Functionalized base-pairs: versatile scaffolds for self-assembly

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This article discusses the development of synthetic supramolecular systems derived from hydrogen bond driven base-pairing, with a focus on the self-assembly of individual nucleobase analogues.

Introduction

The self-assembly of two single-stranded oligonucleotides into a double stranded helix is driven by many intermolecular forces. These include aromatic π-stacking interactions, hydrophobic forces, van der Waals forces, and hydrogen bonding interactions.[1] Of these forces, the self-complementary Watson–Crick hydrogen-bonding interactions[2] that dictate specific base-pairing are arguably the most crucial for establishing the fidelity required for efficient storage, replication, and transcription of genetic information. The question then arises whether hydrogen bond driven base-pairing can be used for purposes other than those intended by nature. Indeed, base pairing within long chain DNA oligonucleotides and artificial nucleic acid base (''nucleobase'') derived polymeric systems can be used to assemble elegant macroscopic structures. Not surprisingly, these systems are attracting considerable current interest as a result of their possible applications in materials chemistry and nanotechnology.[3] Smaller synthetic systems, of a mainly non-biological nature but also inspired by the complementary hydrogen bonding concept embodied in DNA have also been intensively studied.[4] Our entry into this fascinating branch of supramolecular chemistry came from a desire to use the base-pairing paradigm of individual nucleobases as a means of preparing novel synthetic supra-structures. Other investigators have also taken a similar approach and have succeeded in preparing new synthetic structures, many of which are quite elegant.[5] In this article we will highlight some of these contributions, but will focus primarily on retracing the work carried out in our laboratory.[6]

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Base-pairing allows for versatility

Before discussing the various structural architectures that synthetic chemists can prepare using nucleobases, a review of the base-pairing characteristics of the natural nucleobases is appropriate. This is because, from a design perspective the advantages of base-pair derived systems must be recognized and exploited while the disadvantages must likewise be noted and addressed. From the base-pairing patterns elucidated by Watson and Crick two different base-pairs are available (See Fig. 1). The guanine–cytosine (GC) couple ($K_a \approx 10^3$–10^5 M^{-1} in $CDCl_3$)[7,4g] is significantly stronger than the adenine–thymine/uracil (AT or AU) counterpart ($K_a \approx 10^2$ M^{-1} in $CDCl_3$).[8] Hence, the former three-point H-bonding motif is more attractive for the preparation of synthetic supramolecular assemblies. Thus, a large portion of our work uses the GC hydrogen bonding mode. Nevertheless, elegant structures

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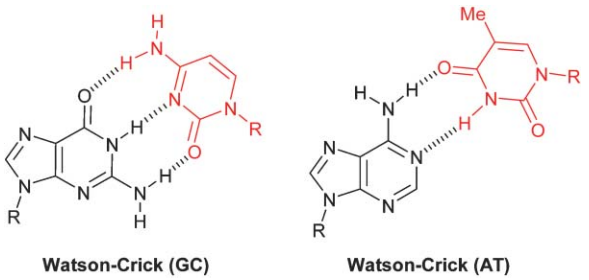

Fig. 1 Canonical Watson–Crick base-pairing modes.

can be formed with AT base-pairs, especially when used in conjunction with other non-covalent interactions or when two or more AT recognition subunits are employed.

Despite the prevalence of Watson–Crick base-pairing within a DNA duplex, many alternative pairing patterns are possible.[9] Some viable ensembles that can be constructed using non Watson–Crick binding modes are illustrated in Fig. 2. Specific attention must be given to the Hoogsteen binding mode that utilizes the C6–N7 face of purine nucleosides.[10] This hydrogen bonding motif is prevalent in DNA and RNA suprastructures and is also found in many protein–DNA and drug–DNA interactions. Other non Watson–Crick base-pairing motifs include the wobble (or mismatched) base-pairs and various homo dimers (self-pairing). The conformation of the sugars with respect to a base-pair (*i.e.*, *cis* or *trans* conformation with regard to the sugar on the complementary nucleobase) can also lead to variant base-pairing modes. For example, the 'reverse' base-pairing mode is defined by a *trans* conformation of the two sugar moieties. Such a conformation can lead to reverse Watson–Crick (see Fig. 2) and reverse Hoogsteen base-pairing modes. Other dimeric binding modes are also possible due to tautomerism and ionization of nucleobases, but these are far less prevalent. In addition to base dimerization, individual nucleobases can also form trimers and other higher order oligomers.

As a result of the non Watson–Crick binding modes that can lead to dimerization and oligomerization (*vide supra*), many complications can arise for synthetic chemists trying to assemble discrete ensembles through Watson–Crick interactions alone. However, judicious manipulation of solute concentrations can minimize the formation of non-discrete oligomeric aggregates, since such species are usually favoured at higher nucleobase concentrations. Furthermore, Watson–Crick base-pairing can be selected for by introducing bulky groups close to, or directly on, certain unwanted hydrogen bonding sites.[11] For example, the N7 nitrogen on guanine or adenine can be selectively alkylated, thereby blocking the Hoogtseen face of the purines.[11a] Steric manipulation with regard to the ribose unit can also pre-organize certain types of assemblies over others. For example, introducing a bulky group onto the C8 position of a purine results in a *syn* relationship about the glycosidic bond; this structural constraint allows for the formation of cyclic guanine tetramers (G-quartets). On the other hand, non Watson–Crick binding modes, such as the Hoogsteen motif, can be exploited to assemble architectures that are not possible to access *via* simple Watson–Crick base pairing. Indeed, a number of

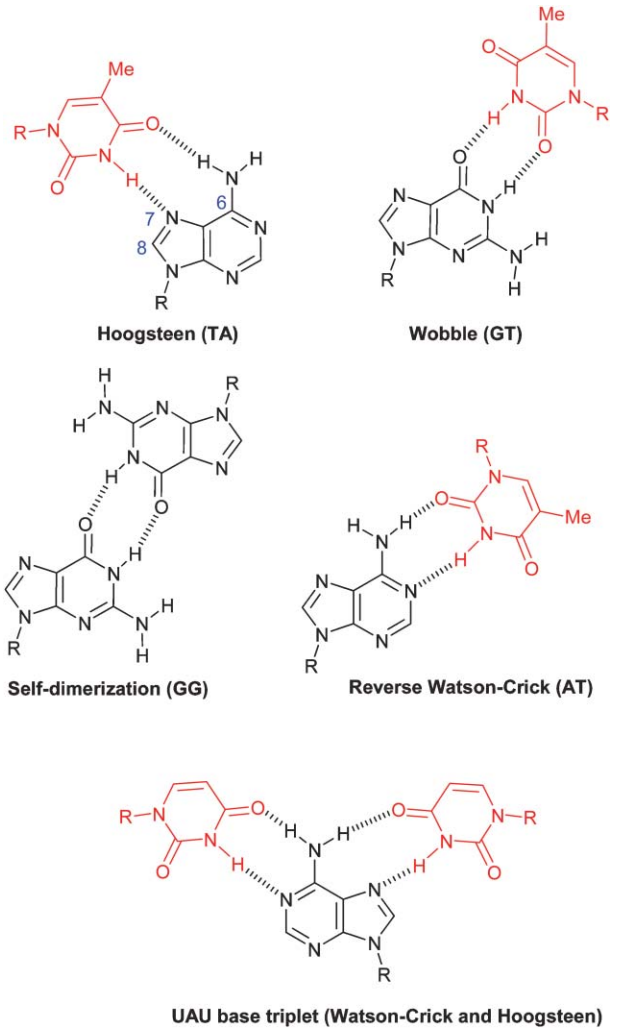

Fig. 2 Some common non Watson–Crick base-pairing modes as well as a base-triplet composed of Hoogsteen and Watson–Crick binding modes.

supramolecular architectures assembled through non Watson–Crick base-pairing interactions will be highlighted in this article.

