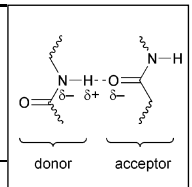
Methods of modulating hydrogen bonded interactions in synthetic host–guest systems



Graeme Cooke*[a] and Vincent M. Rotello[b]

[a] *Centre for Biomimetic Design and Synthesis, Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, UK EH14 4AS*
[b] *Department of Chemistry, University of Massachusetts at Amherst, Amherst, MA 01002, USA*

Received 9th April 2002
First published as an Advance Article on the web 19th July 2002

Hydrogen bonded interactions are among the most important non-covalent interactions in supramolecular chemistry. The strength, selectivity and directionality inherent in hydrogen bonding processes have allowed the creation of complex and efficient molecular hosts capable of selective binding to a wide variety of complementary guests. Major advances in controlling host–guest complexation have occurred in the last decade, principally through systematic modification of the electrostatic properties and/or geometry of the hosts, thereby fine-tuning the molecular recognition event. More recently, systems have been developed which allow the effectiveness and selectively of hydrogen bonding interactions to be reversibly modulated by an external stimulus, more accurately mimicking biological systems and providing building blocks for the construction of novel advanced materials, sensors and devices. In this review, we highlight some of the methods available for modulating the strength and selectivity of hydrogen bonded interactions in synthetic host–guest systems.

1 Introduction

Hydrogen bonding interactions play a crucial role in controlling both the structure and function of biological systems. Highly specific patterns of complementary inter- and intramolecular hydrogen bonds are involved in maintaining the integrity of biomolecular structure, information storage and transfer, replication and catalysis in living organisms.[1] Likewise, hydrogen bonding has arguably become the most useful interaction within the toolbox of supramolecular chemistry. The strength of hydrogen bonding arrays (typically 12–120 kJ mol^{-1} (3–29 kcal mol^{-1})), coupled with their high degree of directionality and selectivity, has been used to create efficient host molecules for a range of biological guests in aqueous and non-aqueous environments.[2] More recently, supramolecular chemists have also directed their attention away from purely biomimetic systems to create host–guest complexes with novel advanced materials applications in the form of novel hydrogen bonded macromolecules[3] and liquid crystalline[4] derivatives.

The reversibility and tuneability of hydrogen bond formation is of fundamental importance in the dynamic environment within biological systems. Indeed, it is well established that the effectiveness of hydrogen bonded interactions between biotic host–guest systems are profoundly influenced by other non-covalent interactions (*e.g.* ion–ion, dipole–dipole, π-stacking and hydrophobic) fine-tuning their structure, reactivity and function. As a result, attention in recent years has focused upon methods of reversibly modulating the strength of hydrogen bonded interactions in synthetic host–guest complexes to provide systems that more accurately mimic the structure and

Graeme Cooke was born in Hartlepool, UK, in 1966. He received his BSc in Chemistry in 1989 from the Hatfield Polytechnic (UK), and his PhD from the University of Durham (UK) in 1992, working on conducting Langmuir-Blodgett films with Professors Martin Bryce and Mike Petty. Following completion of postdoctoral work at Arizona State University (USA) with Professor Robert Pettit, he returned to the UK to become Senior Demonstrator at the University of East Anglia (UK) (1994–1996). Following lecturing positions at the Universities of Teesside (UK) and Northumbria at Newcastle (UK), he was appointed Lecturer of Organic Chemistry at Heriot-Watt University in October 2000. His research focuses upon the nanotechnological and biological aspects of supramolecular electrochemistry.

Vincent Rotello received his BS from Illinois Institute of Technology in 1985. He obtained his PhD in 1990 from Yale University, where his research focused on the synthesis of heterocyclic natural products. From 1990–93, he was an NSF postdoctoral fellow with Julius Rebek Jr. at M.I.T., where he worked on self-replicating systems and recognition in water. Since 1993, Professor Rotello has been at the University of Massachusetts at Amherst as an Assistant Professor from 1993-1998, Associate Professor (1998–2001) and Professor (2001–present) of Chemistry, with appointments in Polymer Science and Engineering, and the Program in Molecular and Cellular Biology. He has been the recipient of the NSF CAREER, and Cottrell Scholar award, as well as the Camille Dreyfus Teacher-Scholar, and the Sloan Fellowships. His research focuses on the application of molecular recognition to devices, polymers, nanotechnology, and biological systems.

function of their biological brethren.[5] These studies also present the longer term benefit of providing systems which could be utilised in the fabrication of sensors and devices.

In this review, we will highlight some of the important methods available for modulating the efficiency and selectivity of hydrogen bonded interactions of synthetic host–guest systems by reference to specific examples from the recent literature. However, due to constraints in the scope of this article, many excellent examples have had to be omitted.

2 Modulation of hydrogen bonding through substituent effects

Hydrogen bonding arises from a combination of electrostatic, induction, charge-transfer, and dispersion energy.[6] Of these effects, electrostatic interactions generally play the largest role (Fig. 1). This allows us to create a model where increasing the positive charge upon the donor (D) proton and/or increasing the negative charge upon the acceptor (A) atom are both expected to increase the strength of the interaction.

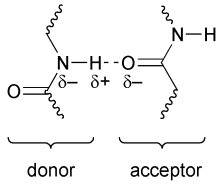


Fig. 1 Typical hydrogen bond, showing donor and acceptor groups, and electrostatic charges.

The strong dependence of hydrogen bonding on electron distribution provides a facile means of controlling the strength of the interaction. The most straightforward and easily regulated means of controlling electron distribution is through substituent effects. In a systematic study, Wilcox and co-workers prepared a series of thioureas including **1a**–**h** that feature a range of substituents and studied their binding to zwitterionic sulfonate **2** (Fig. 2).[7] The first thing apparent from these studies was the

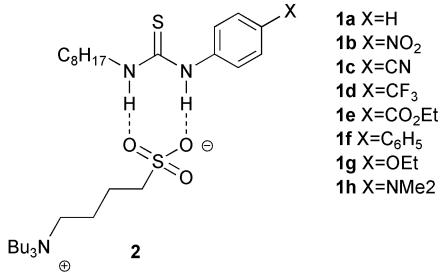


Fig. 2 Urea–sulfonate dyad studied by Wilcox and co-workers.

profound effect of electronics of the recognition process. Association constants (K_a) measured in $CDCl_3$, ranged from 6600 M^{-1} for nitrobenzene-substituted receptor **1b** to 10 M^{-1} for receptor **1h** featuring the dimethylaniline substituent. This difference in binding energy corresponds to a 15.9 kJ mol^{-1} (3.8 kcal mol^{-1}) difference, and arises from the increase in hydrogen bond donating capability of (primarily) the proximal N–H group. Reasonable correlation was obtained in these studies using a variety of linear free energy relationships, with the best fit obtained through fitting to σ-values. Computational studies of these systems were then undertaken. Using 6-31G* single point calculations based on AM1 geometries, excellent correlation was obtained between the surface electrostatic potential of the proximal N–H proton and the observed binding energy. This relationship provides a somewhat less time consuming means of predicting binding affinities, as well as providing further evidence for the primarily electrostatic origins of hydrogen bonding.

The relationship between electronics and hydrogen bonding in a more complex system was studied by Rotello and co-workers (Fig. 3).[8] In these studies, both dimerization of hosts **3a**–**g** (Fig. 3b) and recognition of guest **4** (Fig. 3a) were found to be determined by the nature of the substituents. Dimerization constants (K_{dim}) measured in $CDCl_3$, ranged from 95 M^{-1} for **3a** with a phenyl- substituent to 41 M^{-1} for the *p*-nitrophenyl-substituted **3c**. Good correlation was observed between $\Sigma\sigma_{m,p}$ with electron releasing groups enhancing dimerization and electron withdrawing substituents diminishing recognition over a rather narrow (2 kJ mol^{-1}, 0.5 kcal mol^{-1}) range. Larger substituent effects were observed in host **3**–flavin **4** recognition after explicit correction was made for host dimerization. In these studies, the guest affinity increased with electron withdrawing groups and decreased with electron donating substituents. The K_as measured in ($CDCl_3$) in this study ranged from 97 M^{-1} for *p*-nitrophenyl- substituted **3c** to 12 M^{-1} for *m,p*-dimethoxy-substituted receptor **3h**, corresponding to a 5.0 kJ mol^{-1} (1.2 kcal mol^{-1}) range. As with dimerization, a reasonable correlation was observed between $\Sigma\sigma_{m,p}$ and recognition.

The relationship between substituent and guest affinity in the host **3**–guest **4** system can be understood through examination of the binding surface of **3**. Increasing the electron density at the central nitrogen of the DAD surface of **3** is expected to enhance hydrogen bonding at this site. This enhancement was supported experimentally by the maximum shifts for the N(3) proton of **4**, which increases from 12.2 ppm for **3b** to 19.8 ppm for **3h**. Increases in electron density, however, will also reduce the positive charge on the donor amide protons of **3**, diminishing interactions at these two positions. From the data, it is clear that electronic effects at these two positions outweigh that of the hydrogen bond-accepting nitrogen.

Molecular recognition processes provide a tool for studying electronic communication in complex systems, a key pre-requisite for molecular wires and other devices. The applicability of this method was demonstrated using receptors **5a**–**e**, vinylogous analogues of **3** (Fig. 4).[9] Receptors **5a–e** showed very weak correlation between substituents and dimerization.

