

AAAA-DDDD Quadruple Hydrogen-Bond Arrays Featuring NH \cdots N and CH \cdots N Hydrogen Bonds

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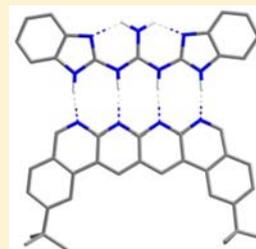
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Supporting Information

ABSTRACT: The X-ray crystal structure of a previously reported extremely strong quadruple NH \cdots N AAAA-DDDD hydrogen-bond array [5·4] ($K_a = 1.5 \times 10^6 \text{ M}^{-1}$ in CH₃CN; $K_a > 3 \times 10^{12} \text{ M}^{-1}$ in CH₂Cl₂) features four short linear hydrogen bonds. Changing the two benzimidazole groups of the DDDD unit to triazole groups replaces two of the NH \cdots N hydrogen bonds with CH \cdots N interactions (complex [5·6]), but only reduces the association constant in CH₃CN by 2 orders of magnitude ($K_a = 2.6 \times 10^4 \text{ M}^{-1}$ in CH₃CN; $K_a > 1 \times 10^7 \text{ M}^{-1}$ in CH₂Cl₂). Related complexes without the triazole groups range in K_a from 18 to 270 M⁻¹ in CH₃CN, suggesting that the CH \cdots N interactions can be considered part of a strong AAAA-DDDD quadruple hydrogen-bonding array. The NH \cdots N/CH \cdots N AAAA-DDDD motif can be repeatedly switched “on” and “off” in CDCl₃ through successive additions of acid and base.



INTRODUCTION

While individual hydrogen bonds are generally weak and have short lifetimes, their enthalpy of formation is additive, meaning that multipoint hydrogen-bonding arrays¹ can very effectively hold together supramolecular assemblies and materials.² Secondary electrostatic interactions between adjacent hydrogen bonds have a significant influence on the stability of a supramolecular complex.³ The binding strength is theoretically maximized if all the hydrogen-bond donors (D) are on one component and all the hydrogen-bond acceptors (A) are on the other,³ a trend that has been experimentally demonstrated with triple⁴ and quadruple⁵ (e.g., AADD-DDAA [1·1] < ADDA-DAAD [2·3] < AAAA-DDDD [5·4], Figure 1) hydrogen-bond motifs involving N–H donors and N or O hydrogen-bond acceptors. Although C–H groups are generally much weaker hydrogen-bond donors than hydrogens bound to heteroatoms, CH \cdots N/O interactions can play important roles in molecular recognition and assembly processes,⁶ including protein–protein interactions,⁷ anion recognition,⁸ and extended crystal lattices.⁹ We recently reported⁵ an extremely strong ($K_a > 3 \times 10^{12} \text{ M}^{-1}$ in CH₂Cl₂) AAAA-DDDD quadruple hydrogen-bonding array ([5·4], Figure 1) based on four NH \cdots N intercomponent hydrogen bonds.¹⁰ Here we report the X-ray crystal structure of [5·4] and the effect on the strength of binding of the quadruple hydrogen-bond array of replacing two of the NH \cdots N hydrogen bonds with CH \cdots N interactions.

RESULTS AND DISCUSSION

A single crystal of [5·4]BArF⁻ (BArF⁻ = [(3,5-(CF₃)₂C₆H₃)₄B]⁻)⁵ suitable for X-ray diffraction was obtained by slow diffusion of hexane vapor into a saturated solution of [5·4]BArF⁻ in CH₂Cl₂. The X-ray crystal structure (Figure 2) shows that the conformation of 4 is locked by two

intramolecular hydrogen bonds that present the four N–H hydrogen-bond donors along one edge of the molecule. The hydrogen-bonding edge of 5 shows a slight curve in the solid state, with the outer pyridine rings closer to the acceptor array than the inner pyridine rings. Accordingly, the peripheral NH \cdots N hydrogen bond lengths (1.769 and 1.807 Å) are significantly shorter than the inner NH \cdots N distances (1.899 and 2.032 Å) (Figure 2a). The four NH \cdots N hydrogen bonds are all close to linear, in contrast to the staggered arrangement observed in the X-ray structure of an AAA-DDD hydrogen-bond array.^{4d} The phenyl groups of 5 are slightly twisted away from the plane formed by the fused pyridine rings (Figure 2b).

The N–H groups of the benzimidazole groups of DDDD partner 4 still partake in short, close-to-linear hydrogen bonds despite being in five-membered rings which are not optimal for presenting the NH groups parallel to each other. It seemed that this geometry could be closely mirrored by triazole groups, readily introduced through a copper-catalyzed alkyne–azide cycloaddition (CuAAC) reaction,¹¹ which would allow the effect of replacing NH \cdots N hydrogen bonds with CH \cdots N interactions in a multipoint hydrogen-bond array to be evaluated.

