Molecular recognition *via* base-pairing

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Hydrogen-bonding interactions in DNA/RNA systems are a defining feature of double helical systems. They also play a critical role in stabilizing other higher-order structures, such as hairpin loops, and thus in the broadest sense can be considered as key requisites to the successful translation and replication of genetic information. This importance, coupled with the aesthetic appeal of nucleic acid base (nucleobase) hydrogen-bond interactions, has inspired the use of such motifs to stabilize a range of synthetic structures. This, in turn, has led to the formation of a number of novel ensembles. This *tutorial review* will discuss these structures, both from a synthetic perspective and in terms of their potential application in areas that include, but are not limited to, self-assembled macrocyclic and high-order ensemble synthesis, supramolecular polymer preparation, molecular cage construction, and energy and electron transfer modeling.

Introduction

The formation of duplex DNA from its single stranded constituents is a result of a panoply of intermolecular forces, including aromatic π-stacking, van der Waals forces, and hydrophobic effects.[1] However, the high fidelity observed in the pairing of complementary DNA sequences is largely due to the unique molecular recognition capability of naturally occurring nucleic acid bases (nucleobases) *via* Watson–Crick pairing and hydrogen-bonding interactions.[2] Related interactions also play a critical role in stabilizing higher-order RNA structures, such as hairpin loops, whereas so-called Hoogsteen base-pairing is important in the formation of triple helix DNA

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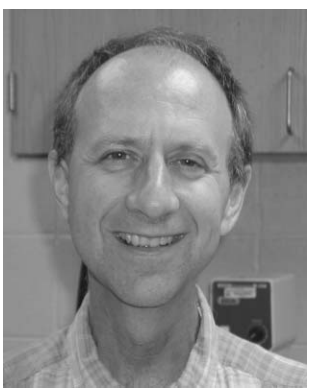

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Professor Jonathan L. Sessler was born in Urbana, Illinois, USA on May 20, 1956. He received a BS degree (with highest honors) in chemistry in 1977 from the University of California, Berkeley. He obtained a PhD in organic chemistry from Stanford University in 1982 (supervisor: Professor James P. Collman). He was an NSF-CNRS and NSF-NATO Postdoctoral Fellow with Professor Jean-Marie Lehn at L'Université Louis Pasteur de Strasbourg, France. He was then a JSPS Visiting Scientist in Professor Iwao Tabushi's group in Kyoto, Japan. In September 1984, he accepted a position as an Assistant Professor of Chemistry at the University of Texas at Austin, where he is currently the Roland K. Pettit Professor. Dr Sessler has authored or co-authored over 375 research publications, written two books (with Dr Steven J. Weghorn, and Drs Won-Seob Cho and Philip A. Gale, respectively) and edited a third (with Drs Susan Doctrow, Tom McMurry, and Stephen J. Lippard). He is the inventor of record on more than 70 issued US Patents. Dr Sessler is also a co-founder (with Dr Richard A. Miller, MD) of Pharmacyclics, Inc., a publicly traded company (pcyc; NASDQ) dedicated to developing biomedical applications of expanded porphyrins. In conjunction with Dr Martin R. Johnson, Dr Sessler has recently co-founded a second company, Anionics, Inc., that is targeting various commercial opportunities associated with anion recognition chemistry. Dr Sessler has served as the co-organizer of several international conferences and numerous symposia at ACS meetings, including, recently, the 3rd International Conference on Porphyrins and Phthalocyanines that was held in July of 2004. In addition to English, he speaks French, German, Spanish, and Hebrew and can get by in Japanese. He serves as Editor of Supramolecular Chemistry and is an Associate Editor for Chemical Communications.

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and so-called G-quartets. Thus, in the broadest sense, hydrogen-bonding interactions involving base-pairs must be considered as playing a salient role in such critical areas as genetic coding, biological information storage, and protein synthesis. One of the core goals of our group and others has been to go beyond the natural realm and to use complementary nucleobase-pairing to construct novel supramolecular assemblies with possible applications in materials chemistry and nanotechnology.[3] This review article will highlight the accomplishments in this field, focusing on the development of discrete dimeric, trimeric, and other higher-order ensembles. Furthermore, in deference to what is a relatively new and exciting direction, the preparation of novel supramolecular polymeric arrays based on nucleobase-pairing will also be discussed. As appropriate for a review of this type, the emphasis will be on work from our laboratory, although an effort has been made to include contributions from other research groups. Some of this work has been covered in other reviews.[4,5] The interested reader is also referred to the contribution from Profs Davis and Spada that is set to appear in this same issue of *Chem. Soc. Rev.*[6]

Versatile hydrogen-bonding motifs through nucleobase-pairing

In order to comprehend better the plethora of synthetic structures that can be constructed through nucleobase interactions, a summary of the various modes of hydrogen-bonding between nucleic acids is in order. The Watson–Crick motif (see Fig. 1), found in a range of DNA- and RNA-containing structures, is the most widely recognized hydrogen-bonding interaction in Nature. This canonical motif is defined by the pairing of guanosine with cytidine and adenosine with either thymidine or uridine. The guanosine–cytidine (GC) couple ($K_a \approx 10^3$–10^5 M^{-1} in $CDCl_3$)[7] is stabilized by a three-point hydrogen-bonding interaction, while the adenosine–thymidine

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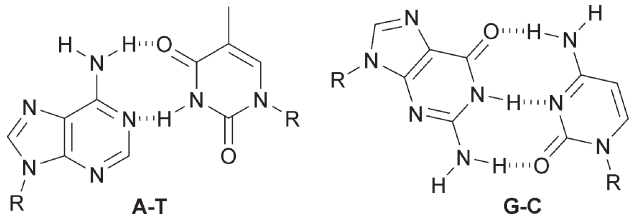

Fig. 1 The canonical Watson–Crick hydrogen-bonding motifs.

(AT or AU) grouping ($K_a \approx 10^2$ M^{-1} in $CDCl_3$)[8] contains a two-point hydrogen-bonding mode. Thus, based solely on the strength of association, the GC couple represents a stronger base-pairing motif. It is therefore more attractive for incorporation as a recognition "subunit" into new structures. For this reason, GC binding interactions have been widely used by our group. However, there are many examples where the AT (or AU) Watson–Crick motif has been used with good effect to stabilize a number of elegant supramolecular structures. Both types of ensembles are covered in this review.

Even though the Watson–Crick mode of bonding is prevalent in natural systems, other hydrogen-bonding motifs are available and expand the possibility for the creation of different structural networks.[9] For example, special attention needs to be paid to the Hoogsteen[10] mode of bonding (see Fig. 2), which is another mode that we have exploited for the development of new, synthetic self-assembled ensembles. Hoogsteen interactions occur on the opposite face, between the C6–N7, of the purine nucleosides. Along with Hoogsteen interactions, other non-traditional base-pairs (see Fig. 2) are found extensively in various DNA and RNA structures. In addition, these modes are also present in protein–DNA and drug–DNA interactions. Other base-pairing motifs include the wobble (mismatched) form, reverse Hoogsteen and reverse wobble. The various reverse modes are defined by a *trans* or antiparallel conformation of the two sugar moieties.[9] Due to nucleobase tautomerization and ionization, other dimeric interactions have also been observed but are far less common. Because many pairing modes are possible, trimers and high-order assemblies can be formed from nucleobases. Further, the aforementioned binding modes can be used in conjunction with other intermolecular forces to prepare synthetic molecular cages and supramolecular polymers.