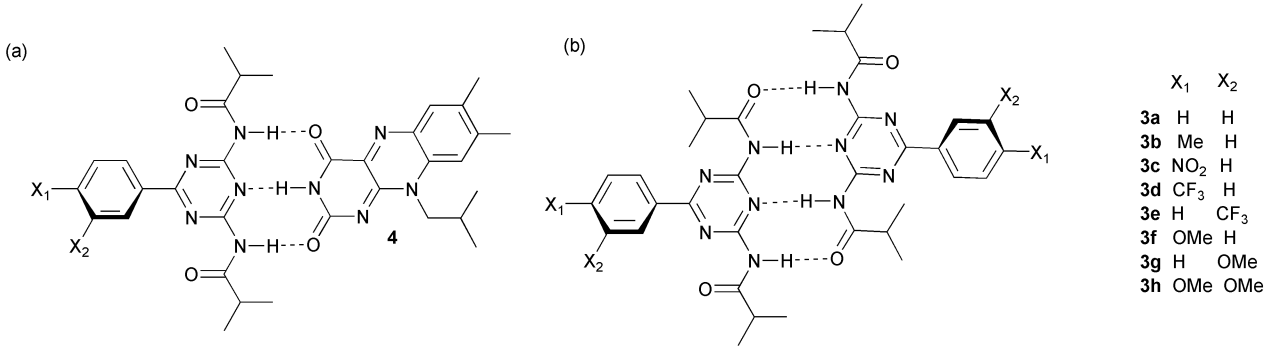


Fig. 3 (*a*) Host **3**–guest **4** binding through a DAD–ADA binding surface. (*b*) Host **3** dimerization through ADAD–DADA binding.

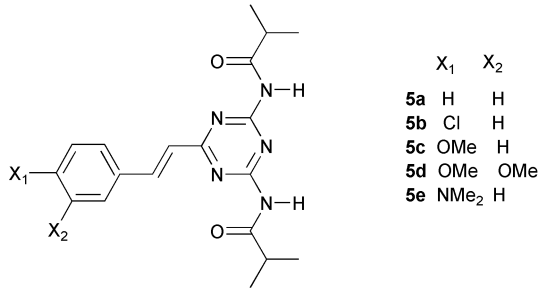


Fig. 4 Extended conjugated system of receptor **5a–e**.

There was, however, an appreciable substituent effect on guest **4** recognition, with a K_a of 82 M^{-1} observed for chloro-substituted receptor **5b**, and 37 M^{-1} observed for dimethylamino-functionalized receptor **5e**. DFT calculations (B3LYP 6-31G*//HF 3-21G) performed on receptors **5b** and **5e** pointed out two interesting facts. Firstly, it was shown that electrostatic effects appear to predominate at the central nitrogen of the DAD bonding face, while polarizability effects dominate for the amide hydrogen bond donating sites. Secondly, dramatic changes in electron density were observed throughout the structure of **5b** upon binding of guest **4**. In contrast, very little change was observed in the 'push–pull' system of host **5e**, suggesting that the dimethylamino serves as an electron 'buffer' donating electrons on demand.

All of the above systems rely to some extent on through-bond communication of electron density. To provide a system for studying 'polar–π' interactions (*e.g.* electrostatic and through-space effects), Siegel and co-workers synthesised receptors **6a–c** (Fig. 5).[10] Through comparison of the pK_a of *m*- and *p*-

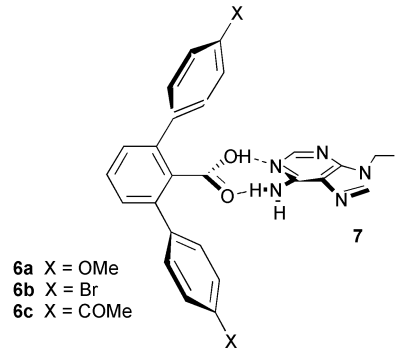


Fig. 5 Systems for studying 'polar–π' interactions.

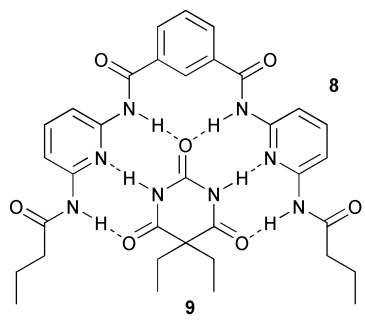
substituted analogues of this system, they concluded that communication between the flanking aromatic rings and the carboxylic acid moiety occurred through π-polarization and field effects. This conclusion could be extended to recognition of 9-ethyladenine **7**, where similar behaviour was observed for receptors **6a–c**. However, the substituent effects were much more pronounced for binding of **7** compared to pK_a, leading to the conclusion that secondary interactions between host and guest take place.

3 Modulation of intermolecular hydrogen bonding efficiency *via* intramolecular host pre-organization and cooperative polarisation

Host molecules that do not undergo significant conformational reorganisation upon binding to a guest are said to be *pre-organised*. The overall free energy of a hydrogen bonded complex is determined by the difference between the unfavourable reorganisation energy required by the host to achieve a complementary binding site for the guest and the enthalpically favourable binding energy upon host–guest complexation. Thus, the preorganisation of the D and acceptor A residues of host systems drastically reduces the overall free energy of complexation by minimizing the necessity for this unit to undergo conformational readjustment prior to binding to the guest.

One early example of a pre-organised synthetic host system was described by Chang and Hamilton.[11] In this study, host derivatives **8** and **10** were synthesised, which both possess the correct D and A arrays to form six hydrogen bonds with complementary barbital guest **9** (Fig. 6). ^{1}H NMR titration data ($CDCl_3$) revealed a 100-fold smaller K_a for the **8·9** complex compared to the **10·9** complex. This difference was explained in terms of the differing degrees of host pre-organisation between these two systems. In macrocyclic host **10**, the diacylaminopyridine units are pre-organised in such a manner to help enforce an inwardly pointing D and A motif. In the acyclic host **8**, however, the hydrogen bonding sites are free to adopt a number of conformations, thereby considerably lowering the degree of pre-organisation, and thus the effectiveness of host–guest complexation.

In recent years a new generation of pre-organised host–guest systems have emerged in which unfavourable intermolecular repulsive interactions between D···D and A···A sites have also been minimised. This work has predominately focused upon the development of host–guest systems that are capable of forming arrays of D and A atoms which can undergo homo- and heterodimerisation through quadruple hydrogen bonds. Of the two possible complementary motifs, the DDAA arrangement is



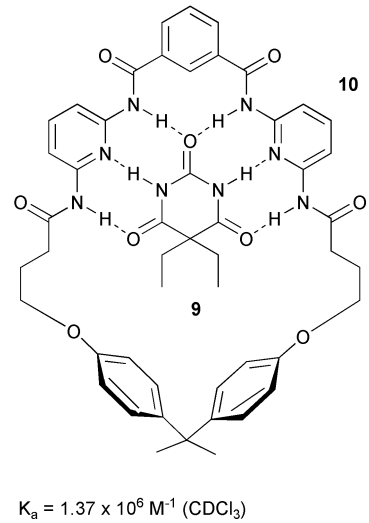


Fig. 6 Effect of host preorganisation on hydrogen bonding efficiency.

more attractive for forming effective hydrogen bonded complexes than the DADA arrangement, principally due to the former giving rise to two repulsive and six attractive secondary interactions, whereas the latter has only six repulsive secondary interactions (Fig. 7).

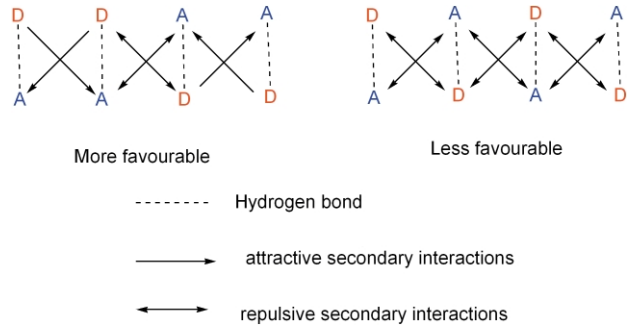


Fig. 7 Attractive and repulsive secondary interactions in quadruple hydrogen bonded systems.

In an elegant series of studies, Meijer and co-workers have developed ureidopyrimidone systems which have the ability to form stable hydrogen bonded dimers in solution *via* quadruple hydrogen bonded interactions (Fig. 8).[12] The predominant pyridimin-4(1*H*)-one was shown to have the propensity to tautomerise to the pyrimidin-4-ol form leading to the formation of dimers *via* pre-organised DDAA or DADA arrays, respectively. In both motifs, the linear array of four hydrogen bonding sites were pre-organised by an intramolecular hydrogen bond, resulting in the formation of self-assembled systems with larger K_{dim} than those predicted for non-preorganised arrays.[13] Indeed, the combined effects of pre-organisation and minimisation of repulsive secondary interactions juxtaposed within in the DDAA motif resulted in a K_{dim} in excess of 10^7 M^{-1}, whereas the pre-organised DADA arrangement led to strong O–H···O=C hydrogen bonds of the pyrimidin-4-ol form and resulted in a lower K_{dim} of around 10^5 M^{-1} ($CDCl_3$).[14]

Using ^{1}H NMR spectroscopy, Meijer discovered that the relative ratios of the pyridimin-4(1*H*)-one and the pyrimidin-4-ol form of the ureidopyrimidone dimers were critically dependent upon the electronic characteristics of the functionality in the 6-position of these heterocycles. For example, electron donating groups resulted in the formation of complementary DDAA arrays characteristic of the pyridimin-4(1*H*)-one form (*e.g.* **11**, 99% pyridimin-4(1*H*)-one), whereas electron withdrawing functionalities gave rise to complementary DADA arrays characteristic of the pyrimidin-4-ol form (*e.g.* **12**, 99% pyrimidin-4-ol). This electronic modulation of tautomer equilibria was rationalised in terms of the electron withdrawing group in the 6-position destabilises the enone structure of the pyrimidinone tautomer, thereby promoting the more favourable pyridiminol form.

