# Conformer independent heterodimerisation of linear arrays using three hydrogen bonds†

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**5-Membered heterocycles are employed to give a conformer independent DDA array of hydrogen bonds, resulting in enhanced binding affinity to a complementary AAD array in comparison to a DDA array employing a 6-membered ring.**

The design and synthesis of linear arrays of hydrogen bonds is a key area of research[1,2] since these arrays represent the building blocks for non-covalent synthesis of stimuli responsive assemblies and polymers.[3,4] Most current designs use linear arrays comprising four hydrogen bonds because of the enhanced strength of association that may be achieved,[5] although high-affinity triply hydrogen bonded systems have been observed.[6] Designing such systems is challenging since intramolecular hydrogen bonding,[7] pre-organisation,[8] secondary interactions,[9] tautomerisation[10] and electronic substituent effects[11] can all have effects upon the strength and fidelity[12] of recognition; with increasing numbers of hydrogen bonds these factors become difficult to mitigate against whilst maintaining synthetic accessibility. We became interested in this problem and observed that most systems that have been studied to date employ 6-membered heterocycles within the hydrogen bonding framework. Herein we describe how 5-membered rings can be useful components of linear arrays, leading to conformer independent binding when compared against their 6-membered counterparts.

Our strategy focuses on intramolecular hydrogen bonding. Pyridylureas *e.g.* **2** are attractive DDA building blocks because of their ease of synthesis, yet they exhibit poor association constants with complementary AAD arrays since an intramolecular hydrogen bond must be broken at an entropic price in order to form three intermolecular non-covalent contacts.[7,13] We hypothesised that this problem could be negated by use of an imidazole[14,15] as in **1a** and **1b** rather than a pyridine heterocycle (Fig. 1a). The intramolecular hydrogen bond would still be present in such a system, however it should act to pre-organise it, as in either of two possible conformers a DDA array would be presented (this concept is similar in nature to degenerate tautomerism).[16,17] As a complementary AAD array we selected amidoisocytosine **3** (Fig. 1b). Surprisingly these synthons have not, to the best of our knowledge, been studied before. In contrast to amidocytosines, amidoisocytosines should be pre-organised as a consequence of an intramolecular hydrogen bond, although two different tautomers are possible only one of which presents the required AAD array.

Ureidoimidazole **1a**[18] was synthesised in one-pot on gram scale without the need for chromatographic purification (see ESI†). Crystals were grown from the slow evaporation of a methanolic solution of **1a** (Fig. 2). An intramolecular hydrogen bond is present as proposed, however only the conformer with an NH···O hydrogen bond is observed. This behaviour is not maintained in DMSO-$d_6$ solution: 2 broad NH signals, one integrating to two protons (presumably the urea NHs) and the other to one (presumably the imidazole NH) are indicative of interconversion between different conformations. The crystal structure also suggests that the molecule may tend towards intermolecular self-association; the imidazole engages in bifurcated H-bonding to the urea fragment and the imidazole NH participates in intermolecular H-bonding to the urea carbonyl. We were unable to study the dimerisation of **1a** in $CDCl_3$ due to poor solubility and therefore synthesised **1b** in 3 steps with a solubilising *tert*-butyl group by extending previously reported methodology for the synthesis of 2-aminoimidazoles (see ESI†).[19] For **1b** in $CDCl_3$ at room temperature, a single set of sharp signals for the *tert*-butyl group and the aromatic protons is observed along with 2 broad NH signals, as is observed for **1a** in DMSO-$d_6$. This suggests fast interconversion between all of the possible conformers/tautomers in addition to any intermolecular association that is occurring. Nevertheless, at room temperature, small shifts in the aromatic resonances of **1b** can be observed upon dilution of a sample in

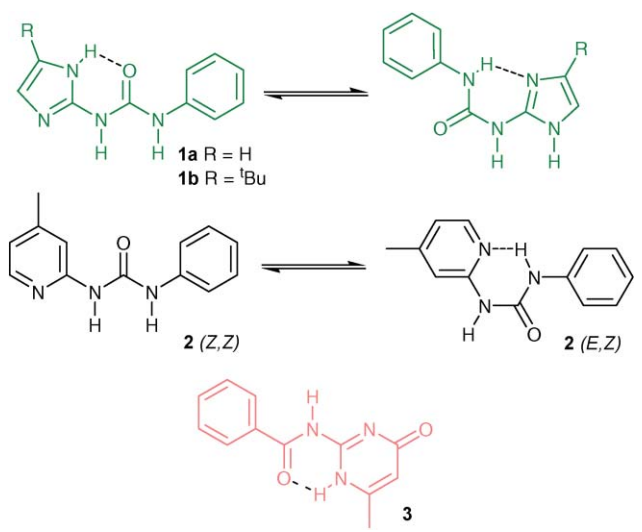


**Fig. 1** DDA and AAD arrays used in this study.

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† Electronic supplementary information (ESI) available: Full details of crystallographic structure determination, synthetic procedures, titration details and curve fitting. See DOI: 10.1039/b712603d

