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Design, synthesis and binding properties of conformer-independent linear ADA hydrogen-bonding arrays

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The design, synthesis and binding studies of a new class of conformer-independent ADA linear hydrogen-bonding array is described. These phenylureidopyrimidine arrays are shown to adopt the hydrogen-bond pre-organised ADA arrangement by X-ray crystallography and ^{1}H NMR experiments. They bind to complementary DAD arrays with moderate $K_a \sim 56\,M^{-1}$ affinity in a conformer-independent fashion as exemplified by ^{1}H NMR titration and ^{1}H–^{1}H NOESY.

Keywords: hydrogen-bonding; linear arrays; supramolecular polymers

Introduction

The ready synthetic availability of linear arrays of hydrogen-bonds (*1–3*) is a key requirement for the non-covalent synthesis of stimuli responsive assemblies and polymers (*3*, *4*). Linear arrays comprising three (*5*) and four hydrogen-bonds (*6–8*) have found widespread use in supramolecular polymer assembly; however, designing such systems is challenging because intramolecular hydrogen-bonding (*9*), pre-organisation (*10*), secondary interactions (*11*), tautomerisation (*8*) and electronic substituent effects (*12*) can all have effects upon the strength and fidelity (*13*) of recognition. For side-chain-functionalised (*14*) and cross-linked supramolecular polymers (*15–17*), the requirement for high affinity is tempered by multivalent effects, and so easy-to-synthesise systems capable of moderate to high affinity heterodimerisation are attractive. In this context, the diamidopyridine–thymine diad (*DAP.T*) has been widely employed (*18*, *19*); however, multistep syntheses of functionalised thymine derivatives are sometimes necessary and these systems can be susceptible to oxidative stress. Ureidopyridine derivatives, e.g. **1**, while synthetically accessible, exhibit poor association constants towards AAD arrays because they preferentially form an intramolecular hydrogen-bond that retards intermolecular interaction [Figure 1; (*9*, *20*)]. We recently described the design and synthesis of conformer-independent ureidoimidazole DDA arrays (e.g. **2**) in which the six-membered pyridine ring was switched for a five-membered imidazole ring (*21*). We reasoned that exchange of the pyridine of the ureidopyridine motif for a pyrimidine would similarly furnish a conformer-independent ADA array (e.g. **3**) and that such a motif may represent an alternative to thymine derivatives (e.g. **4**) in the assembly of supramolecularly cross-linked polymers. Herein we disclose the synthesis and binding studies of such derivatives.

Results and discussion

Phenylureidopyrimidine (*PUPY*) derivatives **3a** and **3b** were obtained in one step by condensation of commercially available phenylisocyanate and 2-aminopyrimidines (Scheme 1). The partner diamidopyridine DAD array **5** was obtained by following previously published methods (*22*) as was *N*-propylthymine **4** (*23*) as a comparison. Similarly, phenylureidopyridine **1** was reported in our earlier study (*21*).

Single crystals of compound **3a** were obtained by slow evaporation of a chloroform/methanol solution. The solid-state structure (Figure 2) confirms the folded nature of the linear array and presence of an intramolecular hydrogen-bond. Furthermore, the motif undergoes self-dimerisation through two pyrimidine NH donor to urea CO acceptor hydrogen-bonds. These solid-state features are similar to those observed for related pyridyl(thio)ureas (*9*, *24*, *25*).

