

Ditopic Triply Hydrogen-Bonded Heterodimers

Supporting Information

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Experimental Section

All reagents were purchased from Aldrich or Alfa-Aesar and used without further purification unless otherwise stated. Triethylamine was distilled from calcium hydride and stored, under nitrogen, over potassium hydroxide pellets. All non-aqueous reactions were carried out under a nitrogen atmosphere. Analytical thin layer chromatography (TLC) was conducted using Merck Kieselgel 0.25mm silica gel pre-coated aluminium plates with fluorescent indicator active at UV₂₅₄. Purification by column chromatography was carried out using Merck Kieselgel 60 silica gel. Routine NMR spectra were obtained using Bruker DMX500 or Bruker AMD300 spectrometers operating at 500MHz or 300MHz for ¹H spectra and 125 MHz or 75 MHz for ¹³C spectra as stated. Proton spectra are referenced to TMS at 0.00 ppm, and carbon spectra to CDCl₃ at 77.4 ppm, unless otherwise stated. Melting points were determined using a Griffin D5 variable temperature apparatus and are uncorrected. IR spectra were obtained using Perkin-Elmer FTIR spectrometer. High Resolution Mass Spectra (HRMS) were recorded on a Micromass GCT Premier using electron impact ionisation (EI) or a Bruker Daltonics micrOTOF using electro spray ionisation (ESI).

Synthetic Procedures

1,6-Di[-N-ureido-N'-(4-(6-dimethylbenzyl)imidazole)]hexane, DUM 5

A solution of 1,6-diisocyanatohexane (0.15 mL, 2.1 mmol) in anhydrous dimethylacetamide (5 mL) at 87 °C under nitrogen atmosphere was added dropwise to a stirring solution of 2-amino-5,6-dimethylbenzimidazole (0.522 g, 3.24 mmol) in a further 1 mL anhydrous dimethylacetamide at 87 °C. The reaction mixture was stirred at 87 °C for 16 hr before being allowed to cool to room temperature and the resulting precipitate filtered. Recrystallisation from dimethylacetamide followed by subsequent washing with methanol, followed by drying over P₂O₅ under reduced pressure yielded the target compound **5** (0.367 g, 0.740 mmol,

35%) as a fine cream-coloured powder; m.p. Decomposes > 360 °C (DMAC); $R_F = 0.15$ (1:9 MeOH–EtOAc); δ_H (300 MHz, DMSO- d_6) = 7.11 (4H, s, ArCH), 3.15 (4H, t, $J = 7.1$ Hz, CH₂), 2.21 (12H, s, CH₃), 1.50 (4H, m, CH₂CH₂NH), 1.26 (4H, m, CH₂CH₂CH₂NH); δ_C (75 MHz, DMSO- d_6) = 156.0, 149.4, 129.9, 31.1, 27.6, 21.4; ν_{max}/cm^{-1} (solid state) = 3368, 3223, 2917, 1709, 1548; ESI-HRMS found m/z 491.2887 [M + H]⁺ C₂₆H₃₅N₈O₂ requires 491.2883.

***N*¹,*N*⁸-bis(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)octanediamide, DAC 6**

2-Amino-4-hydroxy-6-methylpyrimidine (6.02 g, 48.2 mmol) was dissolved in anhydrous dimethylacetamide (DMAC) (50 mL) at 87 °C under nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and anhydrous triethylamine (6.7 mL, 47 mmol) was added dropwise over 10 minutes to the reaction mixture followed by stirring for a further 10 minutes. Suberoyl chloride (3.6 mL, 20 mmol) was then added dropwise at 0 °C to the reaction mixture and the reaction was then heated to 87 °C for 16 hr. The mixture was allowed to cool to room temperature and the remaining DMAC solvent was removed under reduced pressure. The remaining residue was purified by column chromatography (SiO₂, 9:1 dichloromethane–methanol) followed by recrystallisation (1:1 methanol–acetonitrile vs. H₂O) to provide the title compound **6** (5.4 g, 13 mmol, 69%) as a colourless powder; m.p: 180–182 °C; R_F : 0.34 (9:1 dichloromethane–methanol); δ_H (300 MHz, DMSO- d_6): 11.78 (2H, br s, NHCO), 11.56 (2H, br s, NHC(CH₃)), 5.91 (2H, s, pyrimidyl-H), 2.42 (4H, t, $J = 7.2$ Hz, CH₂CO), 2.14 (6H, s, CH₃), 1.60 – 1.30 (4H, m, CH₂CH₂CO), 1.30 – 1.10 (4H, m, CH₂CH₂CH₂CO); δ_C (75 MHz, DMSO- d_6): 176.9, 160.7, 150.7, 107.3, 36.2, 28.3, 24.4, 23.7; ν_{max}/cm^{-1} (solid state) = 3165, 2850, 1711, 1646, 1561; ESI-HRMS found m/z 389.1932 [M + H]⁺ C₁₈H₂₅N₆O₄ requires 389.1937.