Although formation of oligomeric self-assemblies can be advantageous if the goal is to produce a polymeric system, nucleobase oligomerization is generally disadvantageous if the objective is to prepare a well-defined, low molecular weight synthetic structure. In such a case, precautions can be taken to minimize the complications to oligomerization. By far, the simplest alteration is through the adjustment of nucleobase concentrations, which can curtail the formation of aggregates that are often observed at higher concentrations. Synthetic modifications can also be useful in preventing the formation of higher-order aggregates. For instance, introducing bulky protecting groups on one face of the nucleobase and blocking potential hydrogen-bonding sites can be used to define a set of preferential hydrogen-bonding motifs. For example, blocking the N7 nitrogen on a purine enhances Watson–Crick bonding and, as shown in an example later, blocking the N1 nitrogen

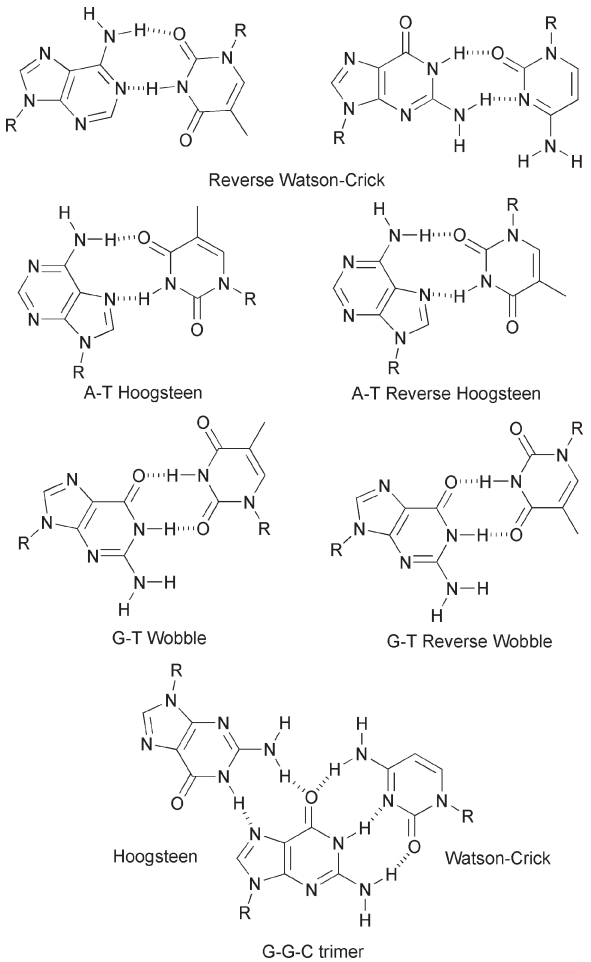

Fig. 2 Non-traditional base-pairing motifs.

leads to modified systems that favor Hoogsteen interactions. Our research group and others have employed both of these strategies, namely control of concentration and specifically targeted synthetic modification.

When designing self-assembled structures based in whole or in part on hydrogen-bonding interactions, a main concern is the choice of solvent. In the biological realm, complementary hydrogen-bonding interactions play a role in bringing together, *e.g.*, double helical oligonucleotides; however, such structures are also stabilized *via* the aid of many other intermolecular forces. In fact, monomeric nucleobases, when found in polar protic solvents, do not exist as hydrogen-bonded pairs. Rather, they tend to form extended columns as a result of π-stacking and hydrophobic interactions. Thus, as would be expected, the solvent competes with the acceptor and donor sites on the nucleobases, leading to decreased hydrogen-bonding interactions with the complementary base. To circumvent this problem, aprotic solvents such as CH_2Cl_2 or $CHCl_3$, have been used by researchers trying to prepare synthetic self-assembled structures. These solvents are suitable for self-assembly since they do not compete appreciably with the donor/acceptor sites needed to establish the base-pairing interactions.

Unfortunately, the parent nucleobases are not completely soluble in non-competing solvents, such as CH_2Cl_2 or $CHCl_3$. Thus, measures such as the synthetic "addition" of lipophilic or solubilizing substituents, have been carried out in the case of most of the core nucleobases, including C and G early on in the case of our own group.[11–13] Another means of improving solubility that we and others have found effective is to include the sugar moiety on the nucleobase, and to protect the alcohol functionality on the ribose sugar with hydrophobic moieties. For example, *tert*-butyldimethylsilyl (TBDMS) group protection, which is stable to a wide range of conditions, engenders solubility in a range of easy-to-work-with non-polar, aprotic solvents. Although this is a useful technique, not all protecting groups give rise to the desired (or at least anticipated) self-assembled structures, as illustrated by some examples from our own group (*vide infra*).

Dimeric ensembles

Although studies of nucleoside self-assembly in non-polar solvents had been carried out early on,[14] our group was among the first to appreciate that nucleobases could be exploited as molecular recognition motifs for the creation of synthetic, self-assembled structures. Our initial efforts were focused on the preparation of dimeric systems as a means of enhancing the recognition efficacy of traditional, single base-pairing modes. Towards this end, a duplex containing two sets of GC base-pairing motifs was constructed (ensemble **I**, Fig. 3).[15] It was thought that the additive effect of the second GC couple would increase self-association. Unfortunately, however, spectroscopic dilution studies performed in DMSO (a competitive solvent) revealed a rather low association constant (K_a = 6.8 M^{-1}). The low binding affinity was attributed to the use of a system that was inherently too flexible, as well as the use of a highly competitive solvent. Therefore, subsequent design generations[16,17] encompassed enhanced rigidity, as well as substituents that would impart increased solubility in non-competitive apolar solvents.

The new duplexes (see Fig. 4) relied on diethynylanthracene and diethynyldibenzofuran spacers to enforce rigidity. They also contained the natural ribose sugars present in nucleosides, albeit protected with lipophilic acetyl or TBDMS groups so as to increase the solubility of the complexed and uncomplexed systems in organic solvents. The duplexes formed from these

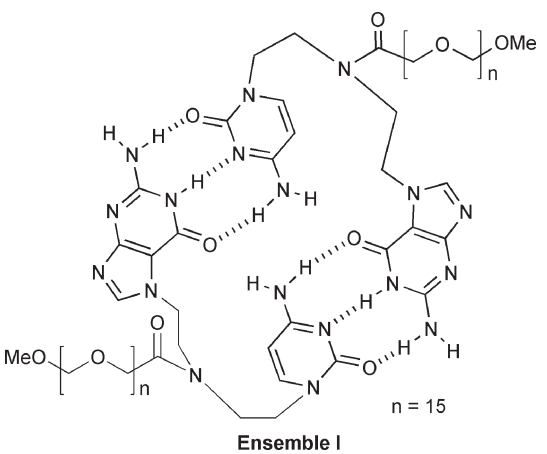

Fig. 3 Flexible dimeric ensemble based on GC coupling.