The choice of solvent is another important factor in the formation of assemblies based on hydrogen bonding. Individual bases do not pair to a large extent in protic solvents due to strong competition for the all-important hydrogen bonding donor and acceptor sites. In fact, the nucleobases tend to stack in columns rather than self-assemble through hydrogen bonds in water. Thus, for the most part, the assembly of individual nucleobase derived systems are carried out in aprotic organic solvents. Unfortunately, the individual bases are not very soluble in these solvents. Thus, methods for enhancing the solubility have been developed. These include alkylating the purines and pyrimidines directly with lipophilic "tails" or by using nucleobases bearing sugar residues functionalized with solubilizing groups. For example, protection of the alcohols on the ribose moieties with *tert*-butyldimethylsilyl (TBDMS) groups greatly enhances solubility in non-polar, aprotic solvents.

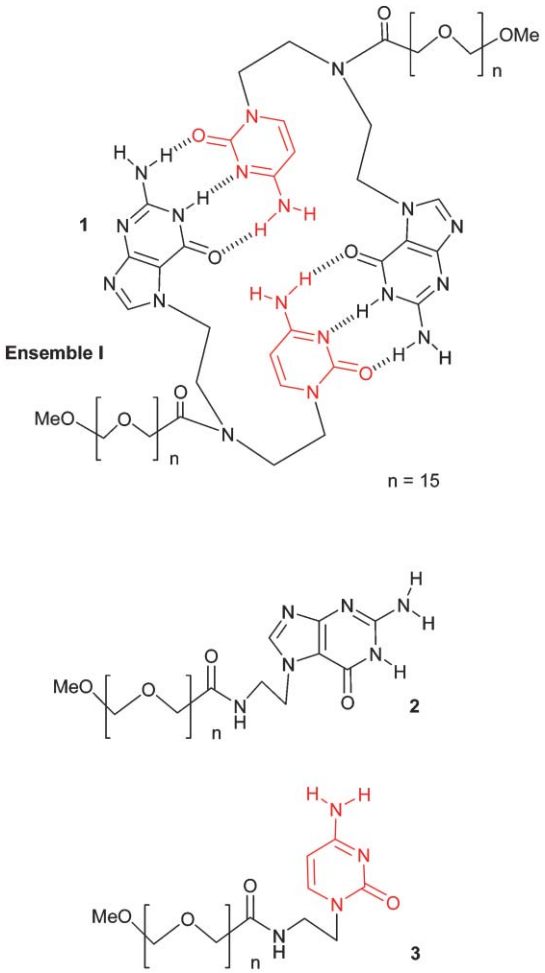

Fig. 3 A duplex of dinucleoside **1** (top) self-assembled to form ensemble **I** through a pair of Watson–Crick bonding modes, and monomeric nucleobases **2** and **3** (bottom).

Development of duplex systems

Early work on individual lipophilic nucleosides verified that these moieties do indeed self-assemble in non-polar organic media *via* Watson–Crick hydrogen bonding.[12] Aware of these seminal studies, we commenced our own work in this area by trying to enhance nucleobase association by preparing dyads that self-assembled through a pair of Watson–Crick GC motifs.[13] Our initial designs, dating to the mid eighties, focused on the base moieties only, leaving out what was at the time considered the "superfluous" sugar functionality. An example is shown in Fig. 3 (ensemble **I**). Here, to enhance the solubility in organic solvents and to preclude any Hoogsteen interactions, the N7 position of the guanine face of **1** was protected with a poly(ethylene glycol) functionalized amide functionality. The other "arm" of this solubilizing bridge was attached to cytosine. Unfortunately, ^{1}H NMR spectroscopic dilution studies in DMSO-d_6 (a competitive solvent) revealed a rather low binding affinity (K_a = 6.8 M^{-1}) that was only slightly enhanced relative to monomeric nucleobases in this same solvent (the K_a for the association of **2** with **3** is 4.7 M^{-1}). The flexibility of the linkers and the low solubility of ensemble **I** in non-polar solvents, such as chloroform, were

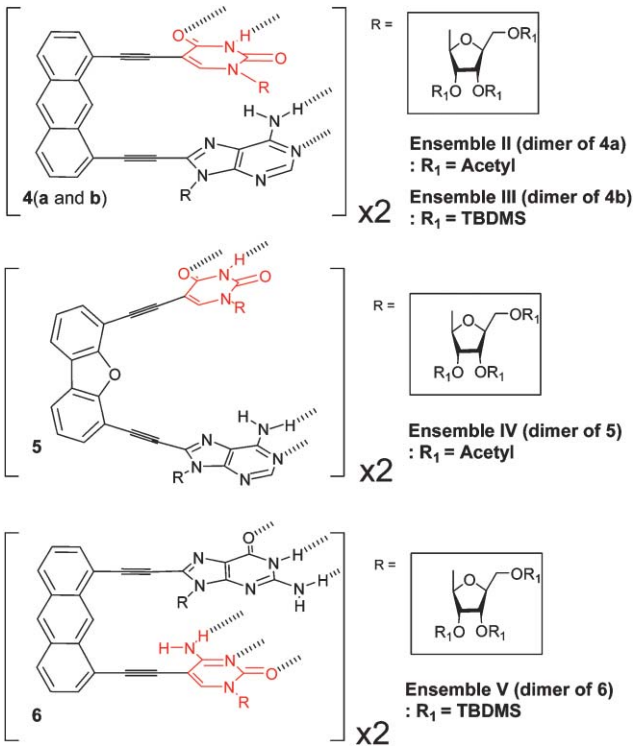

Fig. 4 Second generation duplexes formed through Watson–Crick hydrogen bonding modes.

thought to be responsible for the low self-association seen for this dyad.