 

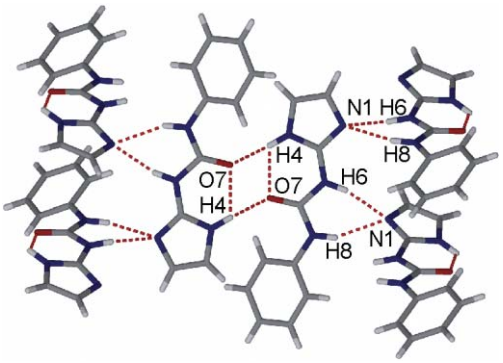


**Fig. 2** X-Ray crystal structure packing diagram of compound **1a** shown in stick format (carbon in grey, hydrogen in white, oxygen in red and nitrogen in blue). Key distances: H4–O7 2.31 Å (intramolecular), H4–O7 2.11 Å, N1–H6 2.09 Å, N1–H8 2.25 Å, (intermolecular).‡

$CDCl_3$. This indicates any self-association is weak and that the formation of supramolecular polymers in solution that mirror the solid state structure is unlikely. Curve fitting to a dimerisation model using the HypNMR program[20] gives a dimerisation constant of 11 $M^{-1}$ ($\pm 2$ $M^{-1}$) (see ESI†). For comparison we also synthesised pyridyl urea **2** (see ESI†). This compound gave sharp resonances in $CDCl_3$ indicative of a single well defined intramolecularly hydrogen-bonded conformation in solution. A dilution study and curve fitting gave a dimerisation constant of 56 $M^{-1}$ (see ESI†) in line with previous observations.[13]

Amidoisocytosine **3** was synthesised in one step on gram scale (see ESI†). An X-ray diffraction study‡ on single crystals grown from the slow evaporation of a methanolic solution in chloroform revealed the presence of two similar molecules of **3** in the asymmetric unit (Fig. 3). For both, the proposed intramolecular hydrogen bond is present, although the undesired tautomer is observed. At this stage it is not clear if this arises due to crystal packing or if this is the lowest energy conformer of **3**. However, acylation has a dramatic effect: isocytosine itself adopts a heterodimeric complex comprising one 6[1*H*]pyrimidinone tautomer and one 4[1*H*]pyrimidinone tautomer.[21] In contrast, only weak intermolecular hydrogen bonds are observed in the structure of **3**. This is mirrored in $CDCl_3$: in this case only one broad signal is observed for the NH resonances and upon dilution only small changes are observed for the aromatic resonances indicative of a

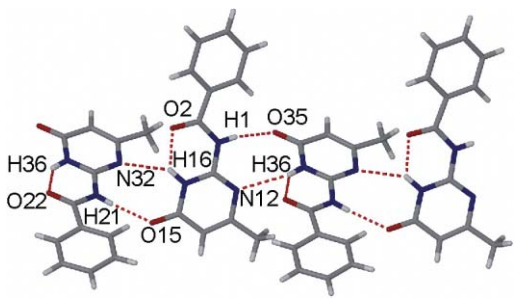


**Fig. 3** X-Ray crystal structure packing diagram of compound **3** shown in stick format (carbon in grey, hydrogen in white, oxygen in red and nitrogen in blue). Key distances: O2–H16 1.94(5) Å, O22–H36 1.99(5) Å (intramolecular), H1–O35 2.11(6) Å, N12–H36 2.54(5) Å, O15–H21 2.07 (4) Å, H16–N32 2.59(4) Å (intermolecular).

weak interaction. Curve fitting gave a dimerisation constant of 4 $M^{-1}$ ($\pm 1$ $M^{-1}$) (see ESI†).