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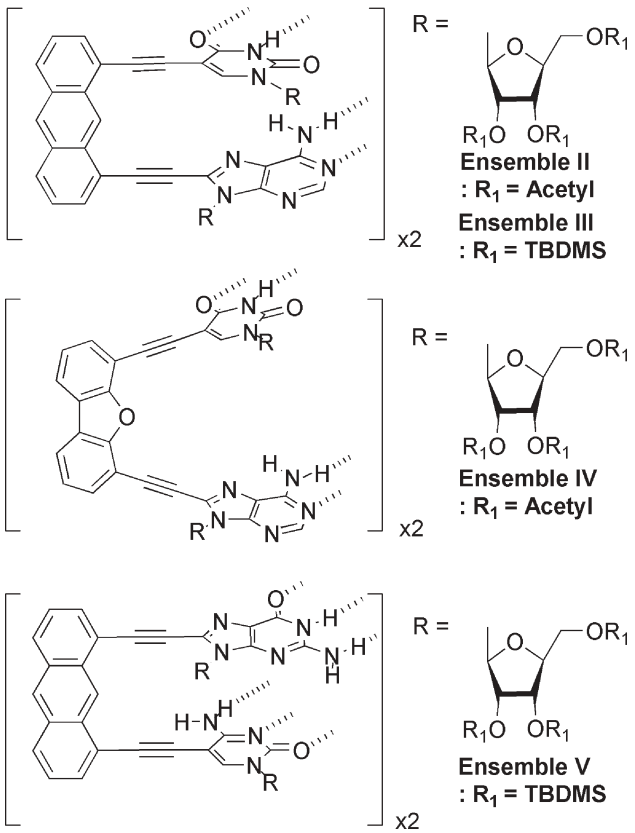

Fig. 4 More rigid second generation dimers.

second generation systems, ensembles **II–V**, were identified initially by mass spectrometry. Further characterization, effected *via* a combination of vapor pressure osmometry (VPO) and variable temperature multi-nuclei NMR spectroscopic studies in $CDCl_3$, confirmed the presence of the proposed self-assembled dimers.

Increasing amounts of DMSO were added to $CDCl_3$ solutions of ensembles **II–V** to examine the effect of a competitive solvent on the hydrogen-bond interactions. Ensemble **II** completely dissociates in the presence of 60% DMSO-d_6 (v/v) *versus* ensemble **III**, which undergoes disassociation in the presence of 30% DMSO-d_6 (v/v). This observation led to the proposal that the protecting groups play a role in regulating overall self-assembled ensemble stability. Ensemble **IV** dissociates in the presence of 25% DMSO-d_6 (v/v), whereas **V** dissociates only when 40% DMSO-d_6 (v/v) is added. By comparing **II** to **IV**, one can see that ensemble **II** not only represents a more rigid system, but it also does not dissociate as easily as the more flexible V-shaped system, **IV**. Surprisingly, a comparison of ensembles **III** and **V** leads to the startling conclusion that, at least for this specific case, the use of the AT couple as the key recognition motif results in a more robust duplex than the corresponding system incorporating the GC motif.

The addition of extra hydrogen-bonds to a monomeric recognition unit is another effective means of enhancing the association of dimeric ensembles based on functionalized nucleobases. For example, Zimmerman and colleagues have synthesized a urea derivative of guanosine (UG) that has been

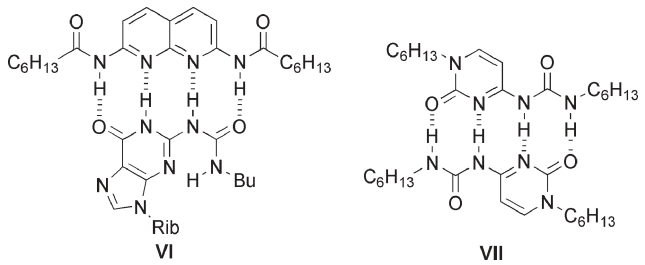

Fig. 5 Four-point dimers developed by Zimmerman (**VI**) and Hailes (**VII**).

shown to bind to 2,7-diamido-1,8-naphthyridine (DAN) through a four-point hydrogen-bonding interaction.[18] The UG–DAN complex **VI** (see Fig. 5) exhibits a remarkably high association constant ($K_a \approx 5 \times 10^7$ M^{-1} in $CHCl_3$), with the competing self-dimerization of the UG unit being calculated to be relatively low ($K_{dimer} < 300$ M^{-1} in $CHCl_3$). Both DAN and UG are relatively easy to synthesize, with UG being prepared in only four steps from a guanosine nucleobase in a process that does not require chromatographic purification. Ensemble **VII**, developed by Hailes *et al.*, represents another example where a strongly associated supramolecular dimer was constructed *via* a four-point hydrogen-bonding network (see Fig. 5).[19] In this case, the functionalized, quadruply bonded, cytosine dimer is held together with a $K_{dimer} = 9 \times 10^6$ M^{-1} in C_6D_6. A bifunctional derivative was also synthesized and found to support the formation of supramolecular polymeric structures, which will be discussed in detail in a later section.

Developed in our research group, ensemble **VIII**, which is built up from a doubly functionalized anthracene monomer (see Fig. 6), is also stabilized *via* four-point hydrogen-bonding interactions.[20] In this case, the paired ensemble contains four modified guanine subunits, with the net result that a very stable supramolecular structure is generated. In fact, neither dilution to the point that the complex signals could not be distinguished using ^1H NMR spectroscopy, nor an increase in temperature led to a detectable decrease in stability. The construction of such dimeric ensembles, based on enhancing traditional nucleobase hydrogen-bonding modes, presents researchers with an effective tool to increase association constants and to enhance the stability of self-assembled

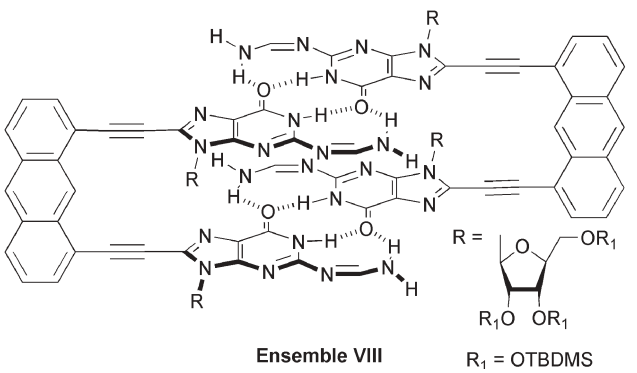

Fig. 6 Guanosine dimer stabilized *via* multiple four-point hydrogen-bonding interactions.

architectures. Thus, with these dimeric systems in hand, it became apparent that further functionalization could lead to the construction of more complex systems such as supramolecular polymeric arrays, high-order self-assemblies, molecular "boxes" or "capsule" systems. Such systems, in turn, are of interest because they could provide a novel means of studying energy and electron transfer in non-covalently bound ensembles. Indeed, it was this appreciation that motivated much of our own work in the area (*vide infra*).

High-order self-assemblies

The supramolecular chemistry of functionalized nucleobases is not limited to the formation of "simple" dimeric ensembles. Indeed, considerable recent effort has focused on the development of higher-ordered self-assembled systems. Not surprisingly, many of these rely on multiple hydrogen-bonding interactions and incorporate a variety of different hydrogen-bonding motifs, including a number of those introduced earlier in this review. For example, the fact that guanine contains functionality that allows it to support both Watson–Crick and Hoogsteen-type interactions makes it an ideal candidate for preparation of higher-order assemblies. In fact, in Nature guanine supports a plethora of self-assembled structures, including ribbons and G-quartets. This is inspiring the study of synthetic analogues of these canonical structures in a number of groups, including those of Davis and Spada, whose contributions are detailed in a separate review included in this issue.[21–24]

G-quadruplexes exist in a variety of natural nucleic acid combinations where guanine-rich strands are found. Stabilization by a bound cation, usually K^+, is considered integral to the formation of such aesthetically appealing supramolecular motifs. Until recently, such cation-based stabilization was also considered to be a necessary feature in the case of synthetic analogues, called G-quartets. This is because the formation of these latter suprastructures, generally obtained from lipophilic guanosine derivatives, could only be obtained in the presence of an appropriate metal ion template. Our own work in this area has focused on formation of G-quartets in the absence of such a templating cation.[21] Success was encountered in the case of the guanosine derivative **1** (see Fig. 7). This particular functionalized nucleobase bears an *N*,*N*-dimethylaniline substituent on the C8 position of guanine. It also contains a ribose subunit that bears isobutyryl protecting groups. The net result is favorable formation of the quartet, ensemble **IX**, in the absence of a templating cation. Such self-assembly, which, as noted above, is without known precedent in Nature, is believed to reflect the presence of the bulky aryl group on the C8 position, as well as the judicious choice of protecting groups on the ribose ring. In particular, the isobutyryl groups are thought to constrain the rotation about the glycosidic bond, locking the structure into a *syn*-conformation, preferentially allowing formation of the quadruplex **IX**.