To circumvent these problems, a series of second generation dinucleosides (**4**, **5**, and **6**) were prepared.[14] As can be seen from Fig. 4, in these second generation systems the sugar motifs were included, with the pendant alcohol functionalities protected with lipophilic acetyl or TBDMS groups. Furthermore, these designs incorporated rigid diethynylanthracene spacers (ensembles **II**, **III** and **V**) or diethynyldibenzofuran linkers (ensemble **IV**). Indeed, these modifications resulted in discrete duplexes as identified by mass spectrometry and vapour pressure osmometry (VPO). More detailed variable temperature and multi-nuclei NMR spectroscopic studies in $CDCl_3$ confirmed the presence of dimers self-assembled through two pairs of Watson–Crick hydrogen bonds. Interestingly, upon addition of increasing amounts of DMSO the duplexes could be broken to form mainly monomeric species. As might be anticipated given the structural differences, the duplexes were seen to display varying stabilities in mixtures of $CDCl_3$/DMSO-d_6. For example, ensemble **II** (a dyad composed of two AT functionalities) dissociates fully into its constituent monomers upon the addition of 60% DMSO-d_6 (v/v). This ensemble is more stable than ensemble **III**, as well as ensemble **IV**, where only 30% and 25% DMSO-d_6 (v/v), respectively, suffices to break the self-assembled duplexes. These examples indicate that duplex strength can be manipulated by correct control of protecting groups and the degree of preorganization of the monomers. For instance, a diethynylanthracene linkage allows for the nucleobases to be parallel and thus form more stable duplexes than the V-shaped structure imposed by an analogous

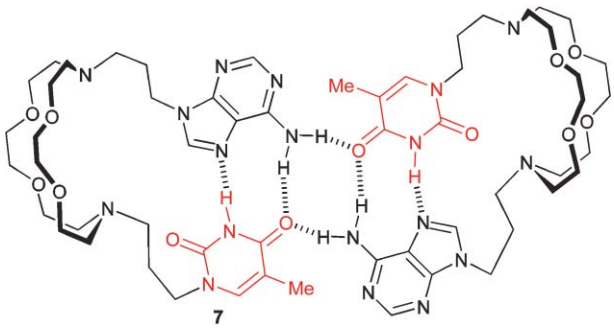

Fig. 5 A molecular box prepared by Gokel and colleagues that is assembled through a combination of Hoogsteen interactions and NH–O hydrogen bonds.

diethynyldibenzofuran spacer. Surprisingly, ensemble **V**, which is expected to associate with 6 hydrogen bonds, is almost completely dissociated by the time the DMSO-d_6 level reaches 40% (in $CDCl_3$). This GC derived complex is more stable than the corresponding AT ensembles, **III** and **IV**. However, the four hydrogen bond based ensemble **II**, is still more robust than even ensemble **V**. These results imply that a simple counting of the potential number of hydrogen bonds does not always predict the most stable complex; other factors, including steric crowding of the protecting groups, can also play pivotal roles in regulating the self-assembly of lipophilic base-pairs.

Dinucleoside-containing molecules do not necessarily have to assemble in a Watson–Crick fashion. For example, in 1994 Gokel and colleagues reported a "molecular box" composed of a dimer of dinucleoside **7** (See Fig. 5).[15] This duplex is of special interest because it is stabilized by a combination of intramolecular Hoogsteen base-pairing and intermolecular one-point NH–O hydrogen bonds.

Another example of a dinucleoside that self-assembles in a non Watson–Crick fashion is illustrated in Fig. 6.[16] Here, the system in question, ensemble **VI**, is held together by a pair of four-point hydrogen bonds, derived from four modified guanine subunits. The net result is a very stable ensemble that is found to remain dimeric in all the solution phase conditions under which it could be tested. Neither dilution nor an increase in temperature (up to 398 °C, in toluene) was found to affect

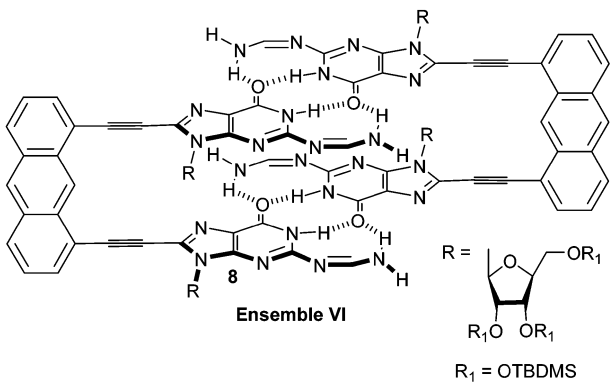

Fig. 6 A duplex structure composed of two guanine dinucleosides **8** (ensemble **VI**) formed as a result of eight hydrogen bonds.

the stability of the complex. Moreover, in direct contrast to what was found for the structurally similar Watson–Crick derived ensembles **II**, **III** and **V**, ensemble **VI** was found to be stable in pure DMSO-d_6, where, again, no dissociation of the self-assembled dimeric species was observed. These examples of non Watson–Crick held base-pairs underscore the remarkable ability of nucleobases to exploit a variety of hydrogen bonding regimes to form self-assembled ensembles. Moreover, these structures can be highly robust, sometimes even more so than analogues based on "pure" Watson–Crick hydrogen bonding interactions.

Self replicating systems

Once ensembles that formed discrete duplexes were developed we asked the question whether these duplexes could lead to systems that might possibly self-replicate. At the time this study was instigated (mid nineteen eighties) non-enzymatic, autocatalytic template-driven oligonucleotide synthesis had already been achieved by von Kiedrowski.[17] However, these latter experiments were carried out in aqueous solutions using biotic oligonucleotides. We conceived a strategy that would exploit the template-driven molecular recognition of appropriately constrained artificial nucleobases in organic solvents to provide, it was hoped, an autocatalytic self-replicating system.[18] The essence of this proposed strategy involves a "twin template" approach as outlined in Fig. 7. Here, two complementary nucleobases, tethered through a linker were expected to allow for the specific recognition and organization of monomeric complements. This, in turn, it was suggested, would facilitate a bond forming reaction that would lead to the production of an identical copy of the original (*i.e.* "parent") template. This process was expected to be autocatalytic since it was envisioned that the new product itself would be a template for the reaction. While this strategy was never reduced to practice in our laboratory, it was demonstrated beautifully by Rebek and co-workers.[19a] Their seminal system relies on a combination of hydrogen bonding (between adenine and an imide derived from Kemp's triacid), and π-stacking interactions between the naphthalene and adenine moieties to stabilize the ready-to-react ensemble **VII** (See Fig. 8). Coupling of the 5′-amino adenosine unit **10** within this ensemble with a napthoyl ester of **11** (See ensemble **VII**; red rectangular box) leads to the production of a new molecule of template **9**. The authors were able to demonstrate autocatalysis, a minimum requirement for self-replication. They were also able to show that it occurs as a result of the hydrogen bond capability of the template **9**, and not some other functionality present on the scaffold (*e.g.* amide, ribose, or the purine ring). Rebek also demonstrated

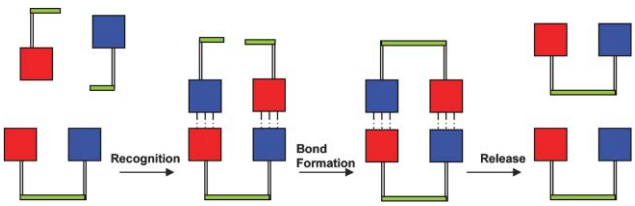

Fig. 7 A twin template approach to self replicating systems.