DOSY data acquisition:

DOSY NMR measurements were made on a Varian Inova 500 MHz spectrometer. All experiments were conducted at 20 °C on 1.0 mM CDCl₃ solutions, and used a 5 mm ID probe. The bipolar pulse pair simulated echo (BPPSTE) sequence¹ was employed operating in ONESHOT mode.² Additional parameters: number of different gradient strengths, 20; gradient stabilization delay 0.002 s; gradient length 0.002 s; diffusion delay 0.03 s; relaxation delay 2.5 s (following measurement of T₁); acquisition time 2 s; kappa (unbalancing factor, 0.2). Data were processed using a 3 Hz line broadening and exponential multiplication. Data were zero-filled once. Spectra were phased and baseline corrected prior to production of the pseudo 2D DOSY plots. For measurement of diffusion coefficients, a calibration curve was plotted (using the Stokes-Einstein relationship) for diffusion coefficient ($\times 10^6 \text{ cm}^2 \text{ s}^{-1}$) versus the reciprocal cube root of the molecular mass ($1/(\text{molecular mass})^{1/3}$). The compounds used for this calibration exercise were 4-aminopyrimidine (95.11 Da, $17.281 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$), Dipyriddy (184.24 Da, 13.573), 4-[2,6,2''-terpyridinyl]benzyl (323.4 Da, 10.197), Benzene-1,3,5-tricarboxylic acid tris(6-methyl-2-pyridinyl)amide (480.0 Da, 11.503), Hexakis(2-pyridylmethyl)CTV (913.11 Da, 8.703), Tris(4-[2-pyridyl]benzyloxy)CTG (910.14 Da, 9.037). The straight line determined was $y = 73.275x + 1.1263$ ($R^2 = 0.93$).

ROESY Data Acquisition

Phase sensitive ¹H-¹H ROESY experiments were performed on a 1:1 mix of components DUM **5** and DAC **6** at 1.0 mM concentration with respect to each component in CDCl₃ solvent. The sample was analysed immediately prior to preparation to avoid uptake of residual atmospheric H₂O. Spectra were recorded on a Bruker Avance DRX500 instrument at 253 K at a frequency of 500 MHz. A mixing time of 350 ms was applied using a constant wave spin lock mixing method. A pulse sequence repetition of 2.2 secs was used.

