Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5938

www.rsc.org/obc

COMMUNICATION

Ditopic triply hydrogen-bonded heterodimers†

Adam Gooch,[a] Simon Barrett,[a] Julie Fisher,[a] Christopher I. Lindsay[b] and Andrew J. Wilson*[a,c]

Received 13th April 2011, Accepted 22nd June 2011
DOI: 10.1039/c1ob05593c

The synthesis and self-assembly of a stable hydrogen-bonded heterodimer comprising ditopic ureidoimidazole and amido*iso*cytosine motifs is described. The heterodimer appears to exhibit high stability in deuterochloroform as evidenced by ^{1}H NMR, DOSY and ^{1}H-^{1}H ROESY.

The design and synthesis of linear arrays of hydrogen-bonds that exhibit well-defined molecular recognition behaviour is an ongoing challenge in supramolecular chemistry.[1] Such motifs represent the key building blocks of supramolecular assemblies and in particular, triple,[2–6] quadruple[7–15] and higher order[16–18] linear arrays remain attractive targets. A number of "rules" have been established to allow the synthesis of motifs with a range of affinities, for instance the number of hydrogen-bonding donor and acceptor atoms, the arrangement and spacing of hydrogen-bonding groups, the tautomeric configuration, the conformation and the strength of individual donor and acceptor atoms may all be varied to exert control over strength and selectivity of recognition.[1] Linking motifs together is less explored[18] as a deliberate strategy to achieve high affinity, although it should be noted that within the context of supramolecular polymerizations, a number of ditopic linear arrays have been studied. These form stable macrocycles at low concentrations and extended polymers at higher concentrations according to the ring chain equilibrium.[19–21] Furthermore judicious choice of linker can favour exclusively the formation of cyclic species.[22] Similarly, separating donors and acceptors also represents an attractive means to obtain high affinity dimerisation.[13,23] In the current manuscript we describe the synthesis and solution self-assembly of a dimer comprising two ditopic heterocomplementary triple linear arrays, resulting in the formation of stable dimers held together by a total of six hydrogen-bonds.

We previously introduced a series of triply-hydrogen-bonded arrays employing conformer independent components.[4,5,24] The donor–donor–acceptor (DDA) ureidoimidazole motif **1** and complementary (AAD) amido*iso*cytosine motif **2** were found to associate with K_a = 33,000 M^{-1} [4,5] whereas the ADA uriedopyrimidine **3** and DAD diamidopyridine motif **4** were found to associate with K_a = 56 M^{-1} (Fig. 1).[24] We subsequently outlined how affinity may be varied over two orders of magnitude through electronic substituent effects for the former pairing **1.2**.[5] Based on these affinities, we considered neither heterodimer to possess sufficient stability to be useful for formation of linear supramolecular polymers in dilute solution. However we did envision that ditopic variants of the ureidoimidazole–amido*iso*cytosine system, would form stable heterodimers.

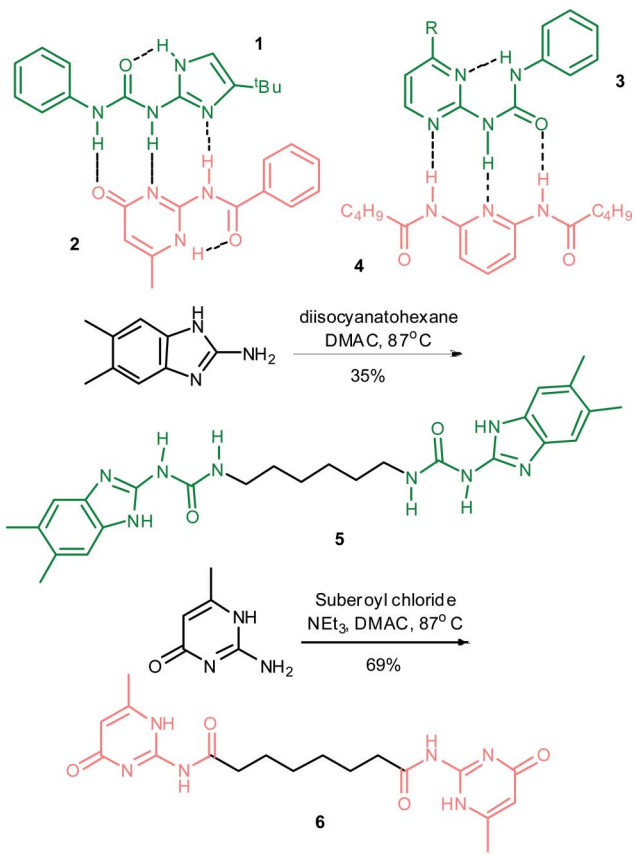

Fig. 1 Structures of hydrogen-bonded heterodimers **1.2** and **3.4** and synthesis of DUM **5** and DAC **6**.

