HYDROGEN BONDING

Attractive arrays

Two readily accessible synthetic building blocks are shown to form a quadruply hydrogen-bonded heterodimer that exhibits exceptional stability and offers new opportunities for the construction of supramolecular assemblies and polymers.

Andrew J. Wilson

Hydrogen bonding is considered by many to be the 'master key' of molecular recognition — owing to its relatively predictable strength and directionality — and plays a major role in the assembly of diverse non-covalent assemblies[1]. Consequently, the study and exploitation of hydrogen bonds has been central to the development of modern supramolecular chemistry. In particular, numerous applied settings — such as catalysis and materials assembly — have benefitted from a greater understanding of the properties and behaviour of hydrogen bonds.

The early focus on DNA bases has generated significant interest in the study of synthetic linear arrays[2] as model systems for understanding hydrogen-bonding interactions. In more recent years, linear arrays have been used to assemble supramolecular polymers[3] — stimuli-responsive materials constructed from small and easy-to-synthesize molecules. Now, writing in *Nature Chemistry*, David Leigh and co-workers report on the design and synthesis of an exceptionally stable quadruply hydrogen-bonded heterodimer in which all of the donor (D) atoms are in one monomer and all of the acceptor (A) atoms are in its complementary partner, namely an AAAA–DDDD array[4].

The affinity with which linear arrays of contiguous hydrogen-bonds interact with complementary partners is determined by a number of factors. These include the hydrogen-bonding propensity of individual donor and acceptor atoms, pre-organization, conformation and tautomerization (all of which can be influenced by intramolecular hydrogen-bonding interactions) and the arrangement of individual donor and acceptor atoms within each component[2]. Where supramolecular polymers are concerned, the affinity with which linear arrays interact is a critical factor in obtaining non-covalent assemblies with a sufficiently high degree of polymerization to exhibit materials' properties — arrays comprising four or more hydrogen-bonds have in general been identified as ideally suited to such applications.

Of the six possible quadruply hydrogen-bonded motifs (ADAD–DADA, AADD–AADD, ADDA–DAAD, AAAD–DDDA, ADAA–DADD, AAAA–DDDD), however, only three have previously been identified as motifs that can be readily synthesized and exhibit sufficiently high affinity to have practical applications in supramolecular polymerizations (Fig. 1a). Of particular significance is the limited availability of heterodimers such as ureidopyrimidinone (UPy)/diamidonaphthyridine (DAN) and ureidoguanosine (UG)/DAN, which are desirable for the assembly of more complicated supramolecular architectures comprising different building blocks

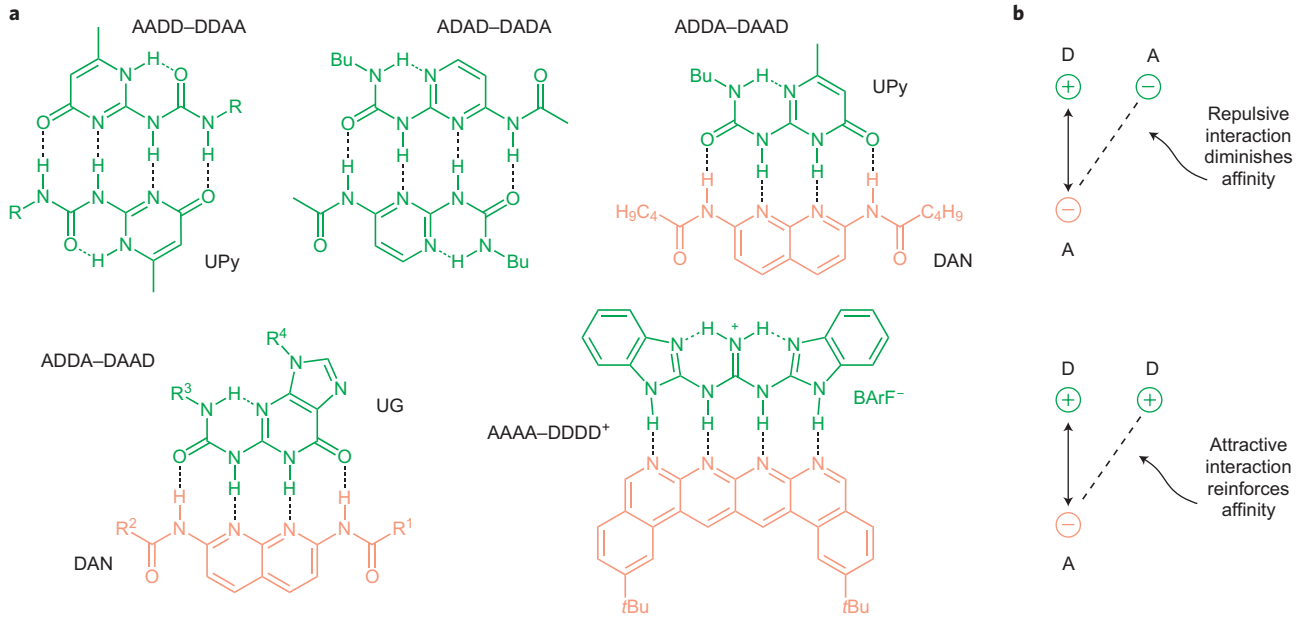

Figure 1 | Linear arrays of hydrogen bonding interactions. **a**, Quadruply hydrogen-bonded homo- and heterodimers built from combinations of ureidopyrimidinone (UPy), ureidoguanosine (UG) and diamidonaphthyridine (DAN) building blocks. **b**, Representation of the secondary electrostatic effect in linear hydrogen-bonding arrays.