We next turned our attention to heterodimerisation. Upon titration of a solution of **1b** into **3** (at 6 mM), significantly larger complexation induced shifts in the aromatic resonances of **3** were observed than had been observed for the dilution study (Fig. 4a). Although the NH resonances failed to sharpen, we were still able to derive an association constant of 8400 $M^{-1}$ ($\pm 1000$ $M^{-1}$) by curve fitting[20] to a 1 : 1 association model that accounts for homodimerisation of both components (Fig. 4b). The stoichiometry was confirmed by JOB plot (Fig. 4b inset) and a similar value for $K_a$ was obtained when the titration was repeated at 2 mM (see ESI†). For both experiments, it seems clear that the simple 1 : 1 complex is not the only species present—at least in the early

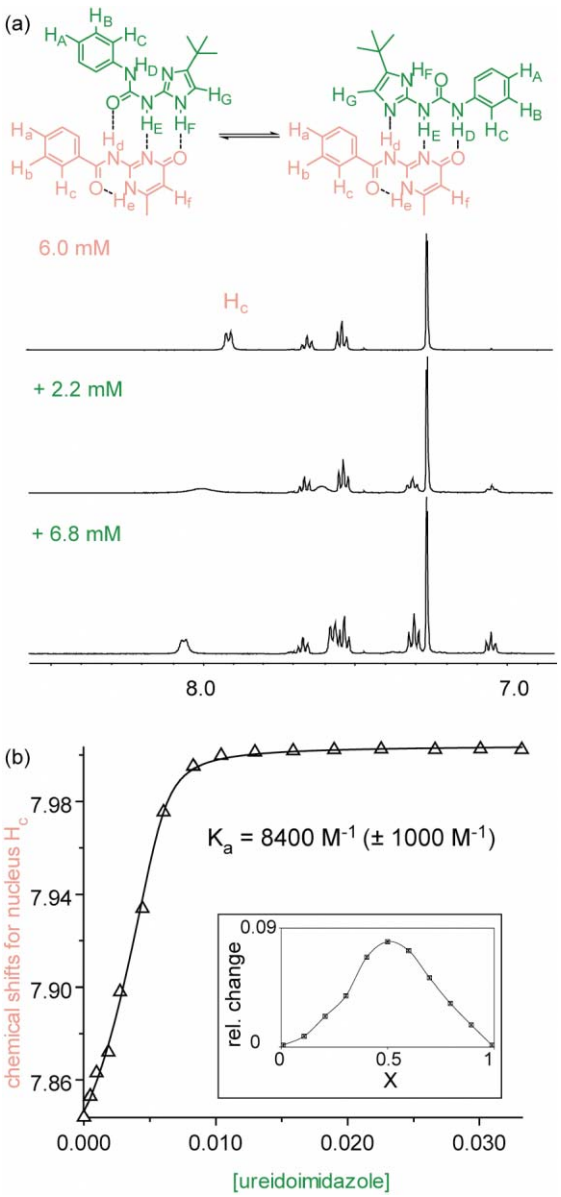


**Fig. 4** (a) Partial $^1$H NMR spectra (500 MHz, $CDCl_3$) of **3** upon addition of **1b**. (b) Chemical shift change of $H_c$ upon addition of **1b** to a 6 mM solution of **3** together; the line shows the best fit curve obtained *via* curve fitting (inset: JOB plot).

part of the titration. The resonance for $H_c$ becomes broad in the titration, whilst the early part of the JOB plot is curved. This suggests the presence of higher order structures; nevertheless the 1 : 1 complex is clearly the dominant species and stable. In contrast upon titration of **3** into **2**, despite larger complexation induced shifts for the NH resonances, the variation with concentration was much less dramatic indicative of much weaker association. Curve fitting[20] (allowing for self-dimerisation of both components) gave an association constant of 84 $M^{-1}$ ($\pm$10 $M^{-1}$), consistent with previous observations for related compounds.[13] Thus, exchanging the pyridine group in **2** for the imidazole group as in **1** results in nearly 3 orders of magnitude difference in binding affinity to complementary partners.

In summary we have shown that conformer independent linear arrays of hydrogen bonds can lead to significantly enhanced association constants with complementary hydrogen bonding partners. This concept represents a useful tool to employ in the design of linear arrays of H-bonds. Our own studies will now focus on a detailed structural investigation of this system and upon enhancing affinity.