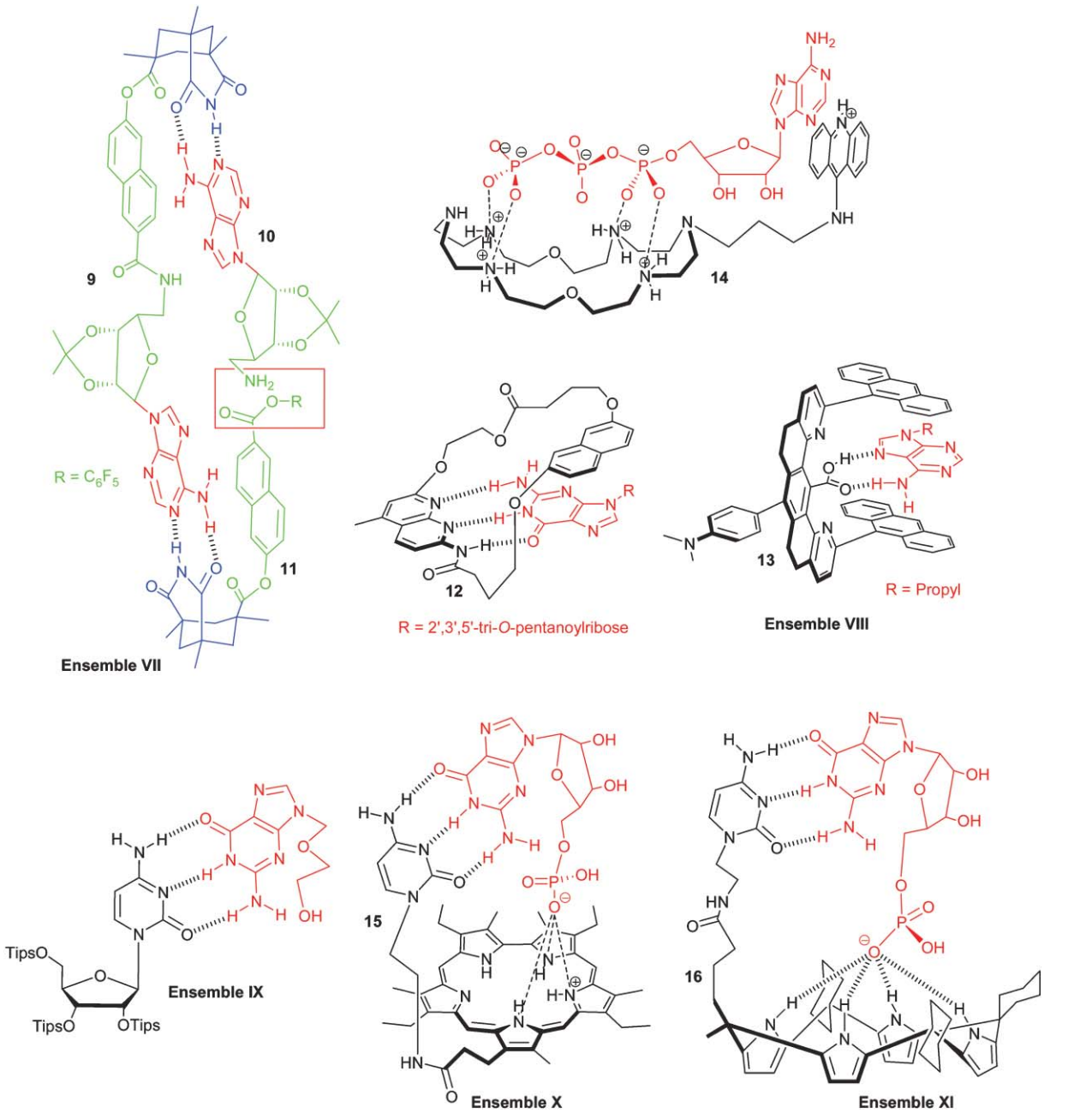

Fig. 8 Rebek's first generation self replicating system (ensemble **VII**) and some molecular receptors that bind various nucleobases. Receptors **12**, **13**, and **14** were prepared by the research groups of Hamilton, Zimmerman, and Lehn, respectively.

that such "extrabiotic" replicators, can show reciprocity, sigmoidal growth, and even mutation, all hallmarks of biotic evolution.[19b–d]

Preparation of receptors for specific nucleobase recognition

The molecular recognition capabilities of nucleobases can be used to tackle other important problems in bio-organic chemistry. One such problem involves the need for synthetic receptors that specifically bind to various targeted nucleobases. A unifying feature of such receptors is that they include multiple recognition units that complement the chemical characteristics of the target nucleobase. Hence, interactions such as hydrogen bonding, π-stacking and electrostatic interactions all represent elements that can be exploited in designing a receptor molecule.

Given the importance of this problem, it is not surprising that it has been tackled by a number research groups including our own. Some of these systems produced as the result of this effort are shown in Fig. 8. Macrocyclic receptor **12**, reported by Hamilton, contains a napthyridine binding unit that is complementary to guanine. This system also contains a naphthalene linker that allows for π-stacking interactions with the targeted nucleobase.[20] In accord with its design, this ditopic receptor was found to bind guanine (K_a = 5.3 × 10^2 M^{-1} in

$CDCl_3$) four times more strongly than napthyridine alone ($K_a = 1.3 \times 10^2\ M^{-1}$ in $CDCl_3$).

Using a similar strategy, Zimmerman and colleagues prepared a so-called molecular tweezer **13**. This system complexes adenine through sandwich-like π-stacking and hydrogen bonding.[21] Interestingly, the authors were able to show that the Hoogsteen face of adenine is involved in binding, rather than the Watson–Crick face. Importantly, ensemble **VIII** has a large association constant ($K_a = 2.5 \times 10^4\ M^{-1}$ in $CDCl_3$), which is thought to endow the receptor with selectivity for A > G ≫ C > U.

Lehn and Hosseini have also utilized a ditopic recognition unit to bind nucleobases. For example, receptor **14**, composed of a polyammonium macrocycle tethered to an acridine moiety, was found to bind adenine triphosphate (ATP) readily through a combination of concurrent π-stacking and electrostatic interactions.[22] Receptor **14** was found to act as a fluorescent sensor for ATP. It was also found to catalyse the hydrolysis of ATP to ADP.

Our strategy involved preparing receptor molecules that could both bind specific nucleobase substrates and act as selective carrier agents for their assisted into-cell transport. It was envisioned that successful transport of antiviral or chemotherapeutic nucleobase analogues into cells through the lipophilic membrane by carrier molecules, would enhance their uptake and hence effective local concentration. A central theme in our design is the use of a nucleobase motif in the receptor molecule, since it was thought that this would allow for the specific recognition of its Watson–Crick counterpart.