Corbin and Zimmerman have developed a heterocyclic receptor **13** which can also form effective homo- and heterodimers (Fig. 9).[15] However, in this case effective dimerisation was not significantly hindered by prototropy (tautomerism resulting from proton shifts), as three major dimerisation motifs were capable of forming strong hydrogen bonds (K_{dim} = 10^7 M^{-1}, $CDCl_3$) through DDAA arrays. ^{1}H NMR spectra were consistent with the formation of **13·13** (13%), **14·14** (39%) and **13·14** (46%), in which the alkyl substituent maintained a similar spatial arrangement. Unfortunately, in addition to the dimers formed through DDAA arrays, a small amount (2%) of **15·15** formed *via* DADA arrays was also detected.

Lippert and co-workers in a series of studies have replaced the weakly acidic proton between hydrogen bonded nucleobases by linear metal fragments to create metal-modified base pairs and larger aggregates.[16] In a recent study, they have synthesised a pre-organised L-shaped host **16** for 1-methylcytosine **17**, in which the N(1) and N(7) positions of the adenine moiety of the host were connected to thymine and guanine, respectively, by two linear *trans*-$(NH_3)_2Pt^{II}$ units (Fig. 10). In aprotic solvents, it was shown that an intramolecular hydrogen bond between the adenine and the guanine moieties helps to further pre-organise the host, allowing guest **17** to be bound to the primary guanine and secondary thymine receptors of **16** by five hydrogen bonds. ^{1}H NMR dilution experiments measured in $(CD_3)_2SO$ revealed a 3 fold larger K_a for **16·17** compared to normal three point Watson-Crick hydrogen bonding motif between cytosine and guanine. Interestingly, the NMR experiments of **16·17** revealed a significant downfield shift for the C(5)H of the 1-methylcytosine guest, which is indicative of this

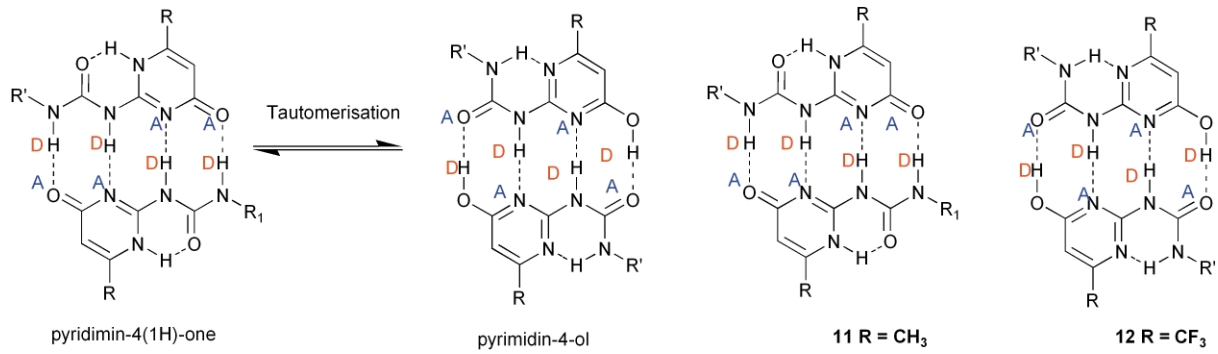


Fig. 8 Dimerisation of ureidopyrimidones.

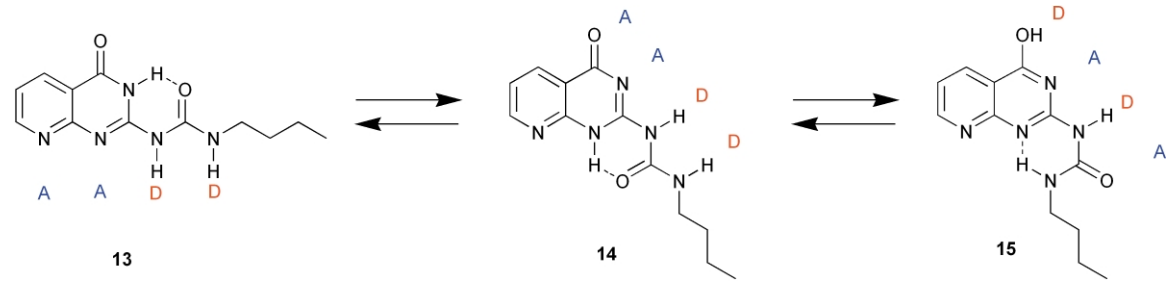


Fig. 9 Tautomerism of heterocycle **13**.

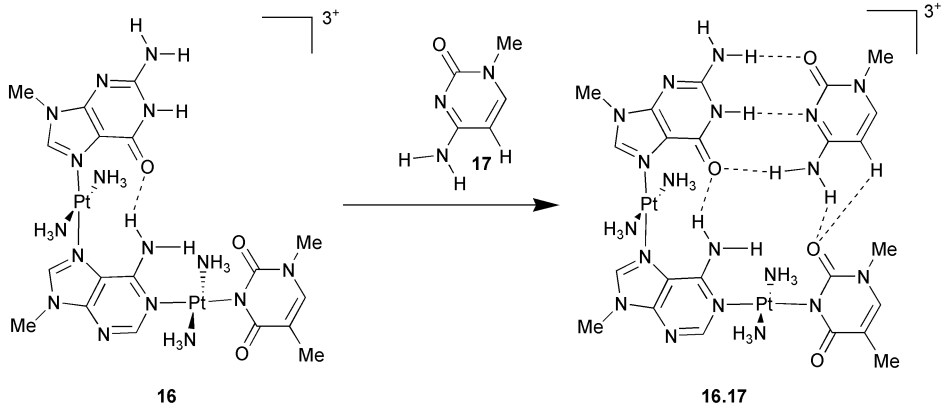


Fig. 10 A pre-organised cationic receptor based upon metal-modified nucleobases.

proton being involved in intermolecular hydrogen bonding with the thymine moiety of **16**.

Cooperative polarization, a phenomenon whereby the Lewis acidity/basicity of a remote unit controls the intermolecular interactions between host–guest complexes by polarising one of the components, are frequently observed in biological polymers. Smith and co-workers have utilised this effect to control the hydrogen bonding and ion-dipole interactions between abiotic amide-based host system **18** and the acetate anion (Fig. 11).[17] In receptor **18a**, a Lewis acid group was attached *ortho*- to a urea group, and as a result, had the ability to intramolecularly polarise the urea carbonyl moiety (*e.g.* **18b**). The increased acidity of the urea NH residues due to this polarisation process resulted in **18b** being an effective host for acetate (**18b·acetate** $K_a = 7 \times 10^3\ M^{-1}$, $(CD_3)_2SO$). The K_as for model compounds **19** and **20** with acetate, where clearly cooperative polarisation cannot occur, were an order of magnitude smaller (**19·acetate** $K_a = 3.9 \times 10^2\ M^{-1}$, **20·acetate** $K_a = 3.7 \times 10^2\ M^{-1}$, $(CD_3)_2SO$).