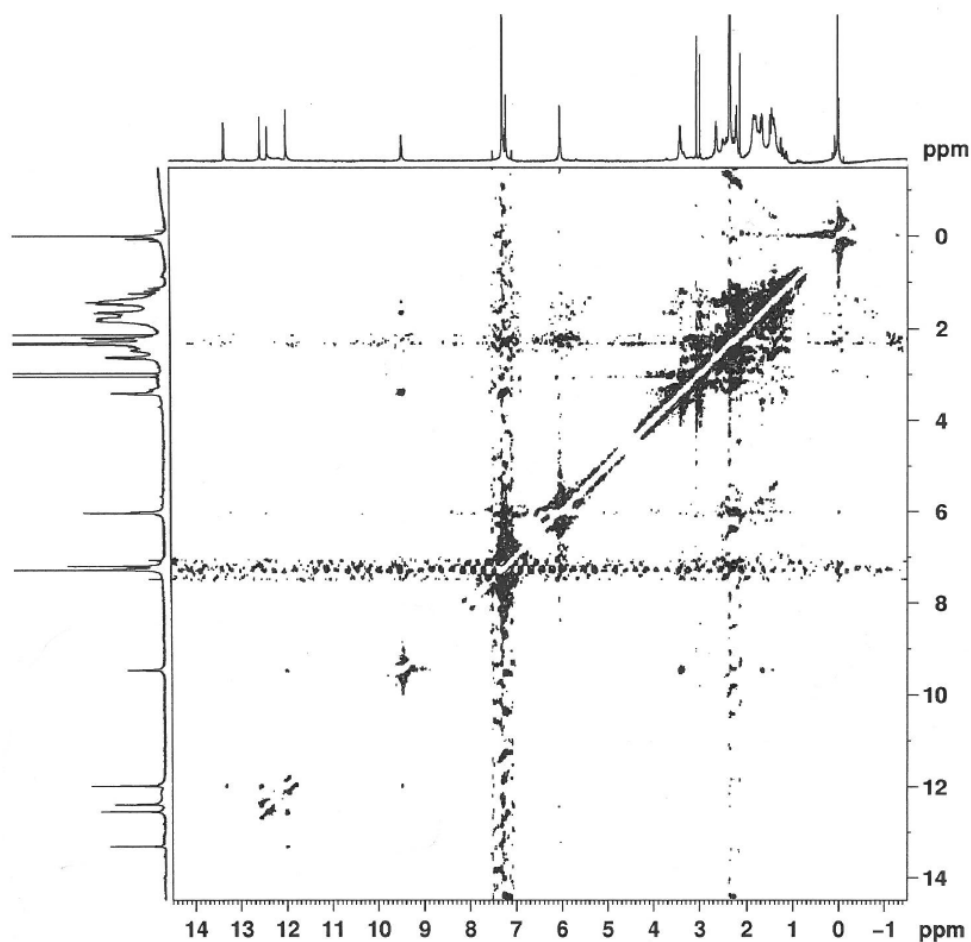


Figure ESI 1 Phase sensitive ^1H - ^1H ROESY spectrum of 1:1 mix of components DUM **5** and DAC **6** at 1.0 mM concentration (with respect to each component) in CDCl_3 , 500 MHz. (Note: The spectrum has been symmetrised for printing purposes)

ESI MS Experiments

Electrospray ionisation (ESI) mass spectrometry also provides evidence for the assembly of DUM **5** and DAC **6** units into higher order structures. The spectrum (Fig. SI3) exhibits m/z signals corresponding to monomer, dimer and trimer formation (whereby trimers are composed of one DUM **5** and two DAC **6** units). The dominant signal derives from the dimer, however the signal intensities should not be considered to be quantitative because the spectrum is composed of a mixture of components which may have different propensities to

ionize. We attribute the presence of the trimer to an increase in sample concentration during the process of ionization.