Our early receptor systems involved simple 2′,3′,5′-tri(isopropylsilyl)-substituted nucleosides (X-Tips, where X is guanine (G), cytosine (C), adenine (A), or uracil (U)).[23] This functionalization imparted lipophilic character to the nucleobase receptors and served to make them soluble in $CHCl_3$, but not in H_2O. Transport studies were carried out using an Aq I–hydrophobic–Aq II liquid membrane system (where, Aq = aqueous layer, and the hydrophobic layer is $CHCl_3$). From these studies it was found that when a carrier molecule is placed in the $CHCl_3$ layer there is an enhancement in transport of the Watson–Crick complementary nucleobase from Aq I to Aq II. For example, transport of the anti-viral agent 9-[(2-hydroxyethoxy)methyl]-9*H*-guanine (acyclovir) was strongly enhanced (*ca.* 400 fold) by the use of a lipophilic cytidine C-Tips carrier molecule (See Fig. 8, ensemble **IX**). This result gave us impetus to study further synthetic receptors designed to effect nucleobase recognition and transport.

Contemporaneous with the above studies, we found that sapphyrin, a pentapyrrolic expanded porphyrin, can bind anions.[24] In fact, sapphyrin acts as a non-specific carrier of nucleotide monophosphates at pH < 4.[25] In related work, it was found that simple mixtures of rubyrin, a hexapyrrolic macrocycle, and an excess of C-Tips resulted in selective transport of guanosine 5′-monophosphate (GMP) at neutral pH.[26] With these results in hand, we decided to prepare several ditopic receptors for nucleotide monophosphates. Our design included a nucleobase functionality for selectivity, and a macrocycle unit that is easily protonated as a site for phosphate binding.[27] The cytosine-functionalized sapphyrin **15** represents an example of such a receptor. It is shown in Fig. 8 bound to GMP (ensemble **X**). Transport studies using a liquid membrane (Aq I–CH_2Cl_2–Aq II) demonstrated an enhancement of GMP transport rate, as well as selectivity. For example, this receptor (**15**) displays a 100 fold selectivity for GMP over cytidine-5′monophosphate (CMP) at pH = 6.15. As might be expected, a higher transport rate was seen when the receiving aqueous phase (Aq II) is highly basic. Such a finding was rationalized in terms of enhanced deprotonation of sapphyrin at the CH_2Cl_2–Aq II interface and hence enhanced release of the substrate (GMP).

We have also studied ditopic receptors with neutral calixpyrrole macrocyclic tethers.[28] The calixpyrrole linked cytosine receptor **16** shown in ensemble **XI**, induces an enhancement of GMP transport. However, as a result of the residual charge in the complex the enhancement in transport is not as large as for the sapphyrin–cytosine conjugate **15** (calixpyrrole is a neutral receptor, whereas sapphyrin is positively charged). Surprisingly, the same study also indicated that the selectivity of **16** can be reversed when it is incorporated into an ion-selective electrode. Under the interfacial membrane conditions employed in these latter studies, receptor **16** shows greater specificity for CMP than for GMP. In any event, these results, when considered in concert, show that receptors containing a macrocyle core and a nucleobase recognition unit can act as selective carriers for various biologically active nucleobases.

Electron and energy transfer model systems

Natural photosynthetic systems successfully harvest light energy through antenna complexes. The collected energy is then funnelled through a cascade of energy transfer steps *via* organic pigments into a photosynthetic reaction center.[29] Here, an electron transfer event occurs, yielding a charge separated radical ion-pair (CSRP). This conversion of solar energy into chemical energy has intrigued chemists in terms of understanding the fundamental processes involved and has served as motivation for constructing artificial photosynthetic reactors.

Natural systems use non-covalent protein–protein interactions to place energy- and electron-transfer partners within close proximity.[30] Inspired by these systems, we envisioned synthetic nucleobases as scaffolds to effect the self-assembly of various donor–acceptor units. Once organized in such a way, electron- and energy-transfer processes could be studied *via* photoactivation in analogy to the methods used to analyze various better studied covalent model systems. While we were one of the first to conceive of such an approach in the early 1990's, it is important to appreciate that concurrent with our efforts other researchers were also working to prepare various hydrogen-bonding motifs for the self-assembly of photoactive units.[31] For example, in 1990 Hamilton reported a multichromophore assembly based on a barbiturate recognition motif and two 2,6-diamidopyridine units.[31a] Shortly thereafter, the research groups of Nocera[31b] (Fig. 9) and Therien[31c] working independently, showed that carboxylic acid dimers could also be used to assemble photoinduced electron transfer (PET) partners. They also succeeded in showing that these H-bonded bridges are, at the very least, competitive with their covalent counterparts in terms of electronic coupling and

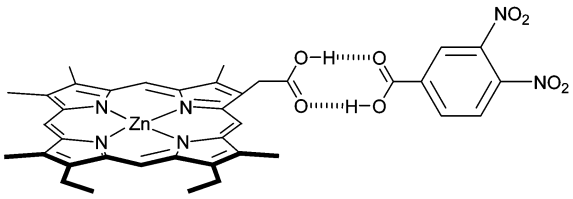

Fig. 9 An example of a carboxylic acid dimer held PET system prepared by Nocera and coworkers.

electron transfer rates. Since these early reports, the study of electron- and energy-transfer in hydrogen bond assisted self-assemblies has expanded rapidly and the reader is directed to some more focused recent reviews on this subject.[32] Here, we summarize our own contributions to the area.

In order to mimic the light harvesting photon antenna units in natural systems, we prepared a GC couple that brings within close proximity free-base and zinc porphyrin chromophores.[33] Subsequent illumination of the cytosine tethered zinc-porphyrin served to effect efficient energy transfer from this chromophore to the guanine linked free-base porphyrin congener (in both the singlet and triplet excited states). Although this work is important in an historic context, it must be noted that two chromophores arranged in space *via* hydrogen bonding represents only a minimalist mimic of the multi-pigment antenna complex found in natural photosynthetic systems. Thus, a higher order trimeric complex was also assembled, wherein two zinc-porphyrins **17** serve to funnel energy into a central free-base porphyrin **18** which serves as the energy trap (See Fig. 10).[34] In this system, singlet energy transfer occurs with a rate constant of *ca.* 9×10^8 s^{-1} and with an efficiency of 60%. This energy transfer process is consistent with the Förster model and, as such, indicates that the hydrogen bonded bridge does not serve to mediate the energy transfer process *per se*. Rather, it acts only as a scaffold that brings the constituent chromophores together in close proximity (*ca.* 22.5 Å). In marked contrast to what is seen for the photoexcited singlet state, triplet energy transfer in this system occurs with almost quantitative efficiency ($k_{et} = 1 \times 10^6$ s^{-1}). It also operates *via* a Dexter type mechanism involving through hydrogen-bond electronic mediation. Ward and Barigelletti have also prepared elaborate energy transfer model systems that are held together within a Watson–Crick framework. These researchers used ruthenium(II)- and osmium(II)-polypyridyl motifs as their energy transfer chromophores.[35]