Unfortunately, **3a** exhibited poor solubility in chloroform – the solvent of choice for studying association of linear arrays – and was not studied further. By contrast, **3b** exhibited good solubility and the ^{1}H NMR spectrum confirmed the intramolecularly hydrogen-bonded conformation. Furthermore, ^{1}H–^{1}H NOESY spectrum of **3b** in chloroform illustrates that both conformers are present in solution as evidenced by cross-peaks from both the C4 methyl and C6 hydrogen groups to the *ortho* hydrogens on the

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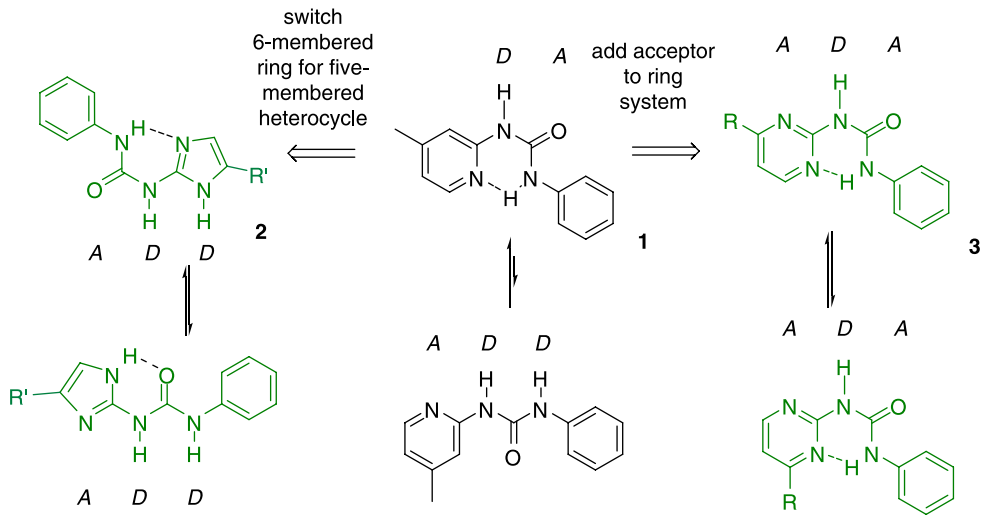
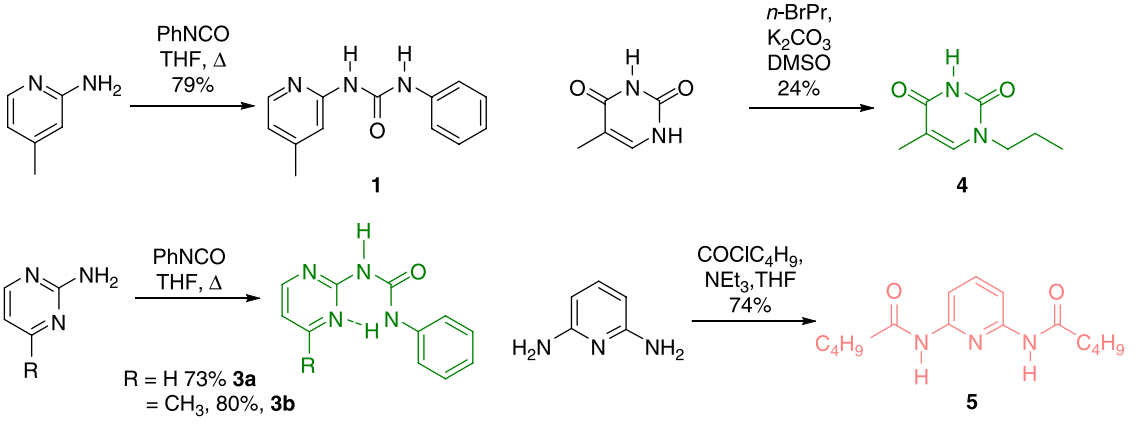


Figure 1. Rational design of conformer-independent linear arrays of hydrogen-bonding sites.