4 Supplementing hydrogen bonding with other supramolecular interactions

The stabilisation of hydrogen bonded interactions *via* π-stacking is a prevalent theme in biological systems. Inouye and co-workers have developed ferrocene-based artificial receptors to model the involvement of π-stacking interactions in the stabilisation of nucleobase recognition (Fig. 12).[18] They exploited the 'atomic ball bearing' character and inter-ring spacing of 0.33 nm of the ferrocene moiety to construct receptors that could simultaneously form hydrogen bonded and π-stacked complexes with 1-butylthymine **22**. The K_as of the complexes of **21a**–**21e** with **22**, determined using ^1H NMR titration in $CDCl_3$, were found to be dependent on the nature of the polycyclic aromatic units. The K_a for system **21e** was nearly double that obtained for receptor **21a**, where additional π-stacking interactions are clearly not possible. Furthermore, the expanse of the π-system was also shown to play a role in the stabilisation of the hydrogen bonded complexes, with receptors

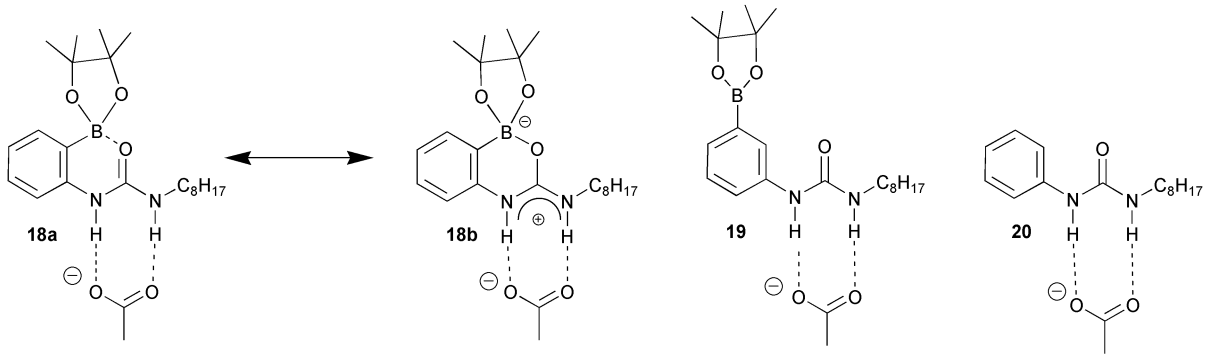
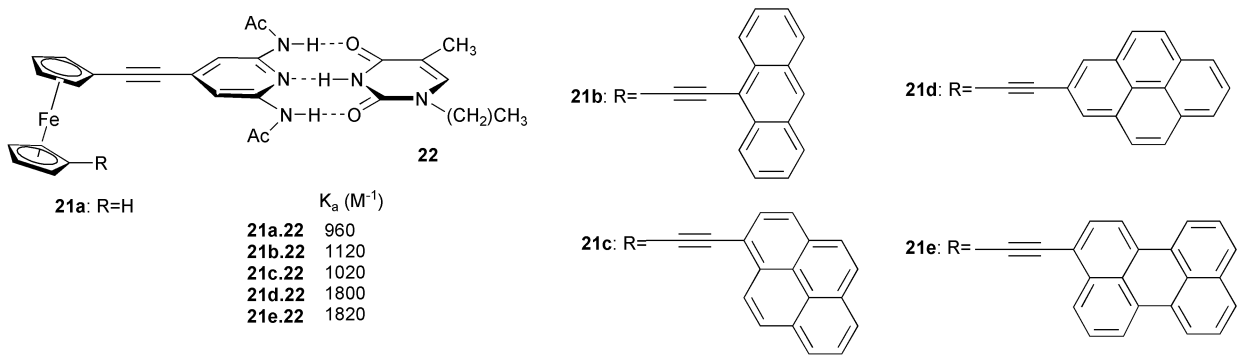


Fig. 11 Control of hydrogen bonding efficiency *via* cooperative polarisation.



	K_a (M^{-1})
21a.22	960
21b.22	1120
21c.22	1020
21d.22	1800
21e.22	1820

Fig. 12 Stabilisation of hydrogen bonds using π–stacking interactions.

21d and **21e** giving rise to larger K_as than systems **21b** and **21c**, where poorer intermolecular π–π orbital overlap was likely to occur.

In recent years, cation–π interactions have become an important non-covalent interaction within the supramolecular chemist's arsenal, and have been utilised in the design of novel host–guest systems. For example, Kim and co-workers have developed a cage-type NH_4^+ receptor **23** which utilised cation–π interactions to supplement hydrogen bonded interactions (Fig. 13).[19] In designing receptor **23**, careful consideration was made to ensure the oxygen lone pairs had the correct geometry to form hydrogen bonds with the tetrahedral NH_4^+ ion **24**. Furthermore, the spatial arrangement of the benzene rings were ideally positioned to allow strong cation–π interactions within the rigid cavity. X-Ray crystallography revealed that **24** is located within the centre of the receptor, and is held in place by a combination of hydrogen bonds formed with the six oxygen atoms and cation–π interactions with the top and bottom benzene rings. To quantify the role of cation–π interactions in stabilising hydrogen bonds, receptor **25** was synthesised and its efficiency of NH_4^+ binding was compared to that of **23**. The K_a for **23·24** was ten times greater that than of **25·24**, where cation–π interactions can only occur between **24** and one benzene ring.

A feature observed in the X-ray crystal structures of some flavoenzymes is a motif whereby the electron deficient flavin nucleus and electron rich donor atoms are juxtaposed. To investigate the role of donor atoms in flavin recognition, Rotello and co-workers have investigated the host–guest complexation between a family of xanthene-based hosts **26a**–**26f** and isobutyl flavin **4** (Fig. 14).[20] In these systems, the rigidity of the xanthene units promoted an architecture in which the donor unit of the aryl moiety was in direct contact with the electron deficient flavin nucleus. NMR and fluorescence-quenching titrations measured in $CDCl_3$ and $CHCl_3$, respectively, have quantified the role of donor atom-π interactions, and have shown that a substantial increase in flavin binding upon the incorporation of a donor atom in receptors **26a**–**26e** compared to control **26f**. It is noteworthy that the thiomethyl receptor **26a** showed the largest increase in K_a, presumably due to enhanced electrostatic overlap due to the size and polarisability of the sulfur atom.

Charge-transfer (C-T) interactions have received relatively scant attention as interactions to supplement hydrogen bonds in host–guest systems. Mallouk and co-workers have developed an electron deficient cyclophane **27**, in which electron rich aromatic guests have been shown to form C-T complexes with the electron deficient viologen walls of the receptor in aqueous solution (Fig. 15).[21] The rigid cyclophane possessed a 1,2-dia-

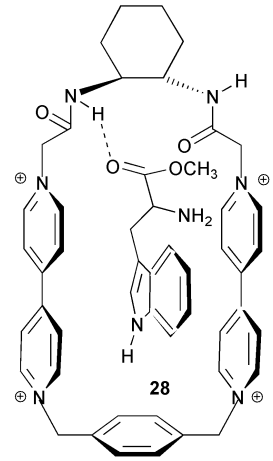


Fig. 15 C-T interactions supplementing hydrogen bonds.

midocyclohexane moiety which had the propensity to also form hydrogen bonds to appropriately functionalised side chains of aromatic amino acid derivatives. Molecular mechanics simulations based upon a tryptophan methyl ester derivative **28** and cyclophane **27**, have indicated the presence of hydrogen bonds between the carbonyl group of the guest and the amino groups of the host together with π-stacking interactions between the electron rich tryptophan unit and the electron deficient bipyridinium rings.

Cooperativity (positive) is a phenomenon whereby an initial supramolecular interaction causes subsequent recognition processes to occur more easily by inducing a conformational change in the host–guest system. Cooperativity plays an important role in maintaining the stability and selectivity of biological systems and, in particular, is partly responsible for the ready formation of the DNA duplex. Hunter and Bisson have exploited

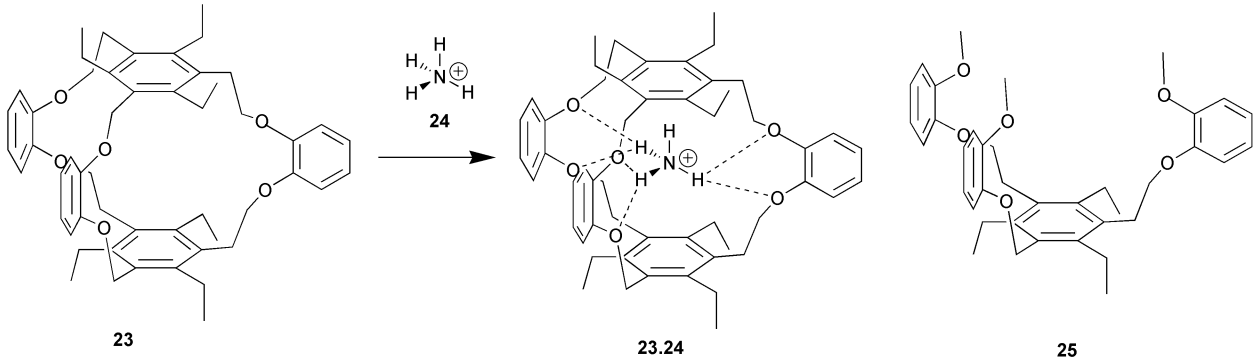
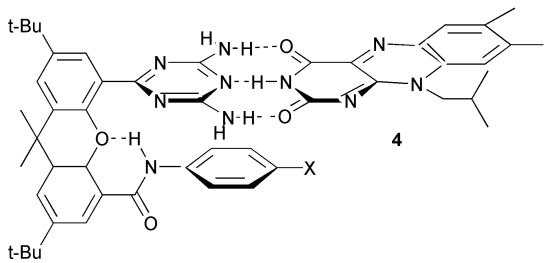


Fig. 13 Supplementing hydrogen bonding with cation–π interactions.



	K_a (M^{-1})
26a X = SCH_3	4830
26b X = $N(CH_3)_2$	3760
26c X = Br	3500
26d X = F	2910
26e X = OCH_3	2210
26f X = CH_2CH_3	960

Fig. 14 Stabilisation of intramolecular hydrogen bonds using donor atom–π interactions.

cooperative interactions to develop a range of double stranded zipper-like synthetic oligomers, which form remarkably effective homo- and heterodimers in solution (Fig. 16).[22] Using a combination of NMR and X-ray crystallography, hydrogen bonded and edge-to-face π-π interactions were implicated in the formation of the zipper structure. Moreover, ^{1}H NMR dilution and titration data ($CDCl_3/CD_3OD$ (95 : 5)) indicated that as the length of the oligomer increases, the cooperativity between individual recognition sites leads to a major increase in the stability of complexes (*e.g.* **29** $K_a = 1.8 \times 10^1\ M^{-1}$ whereas **30** $K_a = 5.5 \times 10^4\ M^{-1}$).