We synthesized diureidoimidazole (DUM) **5** and diamido*iso*cytosine (DAC) **6** which were both furnished with short alkyl chains between the terminal hydrogen bonding arrays as outlined in Fig. 1. In contrast to our earlier work, we used

[a]*School of Chemistry, University of Leeds, Woodhouse Lane Leeds, United Kingdom, LS2 9JT. E-mail: A.J.Wilson@leeds.ac.uk; Fax: +44 (0)113 3436565; Tel: +44 (0)113 3431409*
[b]*Huntsman Polyurethanes, Everslaan 45, 3078, Everberg, Belgium*
[c]*Astbury Centre for Structural Molecular Biology, University of Leeds, Woodhouse Lane Leeds, United Kingdom, LS2 9JT*
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05593c

2-aminobenzimidazole rather than 2-amino-^{t}butylimidazole for synthetic brevity; the former being commercially available whilst the later requires a 3 step synthesis.

Both compounds exhibit poor solubility in chloroform, however, ^{1}H NMR spectra were successfully recorded in $CDCl_3$ of DAC **6** and also of a 1 : 1 mixture of DAC **6** and complementary DUM **5** (see Fig. 2). The spectrum for **5.6** reveals significant complexation induced changes in signals of DAC **6** (Fig. 2b) when compared to the spectrum of DAC **6** alone (Fig. 2a). Although assignment of the NH resonances was not possible for **6** due to significant signal broadening, the signals sharpen and undergo > 1 ppm change in chemical shift upon addition of **5**. In addition H_A also undergoes a complexation induced shift ($\Delta\delta \sim -0.05$ ppm) and broadening upon complexation. This indicates a change in environment of the protons in proximity to the binding site of DAC **6**, suggesting complexation of DAC **6** with complementary DUM **5** occurs *via* association of the intended hydrogen bonding arrays. The spectrum of a 1 : 1 mixture of **5** and **6** is unchanged at 0.1 mM (Fig. 2c); this concentration independence is indicative of an association constant > 10^5 M^{-1} in $CDCl_3$. In pure DMSO-d_6, no changes in the ^{1}H NMR of DAC **6** are observed upon addition of DUM **6** indicating molecular recognition does not take place in this more competitive solvent. Small complexation induced shifts were observed in a mixture of 10% DMSO-d_6 in $CDCl_3$ solution, however the limited solubility of **5** prevented an accurate determination of K_a in this solvent composition.