Dimerization can also support the formation of higher-order homooligomers. For instance, Gottarelli and co-workers have shown that ribbons or tapes can be formed through guanine-based Hoogsteen interactions.[22] The same group has also

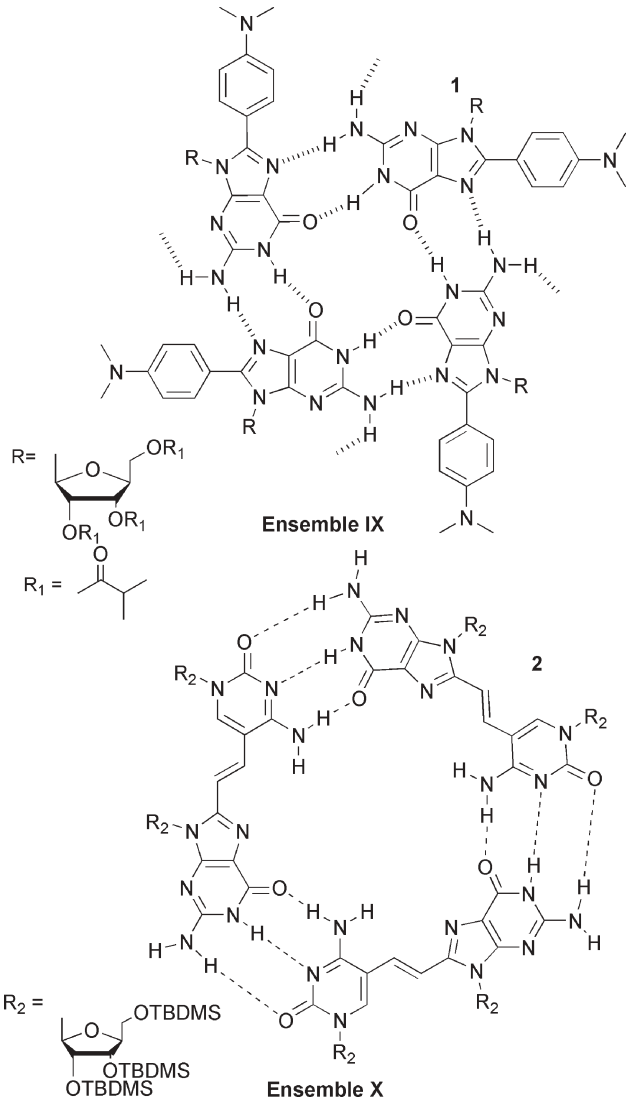

Fig. 7 G-quartet **IX**, formed without a templating cation. Ensemble **X**, a Janus-type structure, relies on controlled guanosine–cytidine interactions.

shown that other derivatives of guanine, containing modified hydrogen-bonding motifs, can self-assemble to form interesting, non-monomeric structures. One example of this approach involves the formation of supramolecular helices *via* self-assembly of oxoguanosine.[23]

Given the importance of guanine dimers and homo-oligomers, it is not surprising that considerable attention has been devoted to the synthesis of higher-order assemblies based on mixed base-pairing interactions (*i.e.*, hetero-pairing). The ability of such mixed binding motifs to stabilize cyclic structures is illustrated by ensemble **X** (see Fig. 7).[25] The constituent dinucleoside, system **2**, was synthesized by first carrying out a set of simple protection reactions, which were then followed by two consecutive palladium coupling steps, using reactions that have been found to be particularly effective in synthetic nucleobase chemistry.[26] The net result was the production of a Janus-type molecule that contains both a guanosine "face" and a cytidine "face".

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An important initial indication that **2**, which contains seven readily identifiable hydrogen-bonding sites, undergoes self-aggregation came from the fact that, in contrast to most modified nucleobase systems, it dissolved completely in hexanes, a strongly apolar solvent. Further support for the proposed formation of ensemble **X** came from ^{1}H NMR spectroscopic studies, electron spray ionization mass spectrometry (ESI-MS), size-exclusion chromatography (SEC), and vapor pressure osmometry (VPO). Two-dimensional NOESY experiments revealed a relationship between the guanosine imino proton (N1–H) and the cytidine amino proton (N4–H), an indication of a close spatial arrangement. Further, ^{15}N–H heteronuclear multiple quantum coherence (HMQC) experiments confirmed that the exocyclic NH amino protons on the cytidine subunit are inequivalent. Taken together, these findings provide support for the suggestion that **2** self-assembles through canonical Watson–Crick-type base-pairing. Additionally, an ESI-MS analysis was performed to determine the size of aggregates, if any. This latter experiment confirmed the presence of trimeric species, but failed to reveal the presence of significant peaks that could be ascribed to the corresponding dimeric product or to other higher-order species. Further, VPO studies revealed a mean molecular weight (M_n) of *ca*. 3900 when sucrose octaacetate was used as the standard, a value that is close to that calculated for the trimeric species (*i.e.*, 3704 daltons). Finally, support for the proposed cyclic structure came when Ensemble **X** was subject to concentration dependant SEC retention studies. Here, over a broad concentration range, only one peak corresponding to the expected cyclic trimer, with an M_n of 3740 daltons, was detected.

Complementing efforts to develop the supramolecular chemistry based on guanine self-dimerization and guanine–cytosine molecular recognition, our research group has also worked to explore the effects of enforcing non-Watson–Crick base-pairing interactions. Within the context of this generalized, ongoing objective, a key initial goal has been to enhance the two-point Hoogsteen hydrogen-bonding mode found in many biologically important, guanine-containing suprastructures. What makes such an effort challenging is that classic Hoogsteen-type base-pairing is characterized by only two, rather than three, hydrogen-bonding interactions. Therefore, in an effort to increase the potential efficacy of Hoogsteen base-pairing, a pyrrole–inosine hybrid **3** (see Fig. 8) was produced.[27] In accord with design expectations, namely that the pyrrole subunit would contribute an additional hydrogen-bond to any base-pairing interaction, the modified nucleobase **3** was found to bind strongly to guanosine, even to the point that it would disrupt the formation of G-quartets. The success of **3** as a Hoogsteen-type base-pairing motif comes from the fact that its potential Watson–Crick bonding interactions are precluded as the result of having the imino NH in **3** "blocked" with a propyl group. Conversely, the enhancement provided by the pyrrole NH functionality allowed for the stabilization of ensemble **XI**. This system, which is characterized by the presence of a donor–acceptor–acceptor (DAA) motif in contrast to the classic ADD binding mode present in most guanosine-containing structures, actually involves reverse, rather than normal, Hoogsteen-type

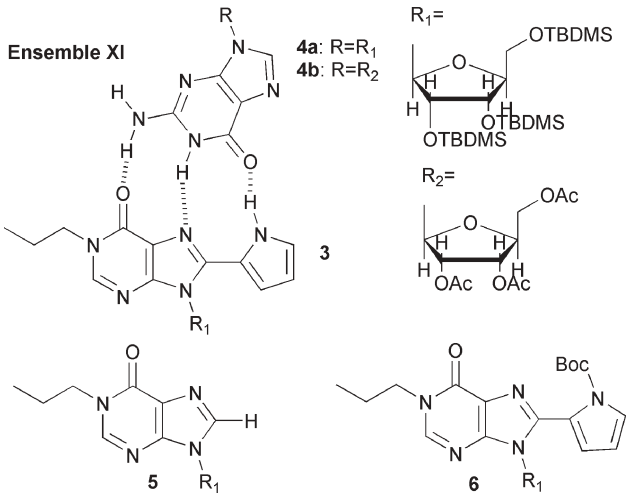

Fig. 8 Pyrrole–inosine **3**, a system designed to enhance Hoogsteen interactions, shown bound to guanosine **4** to form ensemble **XI**. Also shown are the ESI-MS standards **5** and **6**.

base-pairing, a result that is ascribed to the "anti" relationship of the ribose units within the ensemble.