phenyl ring (not shown). We therefore determined dimerisation constants and association constants for appropriate pairings of compounds **1**, **2**, **3b**, **4** and **5** (Table 1). Figure 3 illustrates representative curve fitting performed using the HypNMR program (*26*) and a representative example of the ^{1}H NMR spectrum of **3b** on titration with **5**; as expected, complexation-induced shifts are observed, the most prominent of which is H_e. Binding of **3b** to **5** was found to occur with a modest association constant of $K_a = 56\,M^{-1}$ (accounting for self-dimerisation of both components). The low association constant is probably a function of the significant self-association of **3b** ($K_{dim} = 26\,M^{-1}$) presumably through the mode of interaction observed in the solid-state structure. However, although the value is smaller than the value determined for **4.5** as a comparison (it should be noted that the values for *DAP.T* pairs have been shown to vary over nearly two orders of magnitude in several different studies) (*27–29*), it clearly indicates formation of a well-defined host–guest complex involving all hydrogen-bonding sites of the ADA motif presented by **3b**. In support of this, no association of **1** and **5** was observed: although two hydrogen-bonds may still form between these two compounds, it is probable that complex formation would be disfavoured due to a steric clash between the pyridine ring and unbonded NH donor of **5**.

Further evidence for the structural nature of the association and its conformer independence was obtained from ^{1}H–^{1}H NOESY experiments. Figure 4 shows the ^{1}H–^{1}H NOESY spectrum of a 1:1 mixture of **3b** and **5**. Through space correlations are observed from H_e to H_E, H_c to H_E and H_D, H_f to H_D and H_E, and H_h to H_D. The latter two correlations suggest that both conformers of **3b** form heterocomplexes with **5** while the observation of correlations from both aromatic rings of **3b** to **5** indicates that all three hydrogen-bonding sites are involved in recognition (Figure 4).



Scheme 1. Synthesis of compounds **1**, **3a–b**, **4** and **5**.

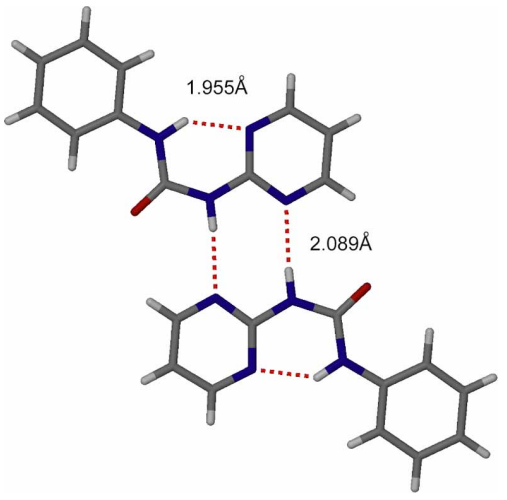


Figure 2. (Colour online) X-ray crystal structure of **3a,** carbon is shown in grey, hydrogen in white, nitrogen in blue and oxygen in red (key interatomic distances are highlighted in Å).

Conclusion

We have shown that *PUPY* represents an easily accessible ADA array that is complementary to the DAD array presented by diamidopyridine derivatives. Although the association constant is lower than that observed for the diamidopyridine–thymine dyad, the ease of synthesis offers opportunities for these new derivatives to be incorporated into side-chain-functionalised supramolecular polymer architectures. Our own future studies will explore this avenue of research.

Experimental

General points

All melting points reported were measured using a Griffin D5 variable temperature apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured using a Bruker DPX 300 instrument operating at 300 MHz. ^{1}H NMR spectra are referenced to tetramethylsilane and all chemical shifts are displayed in parts per million relative to TMS and all coupling constants are reported to the nearest 0.1 Hz. Infrared spectra were recorded using a Perkin-Elmer FTIR spectrometer. Where anhydrous solvents were required, THF was freshly distilled from sodium-benzophenone ketyl radical, and $CHCl_3$ was freshly distilled from calcium chloride under a nitrogen atmosphere. Triethylamine was distilled from calcium hydride under a nitrogen atmosphere and stored, under nitrogen, over potassium hydroxide pellets. Compound **1** was reported previously (*21*).

Table 1. Binding constants determined by ^{1}H NMR in $CDCl_3$.