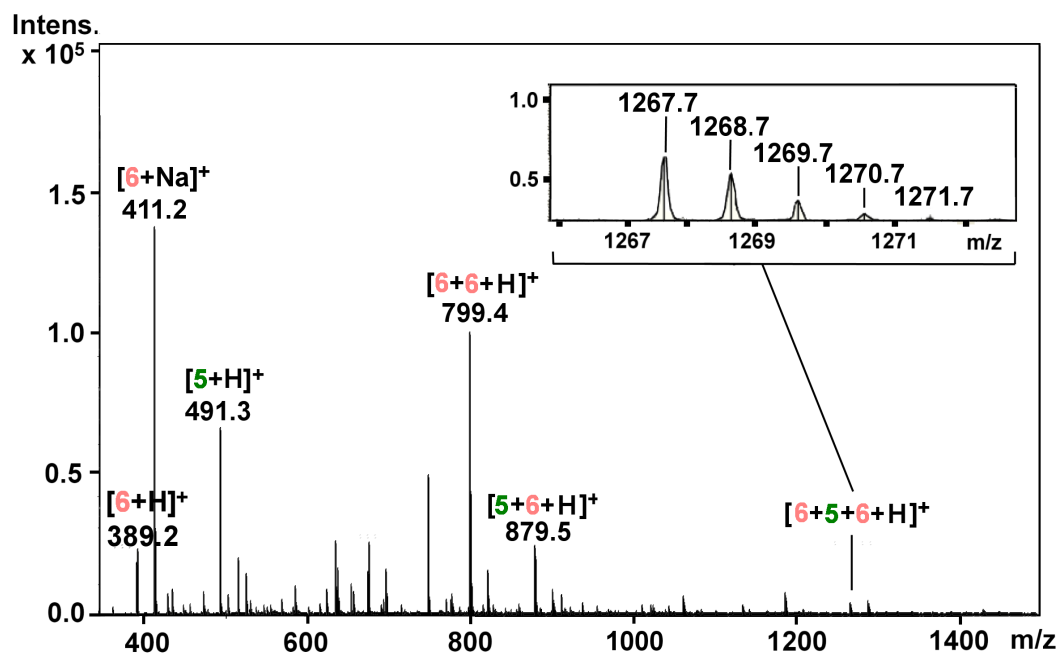


Figure ESI 2 ESI mass spectrum of a 1:1 mixed sample of DUM 5 and DAC 6. Significant peaks are also labelled according to their composition.

NMR studies in 10% DMSO/ Chloroform

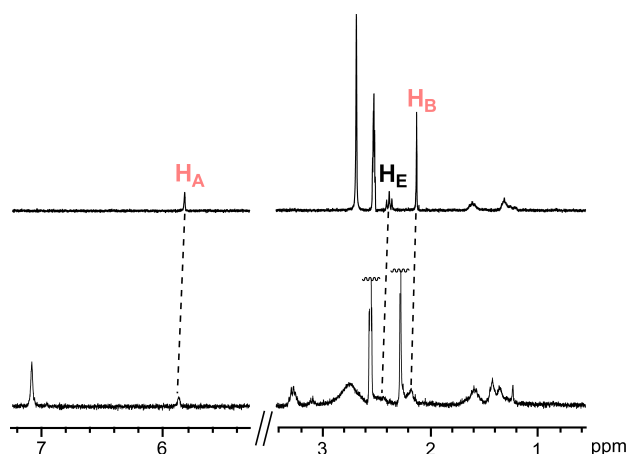
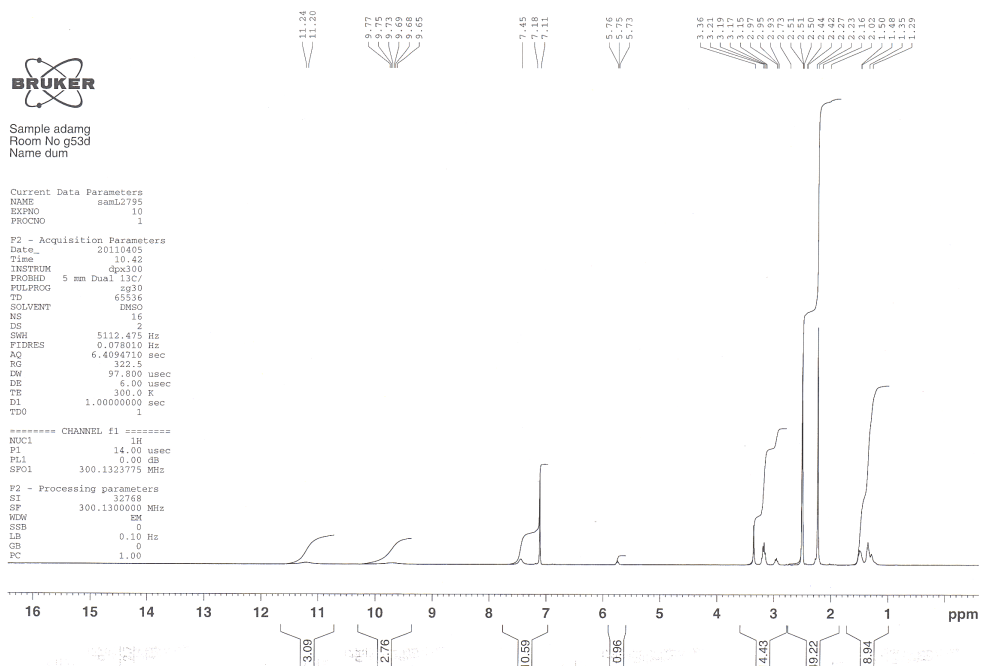