Initial evidence for hydrogen-bonding interaction between **3** and **4a** came from ^{1}H NMR spectroscopic studies, which revealed that the pyrrole NH proton of **3** shifts downfield from 9.6 ppm to 10.5 ppm upon addition of 0.6 equiv. of guanosine. An affinity constant (K_a), corresponding to the interaction between the guanosine and inosine monomers, was estimated at $(1.1 \pm 0.1) \times 10^3$ M^{-1} for a 1 : 1 binding stoichiometry. ESI-MS studies were performed to investigate the interactions of the functionalized inosine with natural nucleobases and, as would be expected, revealed specificity towards guanine. 2′,3′,5′-Tri-*O*-acetylguanosine **4b**, due to mass range limitations, was tested alone in ESI-MS and these results revealed the presence of both a GG dimer peak and signals ascribable to higher-order aggregates. Interestingly, upon addition of **3**, significant decreases in the intensities of the GG dimer and the higher-order guanosine aggregate peaks were seen. Upon addition, the presence of new peaks ascribable to the inosine–guanosine complex was observed. Two controls, **5** and **6**, were tested under similar conditions. Compound **5**, which lacks the extra pyrrole donor, showed similar, but less pronounced behavior. Additionally, the protected *N*-Boc-pyrrole inosine **6** was examined and did not show any significant complexation with, or disruption of, guanosine assemblies.

ESI-MS studies were performed to determine the nature of the interactions between quadruplex-DNA and the pyrrole–inosine nucleosides **3** and **6**. When the dT_2G_5T and $dT_2AG_3T_2AG_3$ oligonucleotides were subject to ESI-MS, ions corresponding to both single stranded and quadruplex species were observed. Upon addition of **3**, peaks corresponding to the binding of **3** to the quadruplexes were seen, but not those corresponding to binding to single stranded-DNA. On the basis of these studies, it was concluded that the additional pyrrole hydrogen donor serves to increase the Hoogsteen-type interactions in the gas phase and that this strategy was one that could be potentially be generalized to include other like systems. In fact, several new functionalized inosine analogues

have been synthesized and several of these show promising results as judged from ongoing ESI-MS studies.

Formation of supramolecular polymeric arrays

One of the appealing extensions of nucleobase self-assembly involves the generation of novel supramolecular polymers constructed *via* hydrogen-bonding. Base-pairing represents a particularly attractive approach to the construction of supramolecular networks because these hydrogen-bonding motifs have the potential to confer both directionality and flexibility within the incipient array (*vide infra*). Moreover, because the building blocks in question are tunable, responsive systems can be conceived that will favor formation of the most stable system under a given set of experimental conditions.[4,28] Until recently, efforts in the base-pairing polymer area have focused on nucleobases appended to covalently linked polymers and the use of such systems to create networks. However, currently, nucleobases are being considered as forming the core or specific constituents of supramolecular polymeric arrays.

One recent example comes from the quadruply bound cytosine dimer, produced by Hailes *et al*. (*vide supra*, Fig. 5).[19] Here, bifunctional polymers were made by attaching the functionalized cytosine to amine terminated poly(ethylene glycol). According to ^{1}H NMR spectroscopic analyses, the four-point hydrogen-bonded system formed from the dimer was maintained after formation of the H-bonded polymer. Also, changes in temperature behavior and the measured diffusion coefficients were consistent with supramolecular polymer formation.

In another approach, Rotello and researchers generated a diamido pyridine polymer **7** that was cross-linked *via* non-covalent means to the bis-thymine unit **8** (see Fig. 9).[29] Specifically, when the bis-thymine **8** was added to the polymer **7**, suspended aggregates were formed. These structures and their properties were tested using laser confocal scanning microscopy (LCSM), differential interference microscopy (DIM), and ^{1}H NMR spectroscopy. The aggregates proved stable, existing in solution for weeks; they also demonstrated thermal reversibility, proving able to undergo multiple heating–cooling cycles without any observable decomposition.

Utilizing Watson–Crick base-pairs, Shimizu and colleagues developed the bis-thymine **9**, bis-adenine **10**, and mixed adenine–thymine **11** systems, all three of which contain bridging alkyl diamides in between the two nucleobases (see Fig. 9).[30] The all-thymine system **9** polymerizes as the result of ''narcissistic'' hydrogen-bonding interactions to produce double helical ropes, while the complementary adenine composition produces only microcrystalline solids. The mixed adenine–thymine structure formed supramolecular fibers. Thus, by incorporating different nucleobases within the same general framework, it proved possible to prepare a variety of supramolecular structures and ensembles.

In other work, Rowan and co-workers succeeded in generating two supramolecular networks by placing nucleobases, functionalized adenine and cytosine subunits, at the end of covalent polytetrahydrofuran polymers.[31] This produced systems that then underwent self-assembly *via*

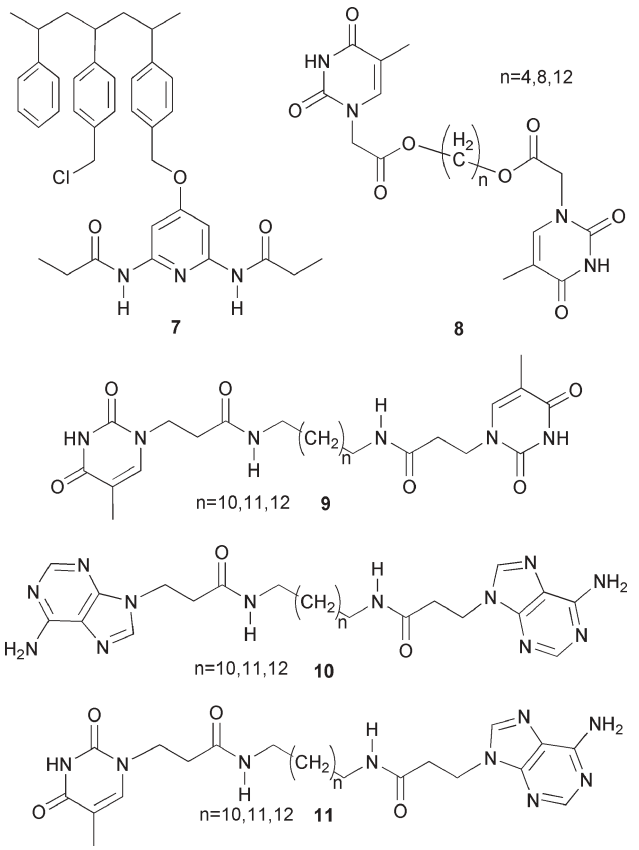

Fig. 9 Rotello's diamido pyridine polymer **7**, which undergoes hydrogen-bonding mediated cross-linking with the bis-thymine **8** to form suspended aggregates. Shimizu's adenine and thymine alkyl diamide polymers **9–11** form hydrogen-bonding self-assemblies.

hydrogen-bonding to generate films. Interestingly, while the adenine-containing films proved brittle, those based on cytosine films were flexible.