Compound	K_a or K_{dim} (M^{-1})
1.1	56 (±6)
3b.3b	26 (±7)
4.4	<1
5.5	4 (±1)
3b.5	56 (±20)
4.5	91 (±9)
1.5	N/A

1-(pyrimidin-2-yl)-3-phenylurea 3a

To a stirred solution of 2-aminopyrimidine (1.90 g, 20 mmol) in THF (80 ml) under a nitrogen atmosphere was added phenylisocyanate (3 ml, 27.4 mmol). The reaction mixture was brought to reflux and heated for 1.5 h and then cooled. This resulted in the formation of a precipitate that was collected and recrystallised from ethanol to yield a white fluffy solid (3.10 g, 73%); m.p. 227.3–229°C (lit. 225–227) (*30*) (found: C, 61.7; H, 4.9; N, 26.2; $C_{11}H_{10}ON_4$ requires: C, 61.7; H, 4.7; N, 26.2); δ_H (500 MHz, DMSO-d_6); 7.06 (1H, t, $J = 7.7$ ArCH), 7.13 (1H, t, $J = 4.6$, PyCH), 7.33, (2H, t, $J = 7.7$, ArCH), 7.60 (2H, d, $J = 7.7$, ArCH), 8.68 (2H, d, $J = 4.6$, PyCH), 10.18, (1H, s, NH) 11.48 (1H, s, NH); δ_C (125 MHz, DMSO-d_6) 115.4, 119.8, 123.4, 129.2, 138.9, 151.8, 158.2, 158.6; $\nu_{max}/cm^{-1} = 3213, 1691, 1600, 1565, 1479, 1417, 1331, 1246, 1156$; ESI-MS $m/z = 215$ $[M + H]^+$.

1-(4-methylpyrimidin-2-yl)-3-phenylurea 3b

To a stirred solution of 2-amino-4-methyl pyrimidine (2.18 g, 20 mmol) in dry THF (80 ml), phenylisocyanate (3.14 g, 28 mmol) was added dropwise via a cannula over 5 min under a nitrogen atmosphere. Upon addition, a white precipitate was observed. The reaction was then heated under reflux for 20 h after which the precipitate was filtered, and the filtrate was dried *in vacuo* to yield the product (3.85 g, 80%) as a fluffy white powder; m.p. 214–215°C (found: C, 63.05; H, 5.30; N, 24.65; $C_{12}H_{12}ON_4$ requires: C, 63.15; H, 5.30; N, 24.55); R_f 0.85 ($CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.54 (3H, s, CH_3), 6.83 (1H, d, $J = 5.1$ Hz, PyCH), 7.12 (1H, t, $J = 7.5$ Hz, ArCH), 7.38 (2H, t, $J = 7.8$ Hz, ArCH), 7.61 (2H, d, $J = 7.6$ Hz, ArCH), 8.54 (1H, d, $J = 4.8$ Hz, PyCH), 8.80 (1H, brs, NH), 11.51 (1H, s, NH); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 24.54, 114.82, 120.4, 124.0, 129.4, 138.7, 152.2, 153.2, 158.0, 168.9; $\nu_{max}/cm^{-1} = 3387, 2968, 1792, 1692, 1599, 1497, 1252$; ESI-MS $m/z = 229$ $[M + H]^+$.

N-*Propylthymine 4*

To a stirred solution of thymine (5 g, 39.6 mmol) and anhydrous potassium carbonate (5.50 g, 40 mmol) in dimethylsulphoxide (50 ml), 1-bromopropane (1.20 ml, 13 mmol) was added dropwise over 5 min under a nitrogen atmosphere. After 16 h, a white precipitate was observed.