The convergence of multiple binding motifs to regulate the structure and reactivity of biological macromolecules is a prevalent theme in nature. This so-called *allosteric effect* has spawned a number of investigations to develop synthetic receptors capable of mimicking the complexity of biological systems. For example, Inouye and co-workers have utilised cation ligation mediated aromatic π-stacking to control the stabilisation of hydrogen bonding interactions between 2,6-diacylamidopyridine and 1-butylthymine (Fig. 17).[23] Addition of Na^+ to a solution of **31·22** resulted in the conformation of oligoethyleneoxy chain to change from a more extended to a "scorpion" like arrangement, which allowed the anthracene ring to stabilise the intramolecular hydrogen bonded complex through π-stacking interactions. The addition of sodium cations to **31·22** resulted in a six fold increase in the K_a of the complex (K_a **31·22** = 1150 M^{-1} and K_a **31·22·Na$^+$** = 7100 M^{-1} measured in $CDCl_3$). The change in the binding constant was not solely controlled by aromatic π-stacking interactions, since synthetic manipulation of the electron density of the anthracene component was also found to influence the degree of allostery.

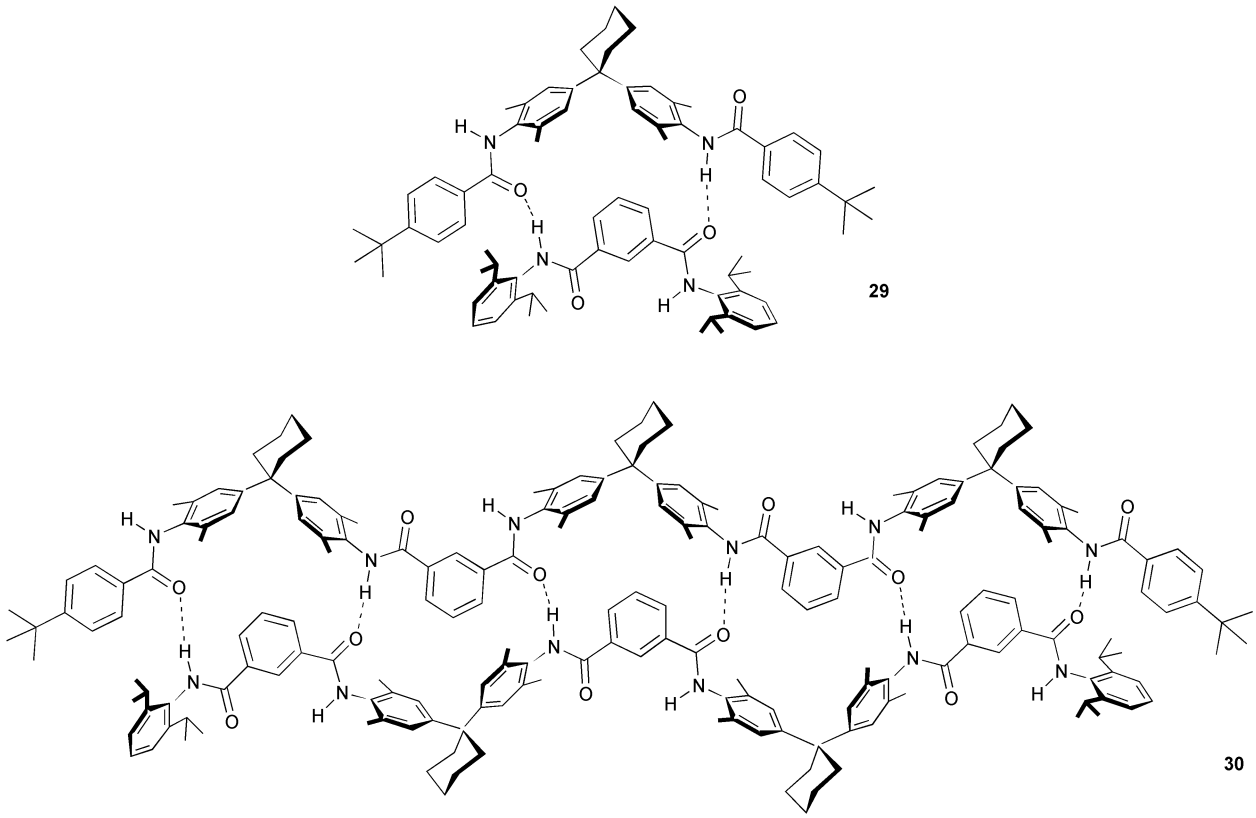


Fig. 16 Cooperativity in the assembly of zipper complexes.

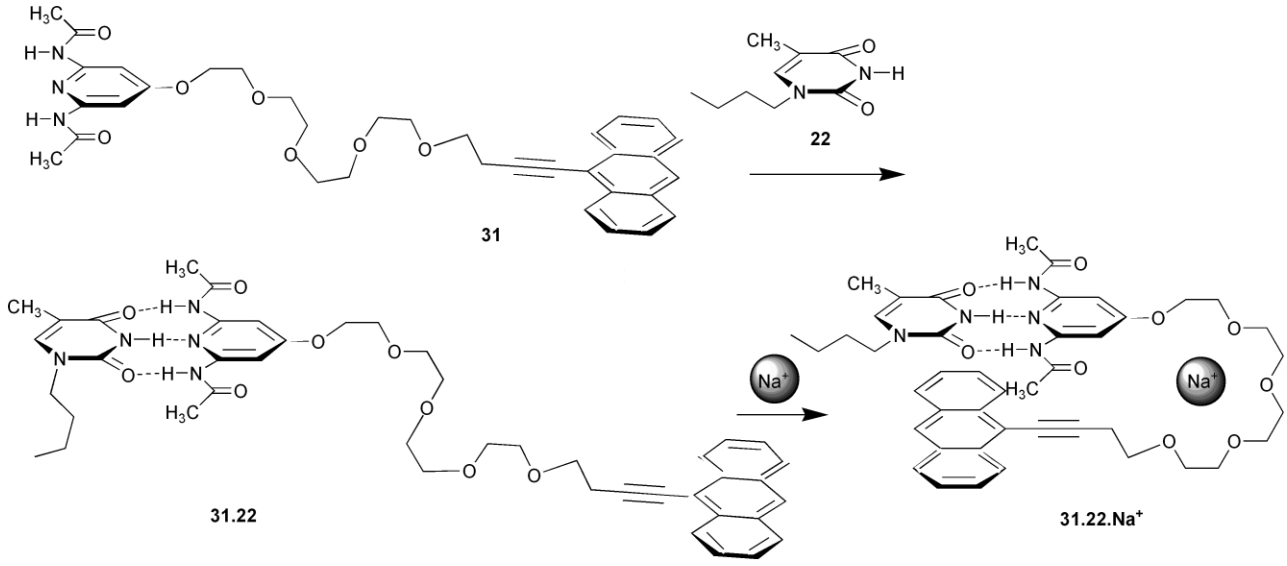


Fig. 17 Stabilising hydrogen bonding interactions using metal ion coordination and π-stacking interactions.

Synthetic receptors where the induced conformational change in receptor geometry brings about a decrease in the binding efficiency (negative allostery) of hydrogen bonded host–guest systems are rare. Recently, Al-Sayah and Branda have reported the hydrogen bonded host–guest dyad **32·33** that can be disrupted upon the addition of Cu^{I} ions (Fig. 18).[24] The diaminotriazine moiety of **32** possessed the appropriate arrangement of D and A sites to allow effective hydrogen bonding interactions to occur with complementary imide-based guests (*e.g.* uracil). However, when **33** was exposed to Cu^{I} ions, the two bipyridine arms rotated towards each other in order to form the metal-ligand coordination complex **34**. The chelation of the bipyridine units to the metal ion forced the exocyclic C–N bonds to rotate by 180°, thereby causing the guest to be expelled from the resulting non-complementary binding site. The process proved to be reversible, as the metal ion could be extracted from the coordination site using an excess of a stronger coordinating ligand (*e.g.* 2,9-dimethyl-1,10-phenanthroline), thereby allowing the original hydrogen bonded complex to be reformed.