While hydrogen-bonding interactions play a major role in stabilizing supramolecular polymers based on nucleobase self-assembly, π–π stacking and metal coordination are also potentially important stabilization modes. A recent example is provided by the work of Castillo, Luque *et al*. in which a non-functionalized purine subunit and an adenine nucleobase were used in conjunction with manganese and copper-oxalato frameworks.[32] In the case of manganese, the purine– and adenine–metal complexes form one-dimensional zig-zag chains, with only the purine N7 coordinated to the manganese. The adenine subunit is not involved in metal coordination directly. However, the manganese(II) cation is coordinated to two water molecules, which are hydrogen-bonded to the adenine subunit. In contrast, direct metal coordination to adenine (through N7) is seen in the case of the corresponding copper-oxalato framework.

Self-assembled polymer systems, including those summarized in this review, are attractive in that their formation and subsequent break-up (including complete potential monomerization) can be potentially controlled through changes in the medium (*e.g.*, by switching from non-polar to highly competitive solvents). In principle, this can lead to the production of self-healing systems or to those that fall apart

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completely when exposed, *e.g.*, to water. Such features could prove extremely useful in the area of materials science since they could support the production of new classes of thermoplastic elastomers, superglues, gels, transistors, and recyclable materials.

Molecular capsules: from receptors and boxes to cages

Over the years considerable effort in the supramolecular chemistry field has been devoted to the construction of so-called container systems that contain well-defined voids suitable for inclosing solvents or substrates. Initially, effort in the area was focused on the generation of covalently linked systems. However, more recently, attention has turned to self-assembled systems, including those stabilized by hydrogen-bonding.[33] Such non-covalent "capsules" (or "cages") are of interest because of their potential utility in a range of applications areas, including sensor development and drug delivery. Since the non-covalent systems in question are held together *via* hydrogen-bonding interactions, they have the appealing feature of being dynamic, in that their formation is not "locked". This section will review efforts to generate non-covalent molecular capsules *via* base-pairing and detail some of the evidence that has been put forward in support of their formation.

An early example of a nucleobase-containing molecular cage comes from Hamilton and Pant. The receptor in question, the naphthyridine tethered naphthalene derivative **13**, was actually designed to bind guanine (see Fig. 10).[34] However, in the presence of guanine in $CDCl_3$ a new ensemble is formed that has a cage-like structure. It is stabilized by a combination of hydrogen-bonds and π–π interactions. Another example of a receptor for a nucleobase that forms a cage-like structure was reported by Rebek *et al*. These researchers found that the addition of adenine to receptor **14** stabilizes the formation of ensemble **XIII** through a combination of Hoogsteen, Watson–Crick, and π–π interactions (see Fig. 10).[35]

Another approach to self-assembled capsule generation relies on the use of nucleobase–nucleobase interactions to produce the key ensemble-producing stabilization. An elegant example of this paradigm comes from Lehn and colleagues, who tethered functionalized uracil units to a porphyrin macrocycle to produce ensemble **XIV** (see Fig. 10).[36] Rotation around the uracil–porphyrin bond is limited due to the ethyl substituents on the porphyrin, thus producing two rotameric forms. Upon addition of 5-alkyl-2,4,6-triamino pyrimidines, a supramolecular cage is formed *via* hydrogen-bonding. ^{1}H NMR spectroscopic studies provided evidence for the existence of the two expected rotamers, while electrospray mass spectrometry revealed no peaks that could be ascribed to higher-order aggregates (*i.e.*, larger than the 2 + 2 species **XIV**).

Carrying the nucleobase-pairing approach to self-assembled container formation one step further, Gokel and Schall developed a molecular box **XV** that is predicated on adenine and thymine base-pairing (see Fig. 10).[37] In this case, evidence for complex formation came from ^{1}H NMR spectroscopic analyses, which provided support for the presence of both Watson–Crick and Hoogsteen hydrogen-bonding interactions. This system is particularly noteworthy since the self-assembled

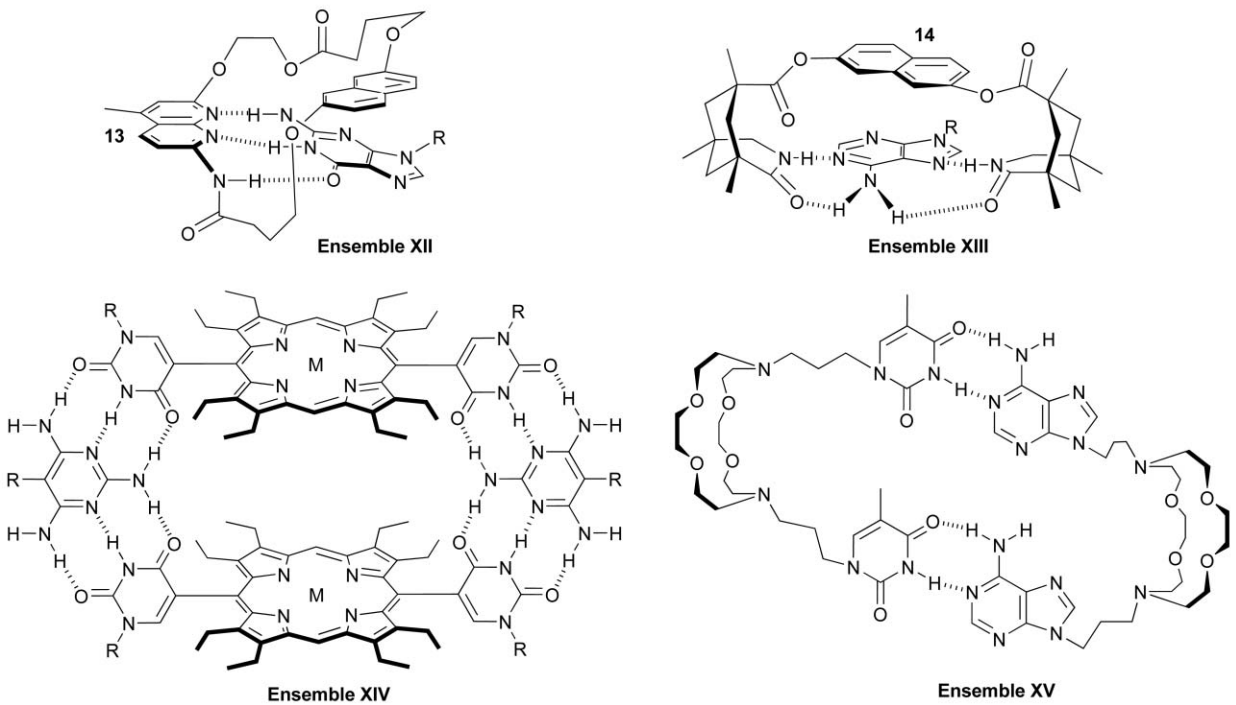

Fig. 10 Molecular cages. Hamilton's naphthyridine receptor **13** for guanine and Rebek's adenine receptor **14**. Both form cages in the presence of their targeted nucleobase substrates *via* a combination of hydrogen-bonding and π-interactions (giving rise to ensembles **XII** and **XIII**, respectively). Lehn's ensemble **XIV** uses porphyrin–diuracil complexes hydrogen-bound to pyrimidines, while Gokel's cage (ensemble **XV**) relies on adenine–thymine base-pairing interactions.

ensemble was found to bind alkyldiamine salts *via* complexation to the crown moiety.