The GC base-pairing motif can also be used to assemble electron donor–acceptor systems. Such systems can be used to model the electron transfer process leading to the CSRP. Our first generation system incorporated donor–acceptor porphyrin–quinone dyads with flexible linkers between the nucleobases and the electron donor or acceptor units.[36] We quickly realized that rigid linkers are more appropriate than flexible spacers. In fact, the enhanced rigidity increases the nucleobase association constants and also allows for constrained molecules where excited state dynamics can be better interpreted. An example of such a rigid system, composed of porphyrin **19** and quinone **20**, is shown in Fig. 11 as ensemble **XII** ($\Delta G_{CS}^{\circ} = -0.5$ eV).[37] Here, an association constant of 9.0×10^3 M^{-1} in CH_2Cl_2 was determined, which is substantially higher than that of a similar system[36] containing a flexible spacer. As importantly, this rigid system proved readily amenable to study and from time-resolved fluorescence experiments an electron transfer rate (*ca.* 8×10^8 s^{-1}) was estimated.

In the recent years, considerable effort has been devoted to increasing the efficiency of the charge separation step within a given class of photosynthetic reaction model system. In principle, this can be done by enhancing the rate of the forward electron transfer process while slowing down the reverse charge recombination step. Such optimization would reduce energy loss through back reaction thereby increasing the lifetime of the CSRP. Our own efforts focused on assembling systems containing a variety of different electron donor–acceptor pairs with varying electronic properties within the same GC couple. In the context of this work, the dimethylaniline–anthracene system (ensemble **XIII**, Fig. 11)

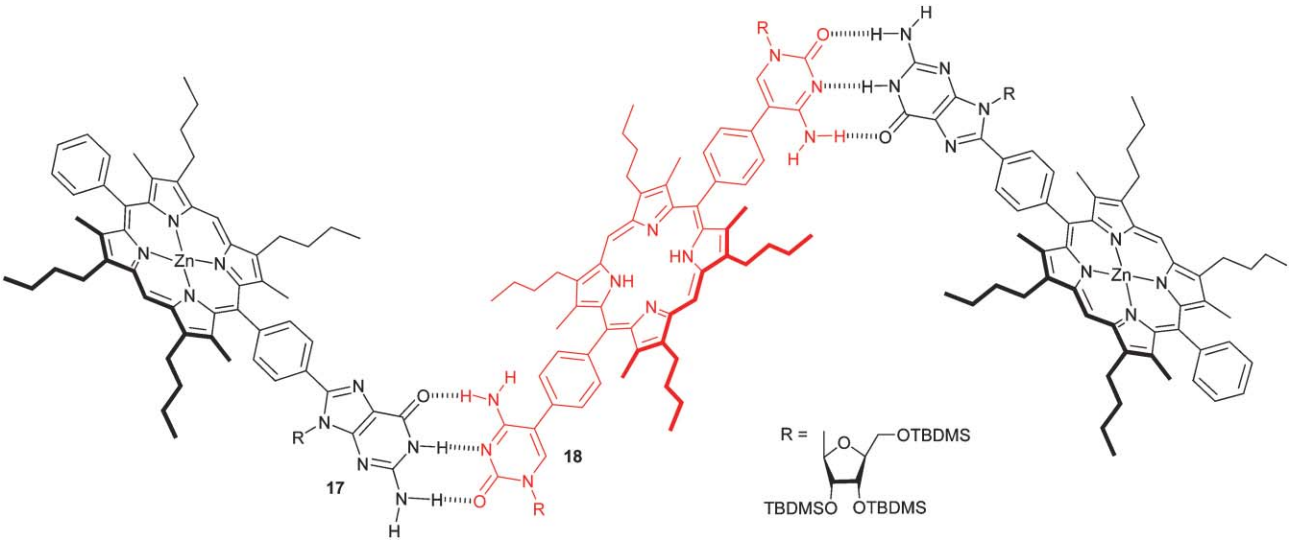

Fig. 10 A trimeric system composed two zinc porphyrins and a free base porphyrin assembled through GC Watson–Crick interactions.