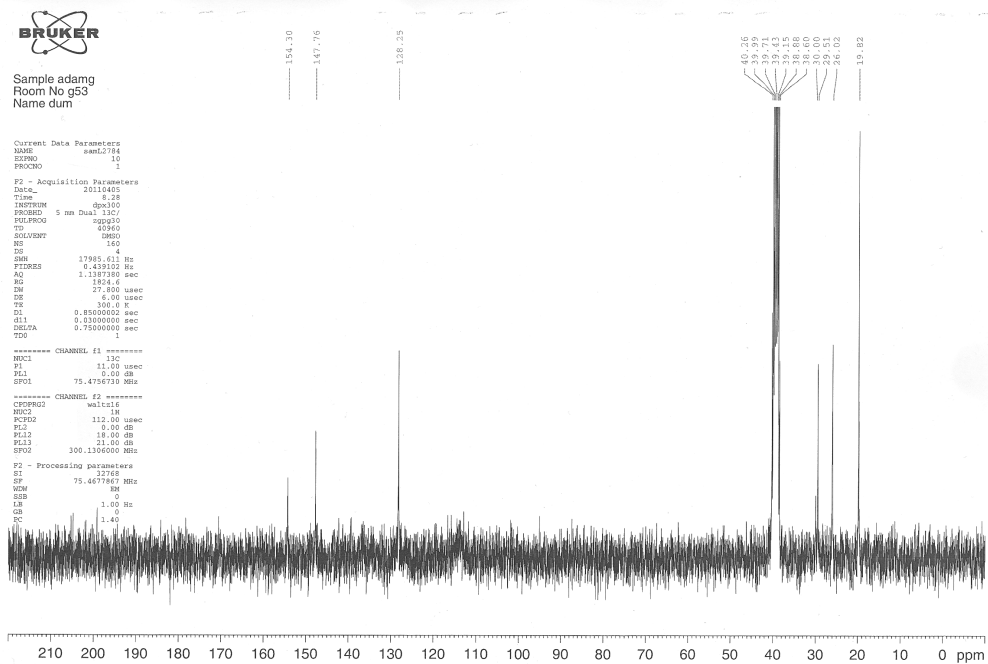
Figure ESI 3 Representative partial ^1H NMR titration spectra of: a) DAC **6** and; b) DAC **6** and DUM **5** in 10% DMSO- d_6 /CDCl $_3$, 300 MHz. Prominent complexation induced signal shifts are highlighted by dotted lines.