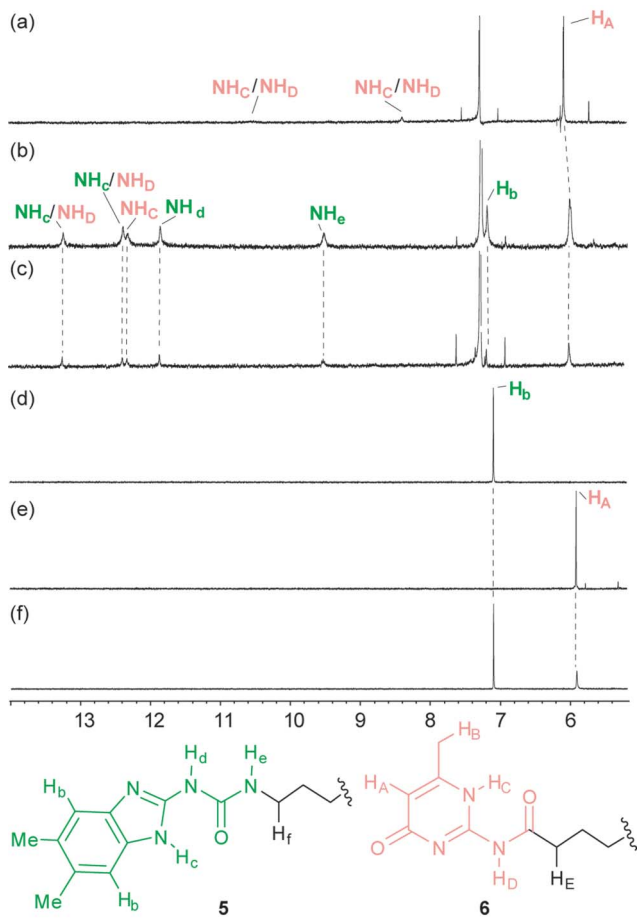

Fig. 2 ^{1}H NMR spectra (a) of **6** (1.0 mM, 300 MHz, $CDCl_3$), (b) of **5.6** (1.0 mM, 300 MHz, $CDCl_3$), (c) of **5.6** (0.1 mM, 300 MHz, $CDCl_3$), (d) of **5** (1.0 mM, 300 MHz, DMSO-d_6), (e of 6 (f) of **5.6** (1 mM, 300 MHz, DMSO-d_6).

Diffusion-ordered spectroscopy (DOSY) studies were performed in $CDCl_3$ solution of DAC **6** (1.0 mM) and a 1 : 1 mix of DUM **5** and DAC **6** (each of 1.0 mM concentration). Coincidence in diffusion coefficient of signals from the DUM **5** and DAC **6** provides further evidence of complexation (Fig. 3a). Diffusion coefficients were determined using two different methods; despite the low sample concentrations used for solubility reasons, both methods used to evaluate self-assembly of DAC **6** with DUM **5** suggested dimer formation. A calibration curve was plotted using the Stokes–Einstein relationship (see ESI†) for diffusion coefficient ($\times 10^6$ cm^2 s^{-1}) *versus* the reciprocal cube root of the molecular mass ($1/(\text{molecular mass})^{1/3}$). Using the calibration curve the molecular mass of DAC **6** estimated from a diffusion coefficient of $11.11 \pm 0.08 \times 10^{-6}$ cm^2 s^{-1} (measured from a 1 mM solution of DAC **6** in $CDCl_3$ at 20 °C) was 395 Da in good agreement with the actual mass of 388 Da. The molecular mass determined for DAC **6** in a 1 : 1 DUM:DAC **5.6** mixture (1.0 mM as before) (based on a diffusion coefficient of $8.49 \pm 0.12 \times 10^{-6}$ cm^2 s^{-1}) was 985 Da; again in good agreement with the actual mass of dimer **5.6** of 868 Da. In the absence of a calibration curve, it is acceptable to compare measured diffusion coefficients of monomer and complex and the known mass of the monomer so as to calculate the mass of the complex as follows: $D_m/D_c = MW_c^{1/3}/MW_m^{1/3}$. Using this approach and a molecular mass for the monomer of 388 then MW_c of the complex **5.6** can is 869 Da in even better agreement with the actual mass of **5.6**. Hence, both methods indicate that even under these dilute conditions the **5.6** complex is dimeric. Electrospray ionisation (ESI†) mass spectrometry also provides evidence for the assembly of DUM **5** and DAC **6** units into higher order structures including the dimer **5.6** (see ESI†).

We were unable to obtain a single crystal of **5.6** and so 2D NMR experiments were performed to provide further structural information. Specifically, ^{1}H-^{1}H ROESY (Fig. 3b) indicates the presence of both possible tautomers. An unambiguous assignment of the ^{1}H NMR spectrum of **5.6** was not possible due to coincidence of aromatic resonances and significant spectral overlap in the alkyl region, however NH_e is present as a triplet and exhibits NOEs with one of the NH's which is assigned as NH_d and is consistent with tautomer *II* (Fig. 3c). Furthermore, the resonance assigned as NH_d exhibits NOEs with two of the remaining NH's which can be assigned as NH_c and NH_D. The former intramolecular NOE is consistent with the presence of tautomer *I* and the later intermolecular NOE anticipated for either hydrogen-bonded tautomer (Fig. 3c). The absence of any correlations involving the remaining resonance NH_c is expected based upon the proposed structures. Observation of only one set of resonances is consistent with rapid exchange between tautomers. Tautomer *II* represents a particularly interesting structure in that folding must occur in order for dimerisation to occur – only one possibility is shown in which self-stacking occurs (Fig. 3c), although an alternative is possible in which heterostacking occurs (see ESI).