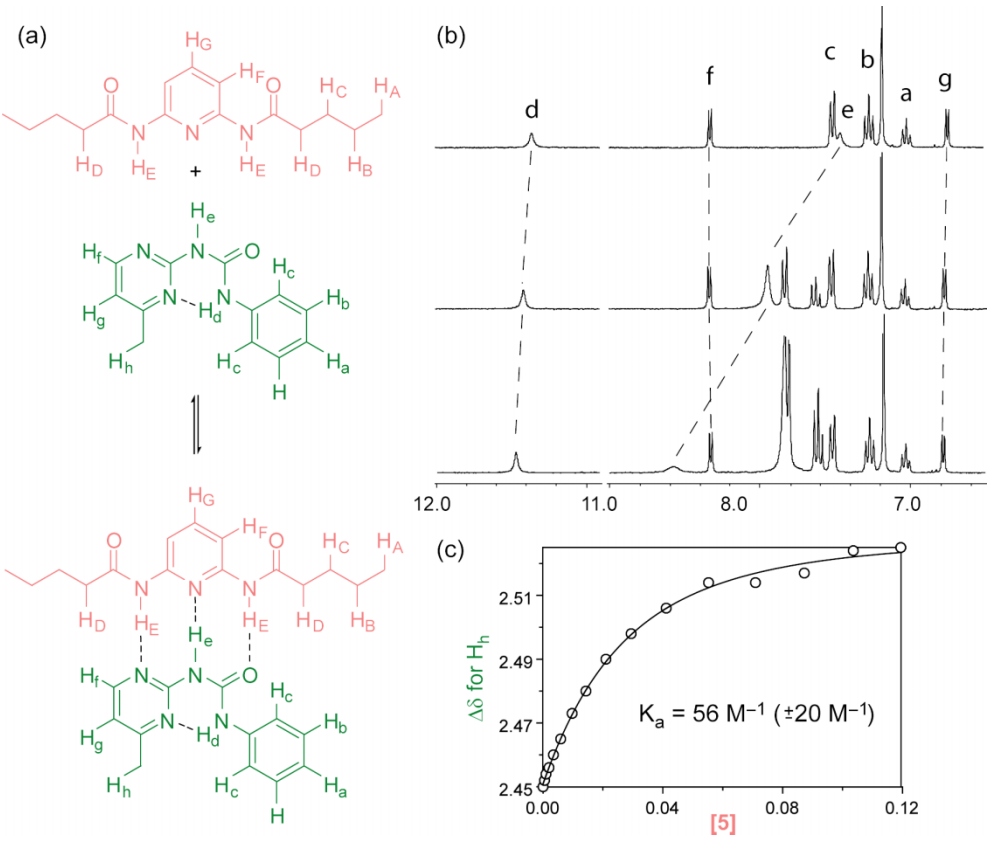


Figure 3. ^{1}H NMR titration data and curve fitting for formation of **3b.5**. (a) Addition of **5** to **3b**. (b) ^{1}NMR spectrum (300 MHz, $CDCl_3$) upon addition of **5** to **3b**. (c) Curve fitting for **3b.5**.

The reaction mixture was then filtered and concentrated *in vacuo* to yield a white solid, which was redissolved in $CHCl_3$ (50 ml) and extracted with water (5 × 50 ml). The $CHCl_3$ extracts were then dried using anhydrous sodium sulphate filtered and concentrated *in vacuo*. Two recrystallisations from ethanol yielded the title compound (0.53 g, 24%) as small white glassy crystals; m.p. 132–135°C (lit 135–137°C) (found: C, 57.05; H, 7.25; N, 16.50; $C_8H_{12}O_2N_2$ requires: C, 57.13; H, 7.19; N, 16.50); R_f 0.32 (100% EtOAc); δ_H (300 MHz, $CDCl_3$) 0.834 (3H, t, $J = 7.5$ Hz, CH_2CH_3), 1.57 (2H, apparent sext, $J = 7.5$ Hz, CH_2CH_3), 1.74 (3H, s, CH_3), 3.57 (2H, t, $J = 7.2$ Hz, $CH_2CH_2CH_3$), 7.53 (1H, s, $CH = CCH_3$), 11.22 (1H, brs, NH); δ_C (75 MHz, $CDCl_3$) 11.0, 12.3, 22.1, 49.0, 108.6, 141.9, 151.2, 164.6; $\nu_{max}/cm^{-1} = 3403, 2976, 2824, 2353, 1861, 1761, 1703, 1472$; ESI-MS $m/z = 169$ $[M + H]^+$ (*23*).

