, **46**, 1567; (f) J. Montenegro, M. R. Ghadiri and J. R. Granja, *Acc. Chem. Res.*, 2013**, 46**, 2955; (g) M. Langecker, V. Arnaut, J. List and F. C. Simmel, *Acc. Chem. Res.,* 2014, **47**, 1807; (h) M. Langecker, V. Arnaut, T. G. Martin, J. List, S. Renner, M. Mayer, H. Dietz and F. C. Simmel, *Science*, 2012, **338**, 932.

39 C. Arnel-Herault, A. Pasc, M. Michau., D. Cot, E. Petit and M. Barboiu, *Angew. Chem., Int. Ed.,* 2007, **46**, 8409.

40 R. N. Das, Y. P. Kumar, O. M. Schutte, C. Steinem and J. Dash, *J. Am. Chem. Soc.*, 2015, **137**, 34.

41 (a) Z. Li and C. A. Mirkin, *J. Am. Chem. Soc.,* 2005, 127, 11568. (b) Irit Lubitz and A. Kotlyar, *Bioconjugate Chem.,* 2011, **22**, 482. N. Borovok, E. Gillon, and A. Kotlyar *Bioconjugate Chem.,* 2012, **23**, 916.

Biography of authors

Dr. Jyotirmayee Dash obtained her Ph.D. in organic chemistry from the Indian Institute of Technology, Kanpur, with Prof. F. A. Khan. Subsequently she was awarded Alexander von Humboldt fellowship with Prof. H.-U. Reissig, Freie University, Berlin; postdoctoral fellowship with Prof. J. Cossy, ESPCI, Paris and Marie Curie fellowship with Prof. S. Balasubramanian, University of Cambridge, UK. She then joined as an Assistant Professor at the Indian Institute of Science Education and Research-Kolkata in 2009. Presently she is working as an Associate Professor at the Indian Association for the Cultivation of Science-Kolkata. Her research interests include synthesis of natural products, self-assembly of nucleobase and recognition and regulation of nucleic acids.

Puja Saha received her B.Sc. in 2011 and M.Sc. in 2013 from University of Calcutta. She has been enrolled as a Ph.D. student in the group of Dr. Jyotirmayee Dash at the Indian Association for the Cultivation of Science, Kolkata. Her current research interest focuses on targeting G-quadruplex and i-motif DNAs with small molecules.

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