Conclusions

We have described the synthesis and molecular recognition of ditopic amido*iso*cytosine and ureidoimidazole arrays. These form

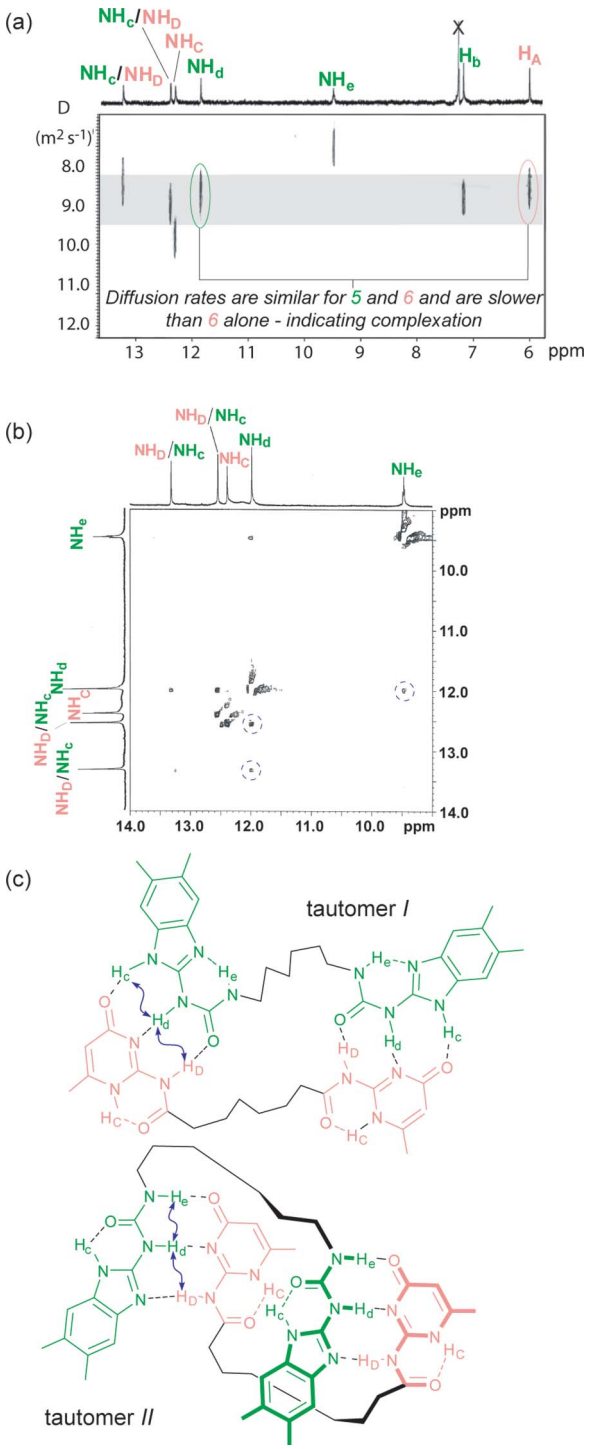

Fig. 3 (a) DOSY of **5.6** (1mM, 500 MHz, $CDCl_3$) **5** and **6** are diffusing at the same rate and more slowly than when separate indicating complexation (b) ^{1}H-^{1}H ROESY of **5.6** (1 mM, 500 MHz, $CDCl_3$) (c) possible structures of **5.6**.

strongly hydrogen-bonded heterodimers held together by six hydrogen-bonds; much attention has been devoted to the design of contiguous arrays that exhibit high affinity dimerisation, however this alternative approach offers a means to achieve high affinity without recourse to lengthy design and syntheses. In addition, linking motifs together represents a first step toward constructing elementary "codons" for construction of more elaborate self-assemblies. Our own laboratory will focus future efforts in this direction.

Acknowledgements

This work was supported by Huntsman Polyurethanes, the Leverhulme Trust [F/00122/AN] and EPSRC [EP/P504988/1].

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