2,6-Dipentanoylamidopyridine 5

To a stirred solution of 2,6-diaminopyridine (1.84 g, 9.5 mmol) in dry THF (50 ml) and triethylamine (5 ml, 33.7 mmol), pentanoyl chloride (4 ml, 33.7 mmol) was added dropwise via cannula over 5 min at 0°C under nitrogen atmosphere. The reaction was stirred for 30 min, at 0°C. The solvent was removed *in vacuo* to yield a black, sticky oil. The oil was dissolved in 30 ml $CHCl_3$ and extracted with water (5 × 100 ml) to afford a mixture of mono- and bis-acylated products. Column chromatography (SiO_2, 3:97 MeOH:$CHCl_3$) was used to isolate the title compound (3.47 g, 74%) as a white solid; m.p. 123–124°C (Found: C, 64.80; H, 8.55; N, 15.2; $C_{15}H_{23}O_2N_3$ requires: C, 64.95; H, 8.36; N, 15.15); $R_f = 0.38$ (EtOAc); δ_H (300 MHz, $CDCl_3$): $\delta = 0.95$ (6H, t, $J = 7.3$ Hz, $CH_3CH_2CH_2$), 1.41 (4H, apparent sext, $J = 7.2$ Hz, $CH_3CH_2CH_2$), 1.71 (4H, apparent q, $J = 7.2$ Hz, $CH_3CH_2CH_2$), 2.38 (4H, t, $J = 7.5$ Hz, $CH_3CH_2CH_2CH_2$), 7.55 (2H, brs, CONH), 7.69 (1H, t, $J = 8.1$ Hz, PyCH), 7.90 (2H, d, $J = 7.8$ Hz, PyCH); δ_C (75 MHz, $CDCl_3$) 14.2, 22.7, 27.8, 38.0, 109.8, 141.2, 149.8, 172.0; $\nu_{max}/cm^{-1} = 3400, 3255, 2958, 2874, 1981, 1754, 1662, 1591, 1463$; ESI-MS $m/z = 278$ $[M + H]^+$.

NMR titrations

For NMR titrations, anhydrous $CDCl_3$ was purchased from Aldrich (Milwaukee, WI, USA). For dilution studies, solutions were made up to a suitable concentration and