Ensemble **III** (see Fig. 4), from our own group, represents a different kind of self-assembled molecular box.[16] In this case, the overall dimeric complex is stabilized as the result of two sets of complementary adenosine–uridine base-pairs. The complex is rigid due to the presence of the anthracene spacer, a feature that allows for greater conformational control. As a consequence of these design features, ensemble **III** remains intact in $CDCl_3$ (as inferred from ^1H NMR spectroscopic studies) up until the point where 30% DMSO-d_6 (v/v) is added. Fast atom bombardment mass spectrometric (FAB-MS) analyses revealed the presence of both the dimeric and monomeric species, whereas VPO studies gave an M_n value of 2210 daltons, which is close to the mass of 2168 daltons calculated for ensemble **III**. A similar box was obtained when two guanosine–cytidine base-pairing interactions were employed (ensemble **V**; Fig. 4).

As in the case of the polymeric systems discussed above, these examples represent what will likely prove to be the initial vanguard of what could emerge as a particularly rich area of investigation. Indeed, a whole plethora of molecular boxes, capsules, and cages may be readily conceived, including ones that have even more apparent three-dimensional topographies. Many of these, it is expected, could be stabilized *via* the use of multiple base-pairing motifs, including ones involving modified nucleobase systems, such as the pyrrole–inosine derivative **3** discussed above.

Energy and electron transfer systems

An exciting area that has benefited from base-pairing derived ensemble formation is non-covalent energy and electron transfer model generation. Energy and electron transfer events take place in many natural processes such as photosynthesis and phosphorylation. Photosynthetic processes in bacteria occur in membrane-bound protein pigments at a reaction center, while green plant antenna proteins funnel light energy into reaction centers.[38] Once in the reaction center, an electron transfer reaction occurs, producing a charge separated radical–ion pair (CSRP) that is used to drive further chemical reactions. The ability to understand this process has intrigued chemists for quite some time. In this context, we and others[39] came to appreciate that non-covalent model systems might have an important role to play. In particular, they could provide important insights into how various factors, such as driving force, hydrogen-bonding pathways, and inter-chromophore orientations can influence electron and energy transfer rates and thus regulate, in a general sense, biological charge separation processes. Given our experience with nucleobase-derived molecular recognition, we elected to pursue such an approach to the construction of the requisite non-covalent model systems. Our contributions, which date to the early 1990s, have been reviewed previously.[5,40] Nonetheless, for the sake of completeness, they are summarized briefly below.

Our first generation systems consisted of free-base and zinc-porphyrins linked to guanosine and cytidine residues.[11,12] The resulting systems, which were found to dimerize extensively in non-competing solvents, underwent rapid energy transfers from both the singlet and the triplet states following photoexcitation. Among these early systems was the three-component ensemble **XVI** (see Fig. 11), wherein the flanking zinc-porphyrins were used to "harvest" light energy after photoexcitation and to "funnel energy" to the central free-base porphyrin, which served as the energy "trap".[41] This transfer process was found to occur efficiently from both the excited singlet and triplet states. In the case of the singlet state, the calculated rate constant (k_{et}) was $\approx 9 \times 10^8\ s^{-1}$, while the efficiency was *ca.* 60%. These values are in accord with what was predicted from Förster theory, leading to the conclusion that transfer does not occur through the hydrogen-bonding network *per se*. In contrast, triplet energy transfer, with a calculated $k_{et} \approx 1 \times 10^6\ s^{-1}$, occurs *via* a Dexter mechanism, which requires, *inter alia*, energy transfer through the hydrogen-bonds.

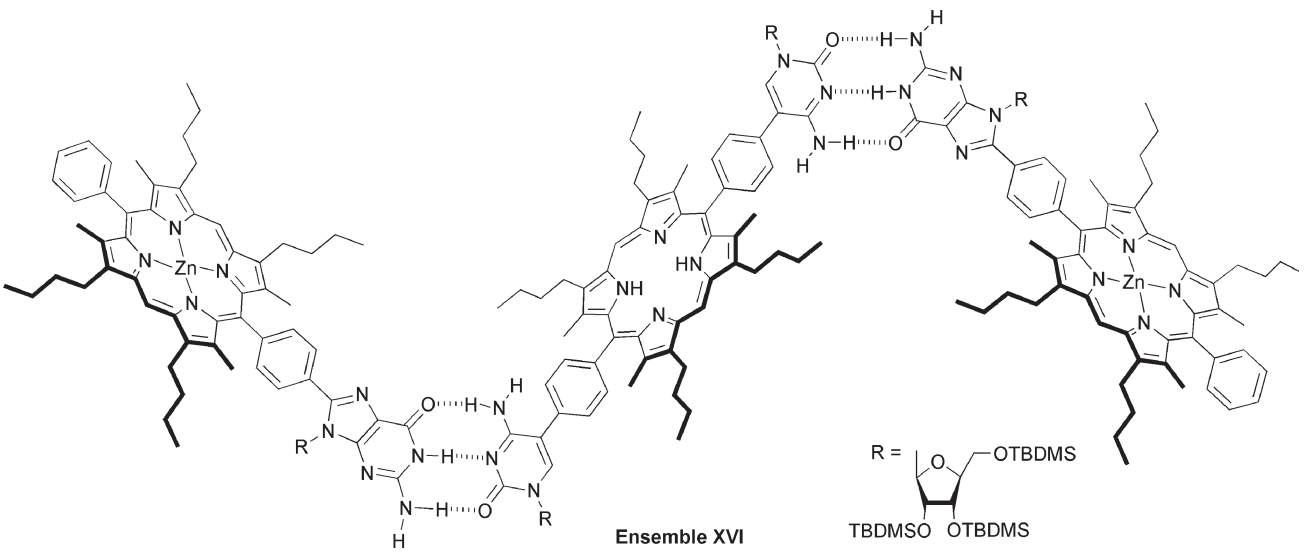

Fig. 11 Non-covalent energy transfer system based on a pair of guanosine–zinc-porphyrin donors and a cytidine–porphyrin acceptor.

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Although the zinc-porphyrin photodonors in our early hydrogen-bonding energy and electron transfer model systems contain a coordinated cation, a more obvious example of metal cation coordination in a non-covalent electron-transfer model system comes from the work of Ward, Barigelletti *et al.* These workers appended ruthenium and osmium polypyridine moieties to guanine and cytosine subunits. The resulting ensembles displayed a ruthenium–guanine to osmium–cytosine energy transfer rate of 8.0×10^7 s^{-1}.[42] The Ru to Os transfer process was found to proceed *via* a Förster mechanism, which, as in the case of our own work, was considered consistent with the conclusion that energy transfer most likely takes place without direct involvement of the intervening hydrogen-bonds.

Ward, Barigelletti *et al.* also synthesized a ferrocene–cytosine complex, which was found to undergo photoinduced electron transfer (PET) when combined with the above mentioned ruthenium–guanine complex. In this case, Dexter-like behavior was seen, which provided evidence for either a ruthenium to ferrocene energy transfer or a possible ferrocene to ruthenium electron transfer, or both. In any case, the key transfer would be expected to be mediated through the guanine–cytosine hydrogen-bonding network.