Although the design and synthesis of an AAAA–DDDD$^+$ dimer has recently been described[5], Leigh and colleagues' report represents the first example of an AAAA–DDDD$^+$ array exhibiting high affinity (Fig. 1a). Such an arrangement of hydrogen-bonding functionalities was previously predicted[6] to exhibit exceptional stability. This claim was made based on the observation that the strength of individual hydrogen bonds is moderated by adjacent donor and acceptor atoms — a property referred to as secondary electrostatics. In particular, a hydrogen-bond acceptor will exhibit diminished affinity for its donor partner if that donor is positioned next to an acceptor, whereas the interaction is reinforced if the donor atom lies adjacent to another donor (Fig. 1b).

The AAAA–DDDD configuration is, therefore, the only one in which all secondary interactions are reinforcing and, as a result, is expected to be the most stable of the six possible configurations. Despite the obvious appeal of this target, its design and synthesis is non-trivial — with each additional hydrogen-bonding heteroatom added to an array, the potential for deleterious tautomeric and conformational possibilities increases. Moreover, the solubility of what is typically a flat rigid target will decrease. In a previous report, however, Leigh and co-workers described a stable triply hydrogen-bonded AAA–DDD$^+$ array[7] with two significant design features, namely (i) aromatic rings were added to the non-interacting face of the AAA unit promoting stability and ease of synthesis, and (ii) protonation of diaminopyridine afforded a cationic DDD$^+$ unit with stronger hydrogen-bonding capability owing to the presence of a charged NH donor.

Building on this prior art, in the current work the first of these design features was elaborated on to produce a hexacene AAAA system constructed in three convergent steps. Similarly, protonation was combined with the use of two benzimidazoles linked through a guanidine group to pre-organize the array through bifurcated hydrogen bonding into the desired DDDD$^+$ motif, which was obtained in only two synthetic steps. Measurement of the dimerization constant was challenging and required a careful set of competition experiments, but the value could nonetheless be estimated at ~10^{12} M^{-1} in non-hydrogen-bonding solvents such as dichloromethane. This value indicates that the stability of this quadruply bonded dimer significantly exceeds that of any previously reported linear arrays, vindicating the earlier predictions regarding the strength of such complexes. Because of the exceptionally high affinity, a strong interaction is still observed in more polar solvents such as acetonitrile and DMSO-chloroform mixtures.

This new hydrogen-bonding motif offers significant promise as a building block for non-covalent assemblies — the design is elegant and the synthesis short. Several challenges remain however. The researchers themselves note that the AAAA system exhibits only modest photostability and the synthesis would need to be modified to obtain arrays that can be incorporated into supramolecular polymers. And once this is achieved, it may even be the case that the dimerization affinity is too high to afford dynamic systems in which hydrogen bonds can form and rupture on a useful timescale. Nonetheless, this study reinforces our fundamental understanding of hydrogen bonding and demonstrates beautifully how high-affinity non-covalent interactions can be realized through design. ❐

Andrew J. Wilson is in the School of Chemistry and the Astbury Centre for Structural Molecular Biology at the University of Leeds, Woodhouse Lane, Leeds LS2 9JT, UK.
e-mail: A.J.Wilson@leeds.ac.uk

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POLYMER FOLDING

ABC of molecular origami

Arranging polymers into well-defined shapes endows them with specific properties; but although it is routinely achieved in nature, accurate origami has proved challenging with synthetic polymers. A surprisingly simple folding strategy has now been described.

Sébastien Perrier

Nature is a constant source of inspiration for scientists, who have tried over the years to mimic — or even improve — natural materials for specific applications. Initial work focused on macroscopic properties, as illustrated in the 1860s by the development of celluloid, a modified cellulose derivative that mimics elephant ivory. Attention has since turned to the nanoscale, and we now know that the function and properties of many natural polymers are closely related to their structure. In the more complex biopolymers, the overall structure is mainly determined by the folding of polymeric chains (the DNA double helix, for example, or the secondary and tertiary structures of proteins). Despite the tools available to modern polymer chemists, however, it remains difficult to design synthetic macromolecules that can fold into structures with the precision of naturally occurring polymers. Writing in *Nature Chemistry*, Jean-François Lutz and colleagues now describe the simple approach they have adopted to control intramolecular covalent folding of linear polymeric chains with good accuracy[1].

Until now, simple synthetic strategies have not produced complex macromolecular origami. Examples have recently been reported[2,3] of polymers folded into compact architectures through the formation of intramolecular bridges — either covalent or non-covalent — but the bridges were randomly distributed in the polymer chains, which means that those strategies fall short of emulating the precision found in nature. And although specific end-groups have enabled chains to be folded into relatively well-controlled shapes (through intramolecular