5 Redox modulation of hydrogen bonding processes

The interplay between redox events and molecular recognition is a widespread theme in biological systems.[25] Redox enzymes use specific enzyme-cofactor interactions to control the redox behavior of organic cofactors such as quinones, flavins, nicotinamides and pterins to regulate the reactivity of the cofactor. This control is exerted through the redox state-specific binding of the protein to the cofactor, a fundamental feature of biology and a useful tool for effecting the electrochemical control of molecular host–guest systems.[26,27]

A study by Rotello and co-workers explored the effect of hydrogen bonding on guest redox potential using a host–guest system featuring the flavin **4**-diaminopyridine **35** dyad as a model for flavoenzyme activity (Fig. 19).[28] In these studies, large changes (+155 mV) in redox potential of flavin **4** were observed upon addition of host **35**. Concomitantly, enhanced binding of **35** to the flavin radical anion $\mathbf{4_{rad}}^{-}$ was observed, but not quantified in this publication. Eqn. 1, however, allows direct quantification of redox-modulated recognition:

$$\frac{K_a(\text{red})}{K_a(\text{ox})} = e^{\frac{nF}{RT}(E_{1/2}(\text{bound})-E_{1/2}(\text{bound}))} \quad (1)$$

where K_a(ox) and K_a(red) are the association constants in the oxidized and reduced form, $E_{1/2}$(unbound) and $E_{1/2}$(bound) are the standard reduction potentials in the unbound and receptor-bound form, respectively, and n is the number of electrons involved in the redox process (one in this case). Using this equation, we can establish that an almost 500-fold enhancement of binding occurs upon reduction of $\mathbf{4_{ox}}$ (from 537 M^{-1} ($CDCl_3$) for $\mathbf{4_{ox}}$ to 250,000 M^{-1} (CH_2Cl_2) for $\mathbf{4_{rad}}^{-}$). In subsequent studies by Smith and co-workers,[29] similar changes in redox potential (+128 mV) were observed upon addition of receptor **35** to the analogous naphthalimide guest **36**. Of special interest, however, was the much larger shift (+207 mV) observed for phenanthrenequinone **37** upon addition of diphenylurea **38**, corresponding to a *3000*-fold increase in binding. In recent investigations, Yano and co-workers have shown that 6-aza-flavin radical anion of **39** was stabilised by multidentate hydrogen bonding to receptor **40** (Fig. 18).[30] This stabilisation was manifested by a substantial +233 mV shift in the redox potential of the flavin arising from the multiple host–guest hydrogen bonds formed.

The large increases in binding affinity observed in the above systems upon reduction arise from the dramatic change in electron density that occurs upon reduction of the guests. For both the flavin **4** (and analogous naphthalimide **36**) and quinone **37** systems there is a dramatic increase in the electron density at the carbonyl oxygens after reduction (Fig. 20). This increase in electron density can readily be seen using computationally-derived electrostatic potential maps (Fig. 21), and enhances the interaction of these sites with the hydrogen bond donors of receptors **35** and **38**, respectively. For the flavin system **4**, the

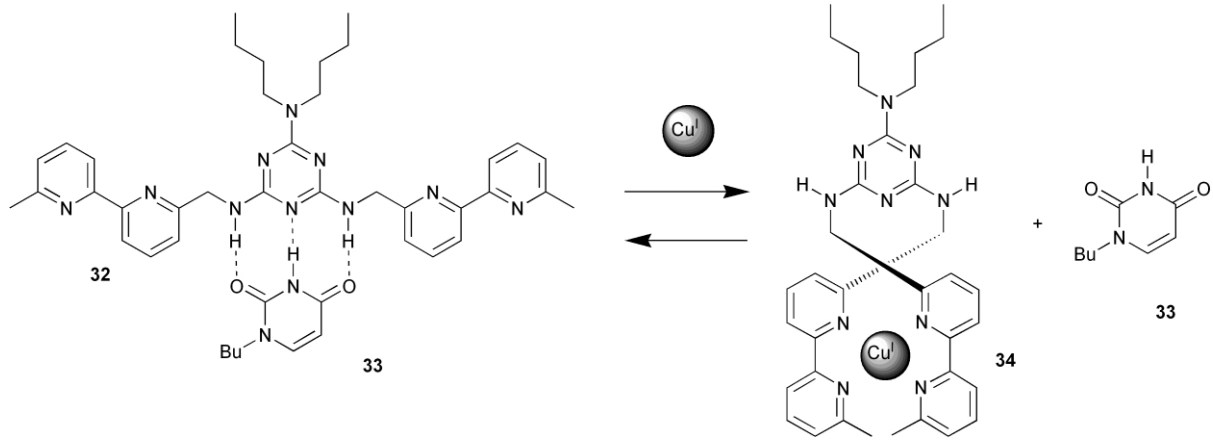


Fig. 18 Control of intermolecular hydrogen bonds *via* negative allostery.

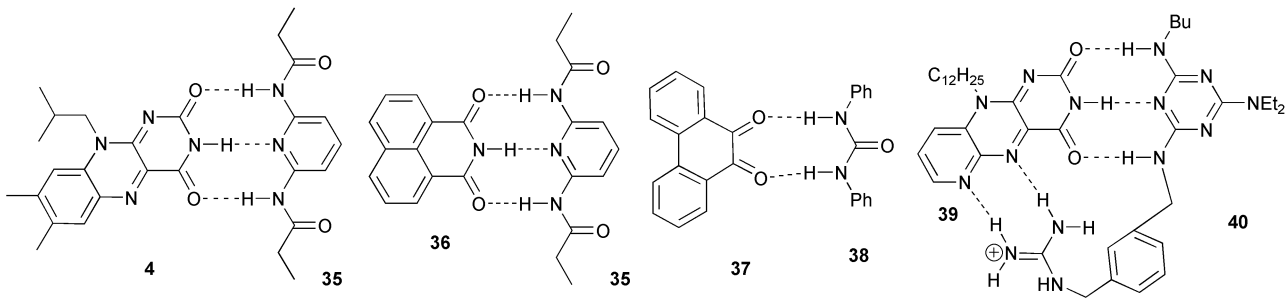


Fig. 19 Electrochemically controlled host–guest complexes.

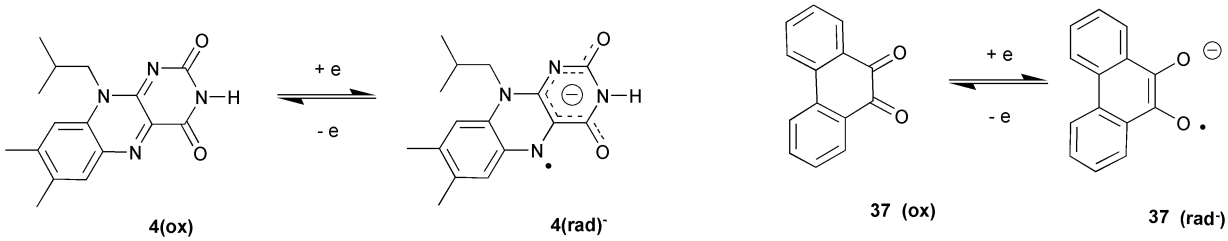


Fig. 20 Reduction of guests **4** and **37**, showing increase in electron density at the recognition surfaces.

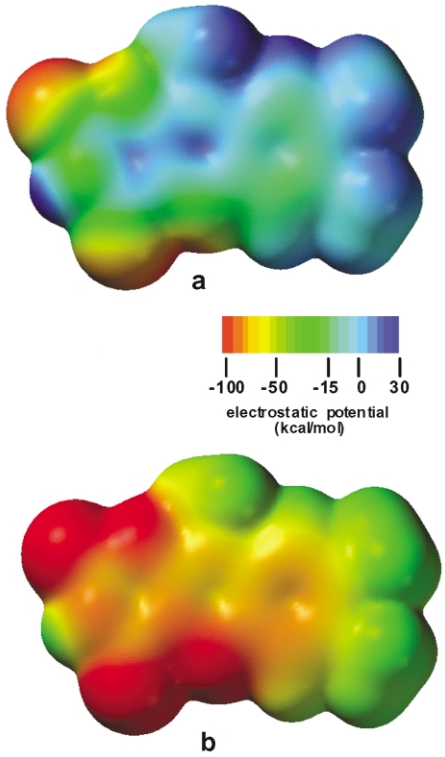


Fig. 21 Electrostatic potential maps obtained from B3LYP-DFT 6-31G*//3-21G UHF calculations for lumiflavin **4** in (*a*) the oxidized $\mathbf{4_{ox}}$ and (*b*) the radical anion form ($\mathbf{4_{rad}}-$).

increase in electron density is expected to concurrently reduce the hydrogen bond donating capability of the imide proton, somewhat diminishing the degree of redox enhancement of binding. This provides an explanation for why larger positive shifts in $E_{1/2}$ are observed for the quinone **37**–urea **38** system relative to the imide-based systems.