Given our initial success, considerable effort in our group was devoted to the construction of new electron donor–acceptor systems based on the GC base-pairing motif. These systems were used to model the basic electron transfer process analogous to that leading to the CSRP. Our first generation system, ensemble **XVII** (see Fig. 12), incorporated a zinc-porphyrin appended to guanine and a quinone appended to cytosine.[13] An association constant (K_a), corresponding to the formation of the ensemble from these constituents, was calculated to be 3100 ± 470 M^{-1}. A time-resolved fluorescence study was performed and lifetimes of $\tau_1 = 1.5 \pm 0.2$ ns and $\tau_2 = 0.94 \pm 0.07$ ns were estimated. Also, from these experiments, a derived rate constant of $(4.2 \pm 0.7) \times 10^8$ s^{-1} could be calculated. Due to the large degree of flexibility inherent in ensemble **XVII**, which was thought to complicate the analyses, a more rigid system, specifically ensemble **XVIII**, was synthesized.[43] Time-resolved fluorescence of this system revealed two lifetimes, of 1.8 ± 0.2 ns and 740 ± 90 ps, following photoexcitation, with a rate constant for photo-induced electron transfer (PET) of 8×10^8 s^{-1}. In this case, the PET event, corresponding to charge separation within the non-covalent donor–acceptor complex, was thought to occur *via* a through hydrogen-bond mediated process.

In the most recent examples of PET systems from our group, the goal was to improve on the lifetime of the photoinduced charge separated state. This, it was thought, could be accomplished by increasing the rate of the forward electron transfer step and decreasing that associated with charge recombination. Such considerations led to the synthesis of the rigid ensemble **XIX** (see Fig. 12), wherein a dimethylaniline and anthracene donor–acceptor couple was constructed *via* non-covalent guanosine–cytidine base-pairing interactions.[44] On the basis of ^{1}H NMR spectroscopic titrations, a high association constant, K_a, of 3.8×10^4 M^{-1} was inferred. Unfortunately, time-resolved fluorescence studies revealed that the charge separation rate ($k_{CS} = 3.5 \times 10^{10}$ s^{-1}) and the charge recombination rate ($k_{CR} = 1.4 \times 10^9$ s^{-1}) were such that the charge separated state had a lifetime of only 705 ps.

In an effort to improve further the lifetime of the CSRP, a new donor–acceptor system, ensemble **XX** (see Fig. 12), was synthesized recently.[45] Here, a cytidine-functionalized zinc-porphyrin was used as the photodonor, while a fullerene (C_{60}) bearing a guanosine recognition unit was used as the electron acceptor. The binding constant for ensemble formation was

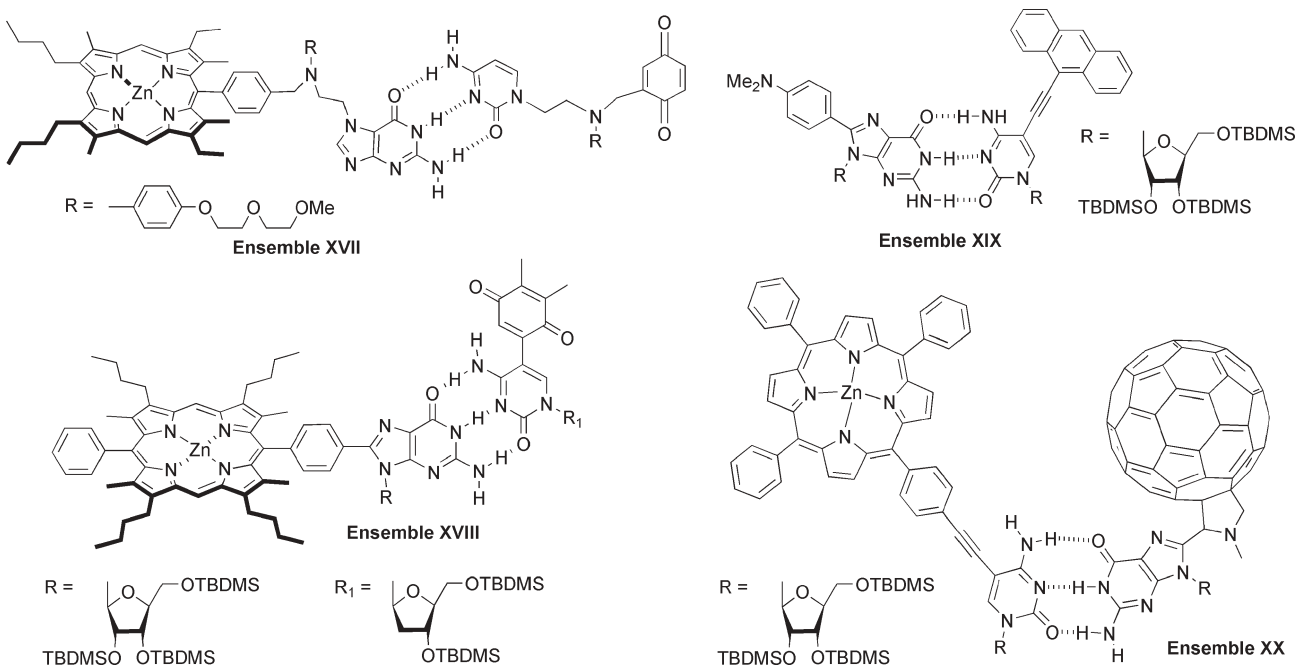

Fig. 12 Non-covalent energy and electron transfer model systems developed in the Sessler group. The flexible first generation ensemble **XVII** was followed by the more rigid second generation ensembles **XVIII** and **XIX**. Also shown is ensemble **XX**, which displays improved charge separation characteristics as the result of incorporating a fullerene acceptor subunit.

calculated to be $K_a = (5.1 \pm 0.5) \times 10^4\ M^{-1}$ in CH_2Cl_2, as judged from steady-state fluorescence spectroscopic studies. Kinetic analyses, carried out using time-resolved spectroscopy, revealed a CSRP lifetime of 2.02 μs, *i.e.*, three orders of magnitude larger than that seen in the case of ensemble **XIX**.

The success we have seen in the construction of guanosine–cytidine stabilized non-covalent energy and electron transfer model systems sets the stage for further work in this area. While a variety of new directions can be envisioned, currently, efforts are largely focused on addressing two fundamental research questions, namely (1) how do the electronics of spacers effect the PET rate? and (2) what effect is seen as the distance and orientation of the donors and acceptors is varied across a canonical base-pairing "gap"? Both questions relate to the so-called β term in electron transfer theory and are thus expected to provide new understanding that will complement that obtained from analogous studies carried out using models based on more conventional covalent donor–acceptor connections.

Conclusions

While many elegant base-pair stabilized hydrogen-bonding motifs have been prepared in recent years, it is nonetheless clear that much remains to be done. The synthetic efforts required to develop early generation dimeric base-pairing systems allowed researchers to understand the key features of self-assembly in functionalized nucleobase systems. As importantly, this work established that such motifs could be used to effect molecular recognition under conditions that differ from those found in typical biological systems. These initial systems have thus paved the way to the development of more elaborate supramolecular structures containing more than two molecular recognition entities, including trimers, quadruplets, hexameric rosettes, and ribbon-like structures. Some of these systems have seen application in the area of energy and electron transfer model studies, whereas others have been exploited to produce supramolecular polymers and molecular cages. In all cases, useful applications can be envisioned or are being actively explored. For instance, novel nucleobase-derived energy and electron transfer systems are allowing key features of the photosynthetic processes to be studied in detail. Likewise, supramolecular polymeric arrays with nucleobase functionalities, although representing a field that is still in its infancy, show promise in the areas of nanotechnology and materials chemistry. Finally, molecular cages show promise as transport agents for various substrates, including potentially a range of pharmaceuticals. In conclusion, therefore, the use of base-pairing motifs in supramolecular chemistry, although marked by significant achievements, represents an area where the best is surely yet to come.

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