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## Notes and references

‡ Crystal data for $C_{10}H_{10}N_4O$, $M$ = 202.22, crystal size 0.36 x 0.19 x 0.05, monoclinic, $a$ = 11.7156(3), $b$ = 6.0176(2), $c$ = 13.3965(4) Å, $\beta$ = 92.3690(10)°, $U$ = 943.64(5) Å$^3$, $T$ = 150(2) K, $P2_1/n$, $Z$ = 4, $\mu$ = 0.098 $mm^{-1}$, $\lambda$ = 0.71073 Å [Mo-K$\alpha$], 12808 reflections measured, 1854 unique ($R_{int}$ = 0.0978), 1533 observed ($I > 2\sigma(I)$). The final $R1$ was 0.0430 (observed reflections 0.0528) and w$R(F^2)$ was 0.1091 (all data 0.1174) for 136 parameters. Crystal data for $C_{51}H_{50}Cl_6N_{12}O_8$, $M$ = 1171.73, crystal size 0.26 x 0.23 x 0.22 mm, triclinic, $a$ = 10.5748(2), $b$ = 11.2109(2), $c$ = 11.8373(3) Å, $\alpha$ = 101.7370(8)°, $\beta$ = 100.6000(8)°, $\gamma$ = 96.1140(13)°, $U$ = 1335.37(5) Å$^3$, $T$ = 150(2) K, space group $P\bar{1}$, $Z$ = 2, $\mu$ = 0.388 $mm^{-1}$, $\lambda$ = 0.71073 Å [Mo-K$\alpha$], 25222 reflections measured, 5222 unique ($R_{int}$ = 0.1042), 3827 observed ($I > 2\sigma(I)$). The final $R1$ was 0.0799 (observed reflections 0.1071) and w$R(F^2)$ was 0.2069 (all data 0.2314) for 370 parameters. CCDC 660530 and 660531. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b712603d

1 A. J. Wilson, *Soft Matter*, 2007, **3**, 409.
2 S. C. Zimmerman and P. S. Corbin, *Struct. Bonding*, 2000, **96**, 63.
3 L. Prins, D. N. Reinhoudt and P. Timmerman, *Angew. Chem., Int. Ed.*, 2001, **40**, 2382.
4 L. Brunsveld, B. J. B. Folmer, E. W. Meijer and R. P. Sijbesma, *Chem. Rev.*, 2001, **101**, 4071.
5 R. P. Sijbesma and E. W. Meijer, *Chem. Commun.*, 2003, 5.
6 S. Djurdejevic, D. A. Leigh, H. McNab, S. Parsons, G. Teobaldi and F. Zerbetto, *J. Am. Chem. Soc.*, 2007, **129**, 476.
7 C.-H. Chien, M.-K. Leung, J.-K. Su, G.-H. Li, Y.-H. Liu and Y. Wang, *J. Org. Chem.*, 2004, **69**, 1866.
8 P. Prabhakaran, V. G. Puranik and G. J. Sanjayan, *J. Org. Chem.*, 2005, **70**, 10067.
9 W. L. Jorgensen and J. Pranata, *J. Am. Chem. Soc.*, 1990, **112**, 2008.
10 T. Park, E. M. Todd, S. Nakashima and S. C. Zimmerman, *J. Am. Chem. Soc.*, 2005, **127**, 18133.
11 V. G. H. Lafitte, A. E. Aliev, H. C. Hailes, K. Bala and P. Golding, *J. Org. Chem.*, 2005, **70**, 2701.
12 E. M. Todd, J. R. Quinn, T. Park and S. C. Zimmerman, *Isr. J. Chem.*, 2005, **45**, 381.
13 P. S. Corbin, S. C. Zimmerman, P. A. Thiessen, N. A. Hawryluk and T. J. Murray, *J. Am. Chem. Soc.*, 2001, **123**, 10475.
14 S. Watanabe, O. Onogawa, Y. Komatsu and K. Yoshida, *J. Am. Chem. Soc.*, 1998, **120**, 229.
15 M. G. Fisher, P. A. Gale and M. E. Light, *New J. Chem.*, 2007, **31**, 1583.
16 P. S. Corbin and S. C. Zimmerman, *J. Am. Chem. Soc.*, 1998, **120**, 9710.
17 P. K. Baruah, R. Gonnade, U. D. Phalgune and G. J. Sanjayan, *J. Org. Chem.*, 2005, **70**, 6461.
18 C. J. Paget, K. Kisner, R. L. Stone and D. C. DeLong, *J. Med. Chem.*, 1969, **12**, 1010.
19 T. L. Little and S. E. Webber, *J. Org. Chem.*, 1994, **59**, 7299.
20 C. Frassineti, S. Ghelli, P. Gans, A. Sabatini, M. S. Moruzzi and A. Vacca, *Anal. Biochem.*, 1995, **231**, 374.
21 L. M. Toledo, K. Musa, J. W. Lauher and F. W. Fowler, *Chem. Mater.*, 1995, **7**, 1639.

 