One of the challenges to the eventual application of the redox-modulated host–guest assemblies described above is the instability of anion radicals to oxygen. This limits the application of these systems to controlled environments. One way of fabricating much more robust redox-controlled systems is through the use of systems that switch at positive potentials. Along these lines, Tucker and co-workers have use amide-substituted ferrocene receptors for mono- and dicarboxylic acids (Fig. 22).[31] With the ferrocene-based system **41**, a

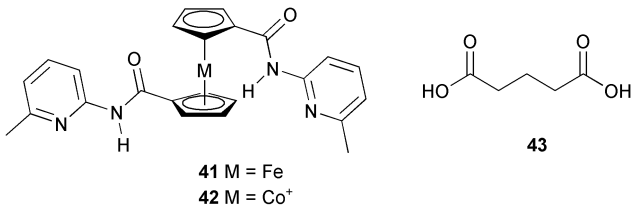


Fig. 22 Metallocene-based receptor and glutaric acid guest.

moderate change in redox potential (−55 mV) was observed upon addition of excess monocarboxylic acids. However, glutaric acid **43** showed a larger effect, with $\triangle E_{1/2}$ values of −90 mV observed, corresponding to a 35-fold increase in binding efficiency. In both cases, the negative shift in reduction potential was consistent with an increase in electron density at the iron centre arising from hydrogen bonding between the carboxylic acid carbonyl and the amide proton. In further studies, very similar results were observed with the analogous cobaltacene derivative **42**, with the cationic Co^{3+} derivative binding much more strongly than the Co^{2+} species.[32]

Redox modulation of hydrogen bonding provides a direct tool for the control of interfacial interactions. Using nanoparticles as a scaffold, Rotello and co-workers immobilised diaminopyridine derivatives to provide colloidal receptor **44** (Fig. 23).[33]

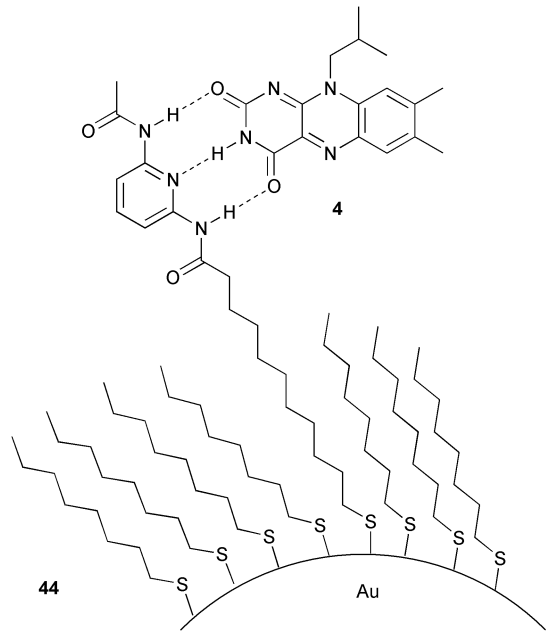


Fig. 23 Electrochemically-controlled hydrogen bonding at a nanoparticle–solution interface using the colloid **44**–guest **4** system.

The behaviour of this receptor with flavin guest **4** was quite similar to that observed for free diamidopyridine hosts, with an association constant of 200 M^{-1} ($CDCl_3$) for the oxidized flavin $\mathbf{4_{ox}}$, and 4000 M^{-1} (CH_2Cl_2) for flavin the radical anion $\mathbf{4_{rad}}-$. The immobilisation of electrochemically controlled host–guest systems of this type, provides a first step towards the development of addressable surfaces with device applications.

6 Photochemical modulation of hydrogen bonded interactions

Photoresponsive supramolecular systems are attracting considerable interest in endeavours to create switchable host–guest systems. Azo compounds and their derivatives are emerging as candidates for incorporation into systems of this type, principally due to their ability to undergo reversible *trans*-to-*cis*- and

cis-to-*trans*- isomerism upon application UV light (λ = 310 nm) and heat, respectively. This photochemically and thermally controlled isomerism offers the exciting prospect of modulating the binding efficiency of host–guest complexes by controlling host geometry. Exploiting this principle, Goswami and co-workers have developed a photoresponsive receptor **45** for adipic acid **46** (Fig. 24).[34] Host **45** incorporated two 6-amino-2-methylpyridine recognition units attached in the 4,4' positions of an azobenzene unit, which had the propensity to form hydrogen bonds with complementary adipic acid. In the ground state, the *trans* form of **45** predominated thereby creating a relatively poor receptor for adipic acid, as only one of the carboxyl groups of this moiety was able to bind to the complementary pyridine moiety of $\mathbf{45}_{trans}$. However, upon UV irradiation the *cis* form became more preferred, thereby creating a cavity in which both of the carboxy groups of adipic acid could bind ($\mathbf{45}_{cis}\cdot\mathbf{46}$). The more favourable binding geometry of the *cis* compared to the *trans* form was reflected by the order of magnitude larger binding efficiencies of the former (K_a = 1.81 $\times$ 10^4 M^{-1}, CH_3CN) compared to the latter (K_a = 5.16 $\times$ 10^3 M^{-1}, CH_3CN).

Rotello and co-workers have utilised the *cis–trans* isomerism of the azobenzene moiety of host **47** to modulate the hydrogen bonding interactions with naphthaldiimide **48** *via* the control of intermolecular π-stacking interactions (Fig. 25).[35] The *trans* state of host **47** in the hydrogen bonded complex **47·48** is stabilised *via* π-stacking interactions between the azobenzene and naphthaldiimide and resulted in a K_a of 9750 M^{-1}($CDCl_3$). Upon irradiation with visible light, the geometry of the azobenzene unit changed form *trans* to *cis*, which resulted in a 16 fold decrease in the binding efficiency of the host–guest complex (K_a = 575 M^{-1}), due to loss of favourable aromatic stacking interactions and possibly the introduction of unfavourable dipolar interactions between the azo group and the naphthaldiimide unit.

In recent studies, Leigh and co-workers have used a photoreducible stopper to provide a light-driven shuttle system (Fig. 26).[36] In this rotaxane, the 'shuttle' moiety consisted of a macrocyclic amide. In the neutral state, the shuttle preferred to be bound to the succinamide functionality (the *succ* state). However, reduction of the naphthalimide unit, greatly enhanced the hydrogen bond accepting nature of this group, favouring the formation of the *ni* state, thereby causing the shuttling process to be induced. While this process could have been driven electrochemically, photoreduction of the naphthalimide (355 nm, using a donor such as DABCO) provided a more direct control of the shuttling process. Through the use of transient absorption experiments, the forward shuttling process (the photoinduced *succ–ni* translation) was shown to occur in ~1 microsecond, while the reverse process (charge recombination between donor and acceptor, followed by shuttling from the *ni* to the *succ* state) occurred over a 100 microsecond timescale. Using the shuttling frequency and the thermodynamics of the system, it was estimated that this shuttle generated ~10^{-15} W of mechanical work per molecule, comparing quite impressively with that of biological motors (*e.g.* kinesin which generate 5 $\times$ 10^{-18} W per molecule).

7 Conclusions and outlook

The majority of examples discussed in this review article have involved the systematic synthetic manipulation of the host units electrostatic properties and/or geometry to modulate the effectiveness of hydrogen bonding interactions to a complementary guest. For example, the modulation of the electrostatic properties *via* the manipulation of the through-bond and through-space communication of electron density to the D and A sites of the hydrogen bond forming surface, have allowed the fine-tuning of the molecular recognition event. However, the changes in the efficiency of dimerisation and host–guest complexation are usually quite small, particularly when the electronic communication is through aryl–aryl link units.

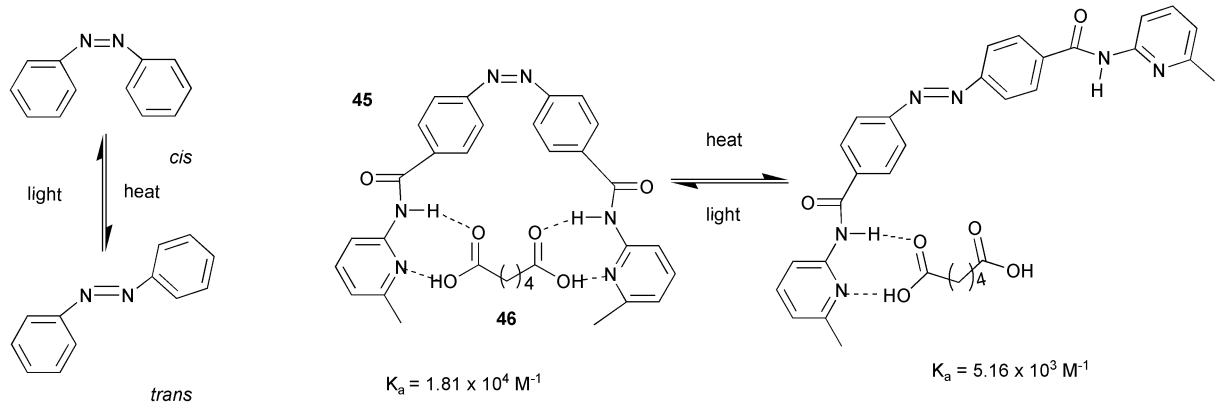


Fig. 24 Control of binding geometry using *cis–trans* isomerism of an azobenzene containing receptor.

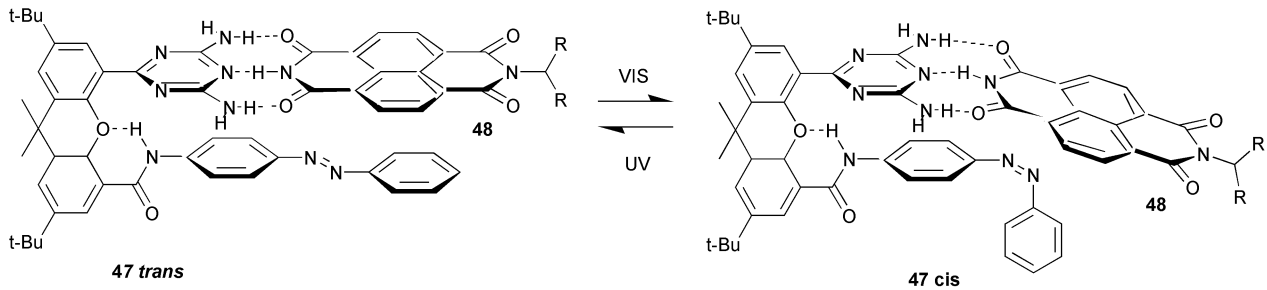


Fig. 25 Modulation of hydrogen bonding efficiency through photochemically modulated π-stacking interactions.