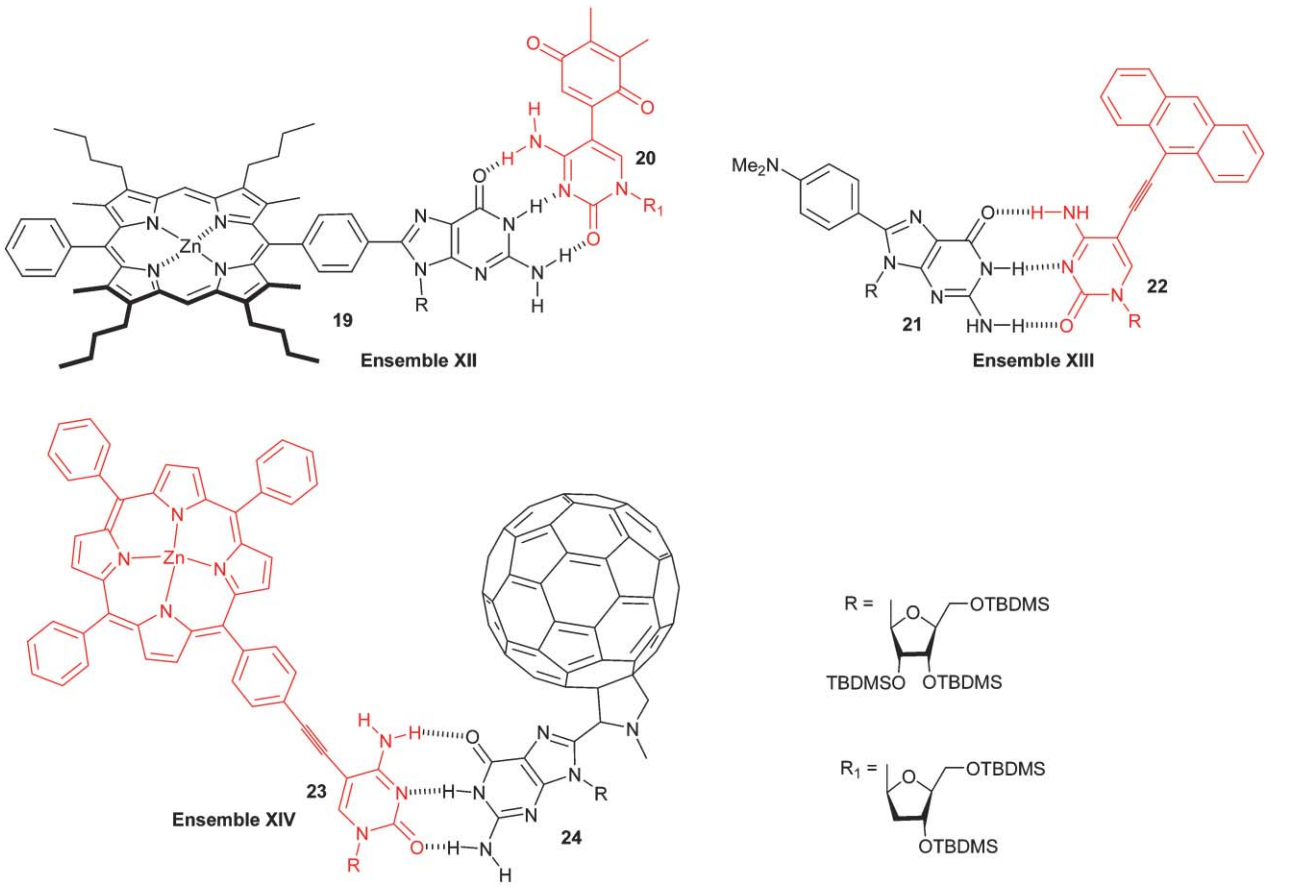

Fig. 11 Various electron donor–acceptor pairs assembled through GC Watson–Crick interactions.

was prepared and studied.[38] This ensemble ($\Delta G_{CS}^{\circ} = -0.41$ eV and $\Delta G_{CR}^{\circ} = -2.5$ eV) has a pronounced affinity constant (3.8×10^4 M^{-1}). Disappointingly, however, the forward and reverse electron transfer rates ($k_{CS} = 3.5 \times 10^{10}$ s^{-1} and $k_{CR} = 1.4 \times 10^9$ s^{-1}) still proved unfavourable (*i.e.*, rather low and high, respectively). In fact, the CSRP lifetime for this system proved to be only 705 ps. On the other hand, quite recently, we have assembled ensemble **XIV**, a Watson–Crick derived donor–acceptor system composed of porphyrin **23** and fullerene **24** ($\Delta G_{CS}^{\circ} = -0.81$ eV and $\Delta G_{CR}^{\circ} = -1.4$ eV).[39] Here, as a result of the incorporation of the fullerene subunit, a dramatically prolonged CSRP is seen (2.02 μs). While still very short compared to what has been achieved in covalent model systems, this lifetime is, nonetheless, three orders of magnitude greater than what was found in the case of the anthracene–dimethylalinine ensemble **XIII**. This leads us to suggest that Watson–Crick base-pairing represents a useful approach to constructing self-assembled PET dyads, and that the judicious choice of individual photoactive subunits can provide an entry into promising light-harvesting systems.

Higher order self-assemblies

In recent years our research efforts have expanded to include the formation of functional higher order supramolecular systems. Guanine is an ideal nucleobase for the preparation of such higher order structures. For instance, it possesses a low oxidation potential, making supramolecular polymers of guanine of interest as possible electronic materials. Furthermore, guanine is highly "narcissistic", forming a variety of self-assembled structures including, ribbons, and tetrameric complexes (see Fig. 12, top left and bottom left). This ability to form ensembles[40] reflects the fact that interactions involving both the Watson–Crick and Hoogsteen faces are often energetically favourable. A particularly dramatic example involves the metal templated self-assembly of guanine derivatives to form G-quartets.

Gottarelli and coworkers have extensively studied the self-assembly of guanine derivatives.[41] For example, they have prepared guanine-based oligomers that can form liquid crystalline phases,[41a] as well as G-quartets that can even separate the potassium salts of chiral amino acid enantiomers *via* selective extraction from an aqueous solution into chloroform.[41b] Guanine has also been used to create self-assembled ionophores.[42] For example, Davis and colleagues have shown that a water stabilized calix[4]arene–guanine conjugate acts as a ditopic receptor system that can bind anions as well as cations.[42b]

A long standing dogma in the field of guanine derived assemblies was the notion that G-quartets could not be formed in the absence of templating cations. However, recent work from our laboratory served to show that it is indeed possible to self-assemble guanine derivatives into a G-quartet without the addition of a metal template.[43] This was achieved by using

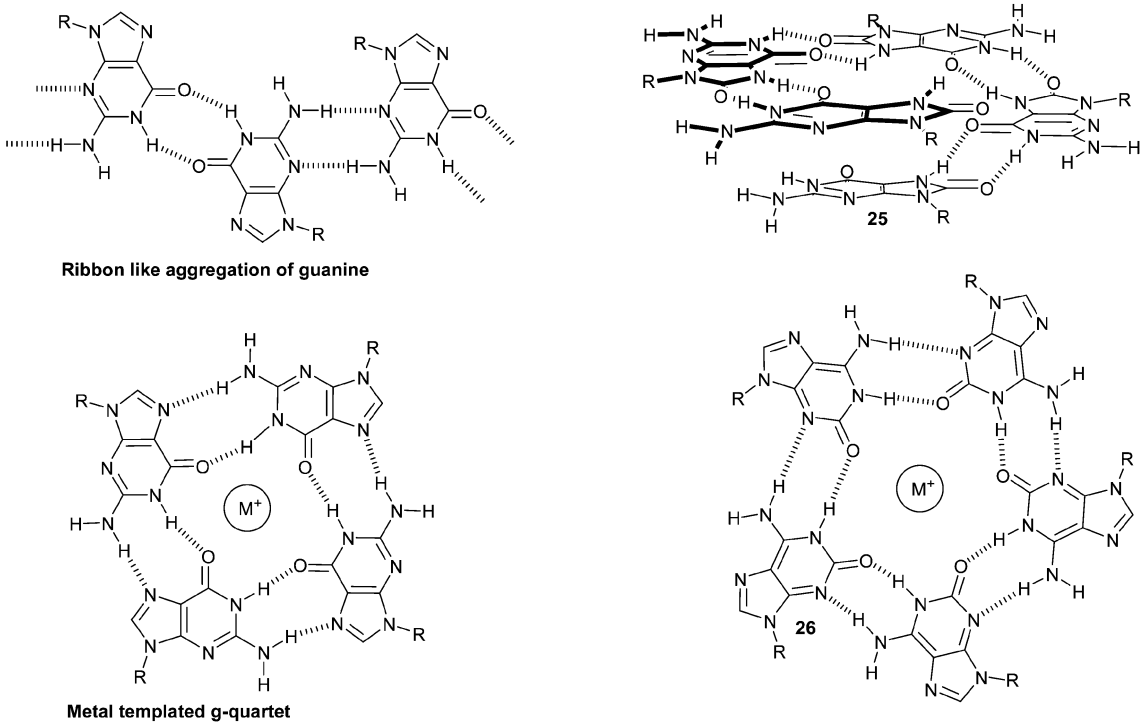

Fig. 12 Supramolecular structures formed by guanine and its derivatives: A ribbon like structure formed by guanine (top left). A metal templated G-quartet formed by guanine (bottom left). A helical assembly made up of 8-oxoguanine **25**, prepared by Gottarelli and colleagues (top right). A caesium cation templated pentameric cycle assembled by isogunanine **26**, prepared by Davis and coworkers (bottom right).

appropriate protecting groups on the ribose subunits of guanine derivative **27** and by attaching a bulky substituent (dimethylaniline unit) on the purine ring. The net effect is that the rotation about the glycosidic bond is constrained and that only the *syn*-conformer is stabilized to an appreciable extent. This conformation, in contrast to the corresponding *anti* atropisomer, precludes the formation of extended or polymeric arrays and allows a guanine quartet to be obtained in the absence of a templating cation. Both solution and solid state analyses (Fig. 13, left) served to confirm formation of the proposed G-quartet.