Figure ESI 4 Alternative arrangement of **5** and **6** for tautomer *II*

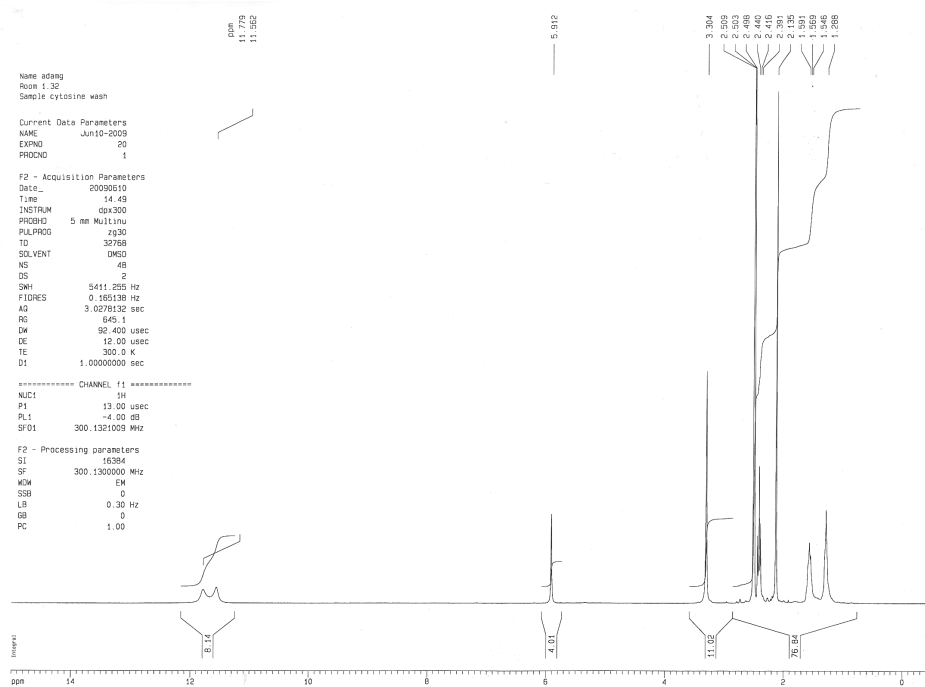
^1H NMR **5** (DMSO- d_6 , 300 MHz)



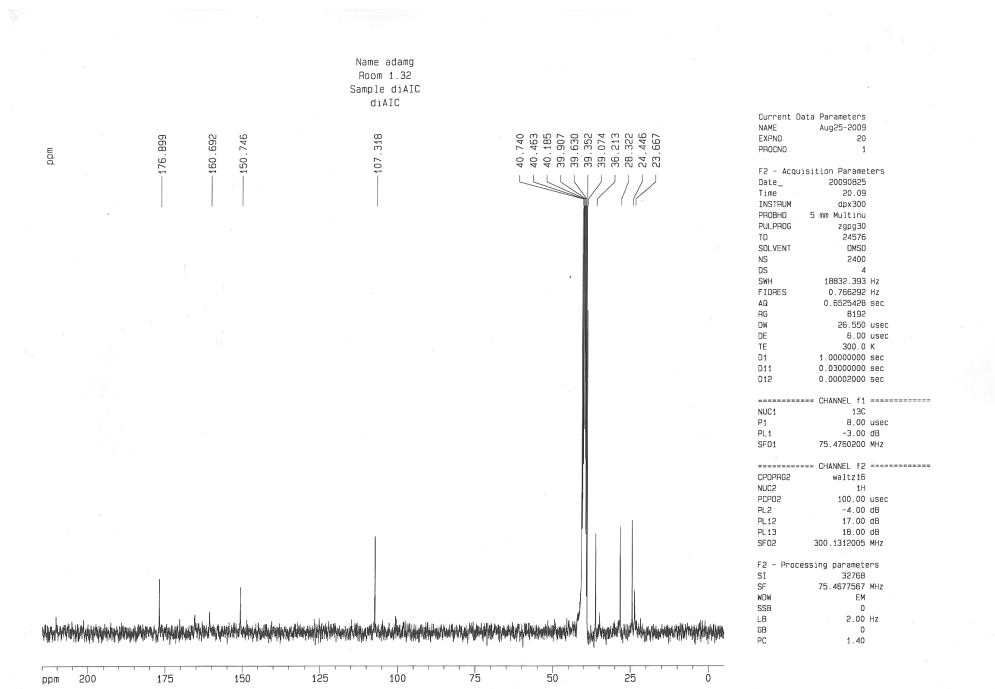
¹³C NMR 5 (DMSO-d₆, 75 MHz)



¹H NMR 6 (DMSO-d₆, 300 MHz)



^{13}C NMR 6 (DMSO- d_6 , 75 MHz)



References

- (1) Pelta, M. D.; Barjat, H.; Morris, G. A.; Davis, A. L.; Hammond, S. J. *Magn. Reson. Chem.* **1998**, *36*, 706-714.
- (2) Pelta, M. D.; Morris, G. A.; Stchedroff, M. J.; Hammond, S. J. *Magn. Reson. Chem.* **2002**, *40*, S147-S152.