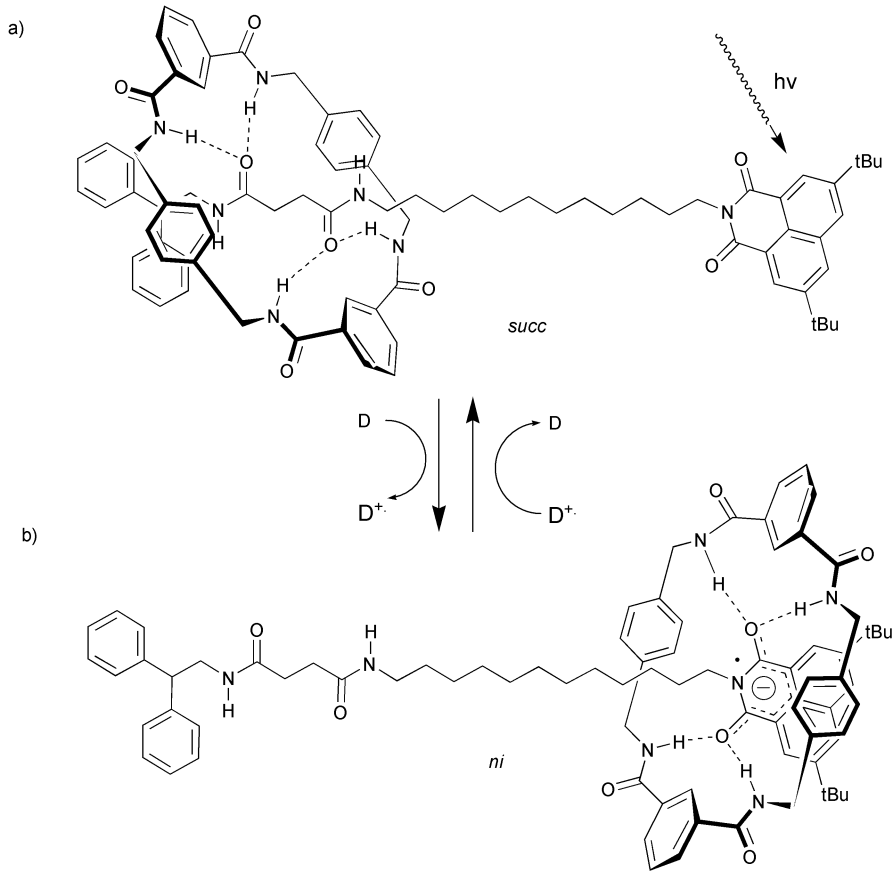


Fig. 26 Photoreduction-driven shuttle. (*a*) *succ* state favoured for neutral molecule. (*b*) *ni* state favoured for the reduced naphthalimide stopper.

Likewise, supplementing hydrogen bonding with other supramolecular interactions (*e.g.* π-stacking, cation–π) can usually only result in subtle modulation of the complexation efficiency. On the other hand, the introduction of host pre-organisation, allostery and cooperativity into hydrogen bonded recognition processes has achieved several orders of magnitude increase in the dimerisation and molecular recognition efficiency. However, this gain in efficiency is often offset by the lengthy routes required to synthesise the complex host units.

Although the synthetic manipulation of the electrostatic properties and geometry of hydrogen bonded host–guest systems is a very important aspect of contemporary supramolecular chemistry, for systems to evolve which can more accurately mimic biological systems, and in the longer term, produce pragmatic nanodevices, the selectivity and strength of hydrogen bonded host–guest systems must be able to be reversibly controlled by an external stimulus. Within this category, electrochemically and photochemically controlled hydrogen bonding interactions appear the most promising, as it has been established that these methods can modulate the efficiency of host–guest systems by orders of magnitude, and in the extreme, be turned "on" or "off" by inducing molecular motion. Therefore, it is confidently expected that the inherent speed, reversibly and convenience of electrochemically and photochemically actuated hydrogen bonded recognition processes will remain the focus of attention for many years to come.

8 References

1 G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer-Verlag, Berlin, 1991.
2 J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, Wiley, Chichester, 2000.
3 (*a*) D. C. Sherrington and K. A. Taskinen, *Chem. Soc. Rev.*, 2001, **30**, 83; (*b*) C. Schmuck and W. Wienand, *Angew. Chem. Int. Ed.*, 2001, **40**, 4363.
4 C. M. Paleos and D. Tsiourvas, *Liquid Crystals*, 2001, **28**, 1127.
5 L. J. Prins, D. Reinhoudt and P. Timmerman, *Angew. Chem., Int. Ed.*, 2001, **40**, 2382.
6 A. J. Stone, *The Theory of Intermolecular Forces*, Clarendon, Oxford, 1996, pp 115–119.
7 C. S. Wilcox, E. Kim, D. Romano, L. H. Kuo, A. L. Burt and D. P. Curran, *Tetrahedron*, 1995, **51**, 621.
8 R. Deans, G. Cooke and V. M. Rotello, *J. Org. Chem.*, 1997, **62**, 836.
9 R. Deans, A. O. Cuello, T. H. Galow, M. Ober and V. M. Rotello, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1309.
10 C. T. Chen and J. S. Siegel, *J. Am. Chem. Soc.*, 1994, **116**, 5959.
11 S. U. Chang and A. D. Hamilton, *J. Am. Chem. Soc.*, 1988, **110**, 1318.
12 F. H. Beijer, R. P. Siijbesma, H. Kooijman, A. L. Spek and E. W. Meijer, *J. Am. Chem. Soc.*, 1998, **120**, 6761.
13 J. Sartorius and H.-J. Schneider, *Chem. Eur. J.*, 1996, **2**, 1446.
14 S. H. M. Söntjens, R. P. Siijbesma, H. H. P. van Genderen and E. W. Meijer, *J. Am. Chem. Soc.*, 2000, **122**, 7487.
15 P. S. Corbin and S. C. Zimmerman, *J. Am. Chem. Soc.*, 1998, **120**, 9710.
16 For a recent example see: M. S. Lüth, E. Freisinger and B. Lippert, *Chem. Eur. J.*, 2001, **7**, 2104.
17 M. P. Hughes and B. D. Smith, *J. Org. Chem.*, 1997, **62**, 4492.
18 M. Inouye, Y. Hyodo and H. Nakazumi, *J. Org. Chem.*, 1999, **64**, 2704.
19 S. Y. Jon, J. Kim, M. Kim, S.-H. Park, W. S. Jeon, J. Heo and K. Kim, *Angew. Chem., Int. Ed.*, 2001, **40**, 2116.
20 E. C. Breinlinger, C. J. Keenan and V. M. Rotello, *J. Am. Chem. Soc.*, 1998, **120**, 8606.
21 J. A. Gavin, N. Deng, M. Alcalá and T. E. Mallouk, *Chem. Mater.*, 1998, **10**, 1937.
22 A. P. Bisson and C. A. Hunter, *Chem. Commun.*, 1996, 1723.
23 M. Inouye, T. Konishi and K. Isagawa, *J. Am. Chem. Soc.*, 1993, **115**, 8091.
24 M. H. Al-Saya and N. R. Branda, *Angew. Chem., Int. Ed.*, 2000, **39**, 945.
25 A. Niemz and V. M. Rotello, *Accounts Chem. Res.*, 1999, **32**, 44.
26 J. H. R. Tucker and S. Collinson, *Chem. Soc. Rev.*, 2002, **31**, 147.
27 A. E. Kaifer, *Acc. Chem. Res*, 1999, **32**, 62.

28 E. Breinlinger, A. Niemz and V. M. Rotello, *J. Am. Chem. Soc.*, 1995, **117**, 5379.
29 (*a*) Y. Ge, L. Miller, T. Ouimet and D. K. Smith, *J. Org. Chem.*, 2000, **65**, 8831; (*b*) Y. Ge, R. R. Lilienthal and D. K. Smith, *J. Am. Chem. Soc.*, 1996, **118**, 3976.
30 T. Kajiki, H. Moriya, S. Kondo, T. Nabeshima and Y. Yano, *Chem. Commun.*, 1998, 2727.
31 J. D. Carr, L. Lambert, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik and J. H. R. Tucker, *Chem. Commun.*, 1997, 1649.
32 J. D. Carr, S. J. Coles, M. B. Hursthouse, M. E. Light, J. H. R. Tucker and J. Westwood, *Angew. Chem., Int. Ed.*, 2000, **39**, 3296.
33 A. K. Boal and V. M. Rotello, *J. Am. Chem. Soc.*, 1999, **121**, 4914.
34 S. Goswami, K. Ghosh and M. Halder, *Tetrahedron Lett.*, 1999, **40**, 1735.
35 A. Goodman, E. Breinlinger, M. Ober and V. M. Rotello, *J. Am. Chem. Soc.*, 2001, **123**, 6213.
36 A. M. Brouwer, C. Frochot, F. G. Gatti, D. A. Leigh, L. Mottier, F. Paolucci, S. Roffia and G. W. H. Wurpel, *Science*, 2001, **291**, 2124.