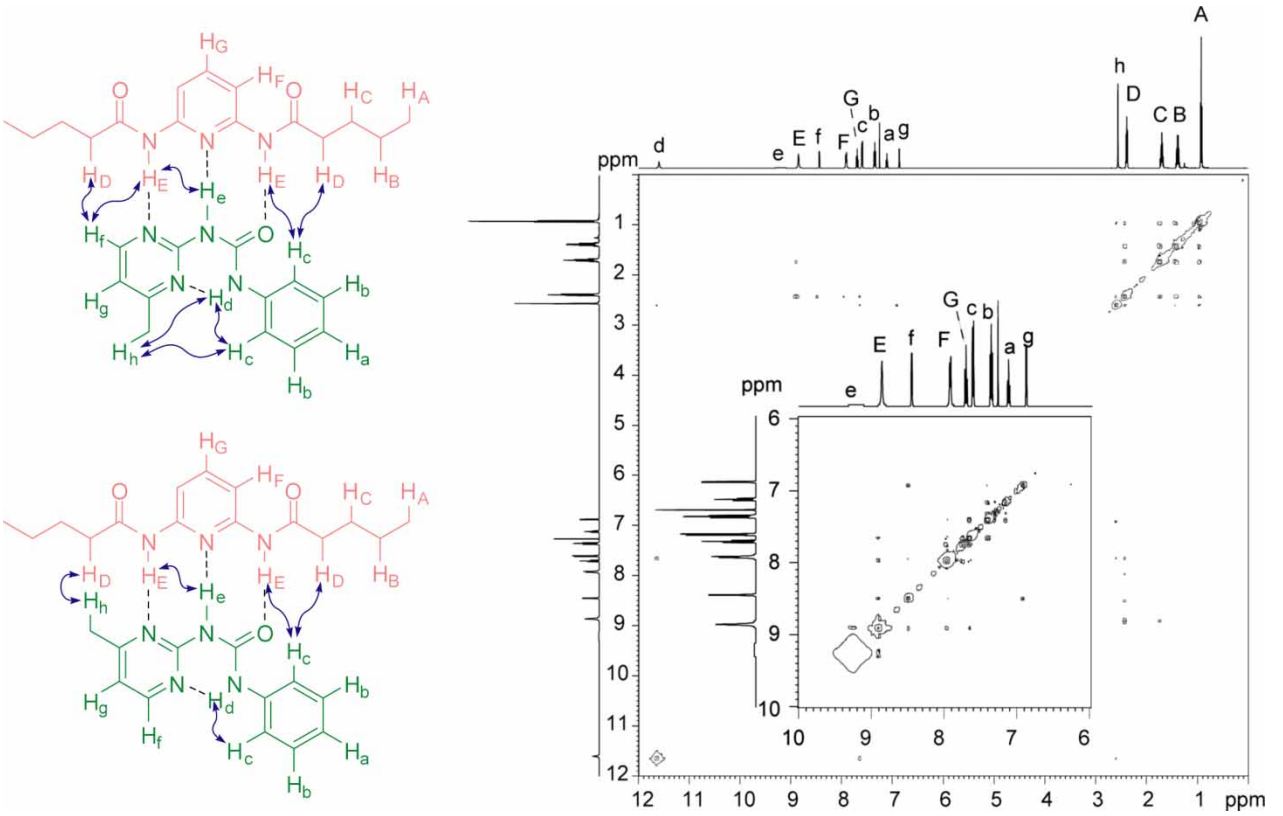


Figure 4. $^{1}H-^{1}H$ NOESY spectrum of a **3b.5** (500 MHz, $CDCl_3$).

then the ^{1}H NMR spectrum recorded upon each sequential dilution with $CDCl_3$. For titrations, the ^{1}H NMR spectrum was recorded of a solution of host (2–10 mM) in $CDCl_3$ upon sequential additions of a solution of guest (20–120 mM) containing host (2–10 mM) in $CDCl_3$. The change in chemical shift of key proton resonances was recorded at each dilution/titration point. The data were subsequently analysed using the HypNMR program (*26*) using the appropriate model. HypNMR uses data from multiple resonances for curve fitting.

Crystal structure determination for 3a

Single crystals were grown by the slow evaporation of a solution of **3b** in chloroform/methanol. X-ray diffraction data were collected at the University of Leeds using a Bruker APEX2 instrument. Crystal data: $C_{11}H_{10}N_4O$, $M = 214.23$, crystal size 0.4 × 0.4 × 0.1 mm, orthorhombic, $a = 28.720(4)$ Å, $b = 9.5618(11)$ Å, $c = 7.6408(9)$ Å, $\alpha = \beta$, $\gamma = 90°$, $U = 2098.2(4)$ Å^3, $T = 173(2)$ K, Pbcn, $Z = 8$, $\mu = 0.093$ mm^{-1}, $\lambda = 0.71073$ Å [Mo-Kα], 2484 reflections measured, 1875 unique ($R_{int} = 0.0232$), observed ($I > 2\sigma(I)$). The final R1 was 0.0387 (observed reflections 0.0573) and wR(F2) was 0.0963 (all data 0.1062) for 157 parameters. CCDC 693194 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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