While supramolecular assemblies made from guanine show considerable promise, particularly as regard to the study of G-quartets, modification of the purine can result in supra-structures that are not attainable *via* the use of simple guanine. For example, just as it is true for guanine, isoguanine (iso-G)

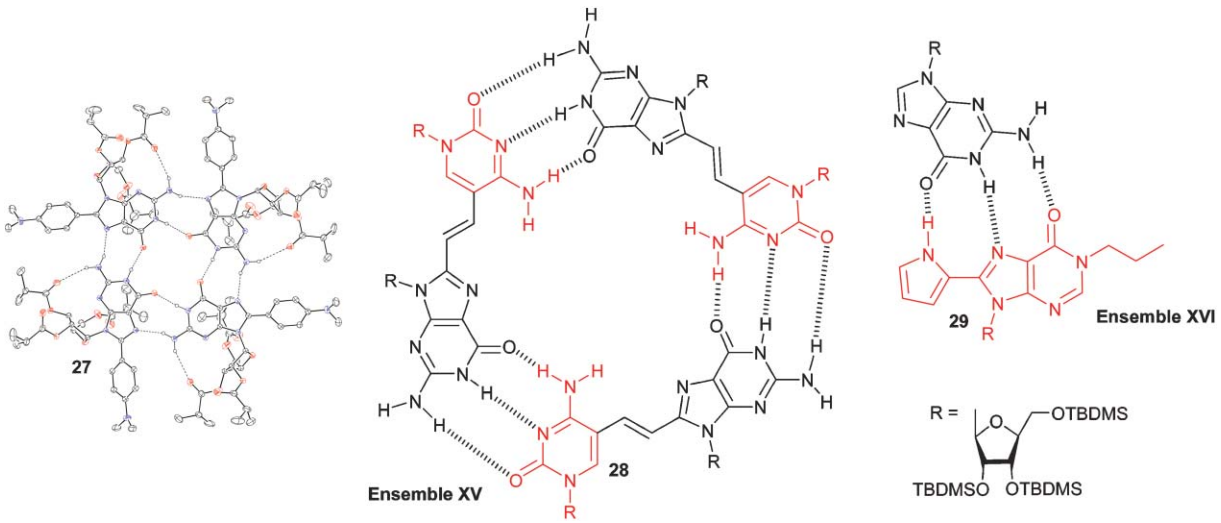

Fig. 13 Various structures formed by guanine based derivatives: An X-ray structure of a G-quartet (in the absence of any templating cations) formed by guanine derivative **27** with bulky dimethylaniline substituents at the C8 position (left). A trimeric supramolecule formed *via* Watson–Crick GC hydrogen bonding interactions (middle). A purine nucleoside **29** that binds guanine *via* a three-point reverse Hoogsteen type interaction (right).

26 can also form G-quartet like structures. However, as shown elegantly by Davis, when an appropriate metal cation (caesium, in this case) is used as the template, iso-G assembles into two pentamers (Fig. 12, bottom right) that sandwich the metal cation.[44]

The electronic properties of guanine can also be enhanced by modification. For example, Gottarelli has recently prepared assemblies composed of 8-oxoguanine **25** (which has an even lower oxidation potential than guanine).[45] These researchers showed that 8-oxoguanine forms helical structures (see Fig. 12, top right), resulting in liquid crystalline phases. Under the same experimental conditions simple guanine only forms ribbon like structures. Cyclic structures of guanine tend to form as a result of a series of two-point hydrogen bonds.

In an effort to form cyclic structures that are held together through three-point hydrogen bonding interactions, we have recently prepared a Janus type dinucleoside **28** that has a guanine face and a cytosine face.[46] In this case, NMR spectroscopic experiments provided evidence for the formation of Watson–Crick base pairs, as expected. In addition, vapor pressure osmometry and ESI-MS studies indicated that the molecular weight of the aggregate corresponds to that of a trimer. Further studies, involving the use of size-exclusion chromatography at varying concentrations, served to corroborate the presence of a trimer, while providing important support for the conclusion that the trimeric species in question was cyclic (ensemble **XV**, Fig. 13).

In order to make useful materials *via* nucleobase self-assembly, the de-aggregation phenomena of these species must also be studied. One method of disrupting nucleobase assemblies is to add a competing nucleobase. For example, Reinhoudt and Shinkai have reported a uracil derived cholesterol organogelator that forms helical gel fibers.[3a] However, the resulting organogel is destabilized by the addition of competing nucleosides. In a similar fashion guanine based self-assemblies can be disrupted by the addition of cytosine, which serves to tie up the Watson–Crick H-bonding sites. In an effort to prepare other nucleobase analogues that are also capable of competing with guanine aggregation, we have prepared purine nucleoside **29**.[47] This nucleoside bears an appended pyrrole, and binds guanine with high affinity. Moreover, it has also been shown to disrupt G-quartet formation. The binding between guanine and **29** is thought to occur through an extended three-point reverse Hoogsteen type interaction as shown in Fig. 13 (ensemble **XVI**).

Since first writing this feature article, Rivera and coworkers have published the preparation and self-assembly properties of a guanine derivative where the concept of extending the Hoogsteen edge is also detailed.[5q] Such modifications resulted in G-quartets with increased stability. This very recent result provides further support for the notion that extended Hoogsteen type interactions may prove useful in preparing novel nucleobase derived supramolecular systems.

Outlook

It was our early goal to use the hydrogen bonding interactions of nucleobases to prepare simple "artificial duplexes" in organic solvents. Since that time, we have worked to prepare more elaborate systems that can recognize and transport given specific nucleotides. We and others working in the field have also shown that base-pairing can be used to access non-covalently assembled structures that address problems in photo-induced electron- and energy-transfer. More recently, our group and others have demonstrated how base-pairing modes can be used to prepare higher order self-assembled ensembles. Towards this latter end, we have introduced several new nucleobase synthons with unique attributes both in terms of their propensity to self-assemble and stabilize distinct supramolecular structures. While considerable progress has been made, it is clear that the field of self-assemblies based on individual nucleobase "building blocks" (as opposed to oligonucleotide arrays), is still in its infancy. Nonetheless, the range of nucleobase "starting materials" that can be conceived and the elegance of the structures that can be obtained leads us to predict that this approach will be one that will continue to attract the attention of supramolecular and biomimetic chemists for years to come.

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