A potential quadruple N–H/C–H hydrogen-bond donor 6 was synthesized in five steps from triazole 7¹² as shown in Scheme 1 (see Supporting Information for details). Amine 8 was produced via a Curtius rearrangement followed by deprotection with trifluoroacetic acid and subsequent thiourea formation with carbon disulfide in pyridine (Scheme 1, i–ii). Thiourea 9 was transformed into guanidine 10 via a carbodiimide intermediate and precipitated as the hexafluor-

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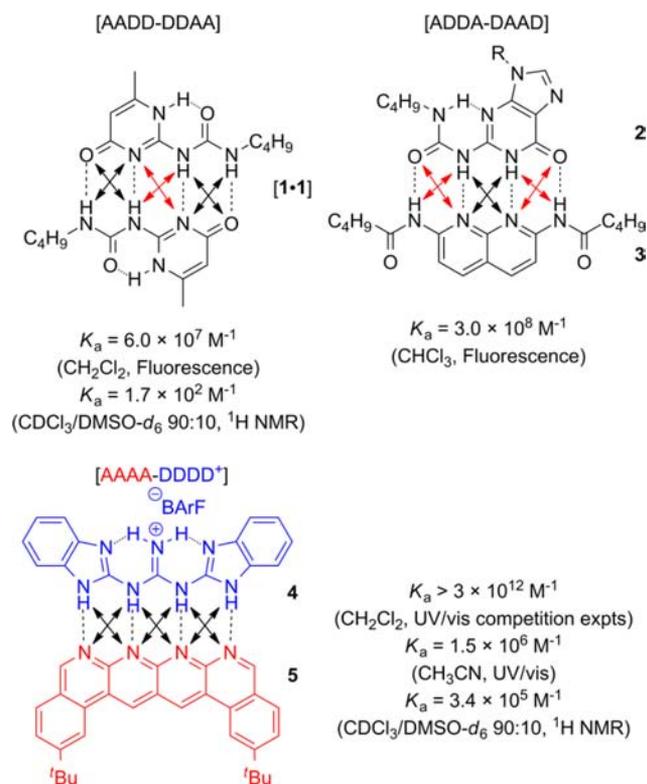


Figure 1. Examples of quadruple hydrogen-bond arrays and their association constants in various solvents (method of binding constant determination shown in parentheses): AADD-DDAA [1·1],^{10c} ADDA-DAAD [2·3],^{10h} and AAAA-DDDD [5·4].⁵ Black arrows show stabilizing secondary electrostatic interactions between adjacent hydrogen-bonding sites; red arrows indicate destabilizing secondary interactions.

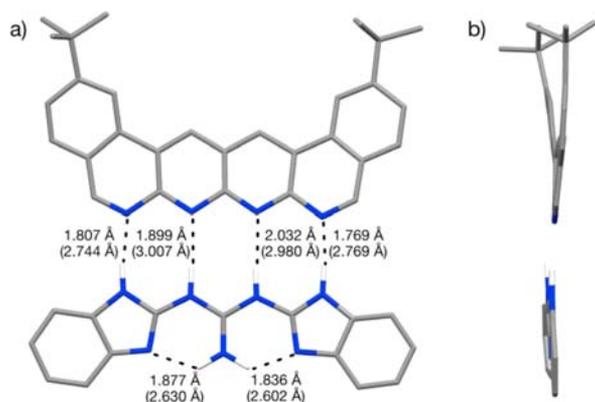
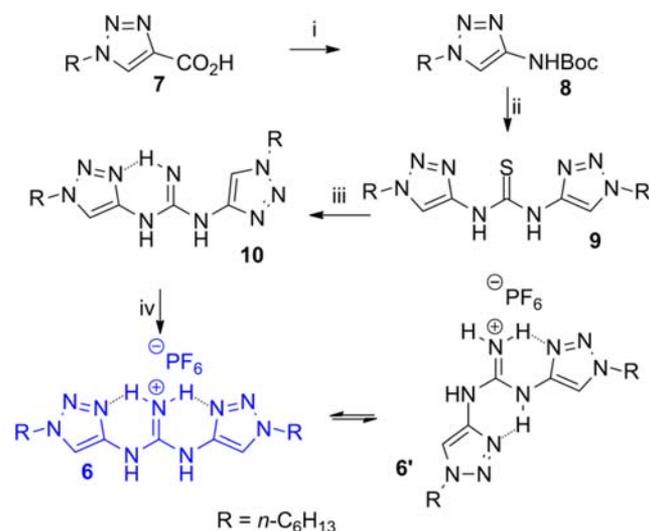


Figure 2. X-ray crystal structure of AAAA-DDDD complex [5·4]-BARF⁻ obtained from a single crystal grown from slow diffusion of hexane into a saturated solution of the complex in CH_2Cl_2 (see Supporting Information). Carbon atoms are shown in gray, nitrogen atoms in blue, and N–H hydrogen atoms in white. The counteranion and 0.25 molecule of MeOH (introduced unintentionally, probably when screening solvents for the crystallization experiments) in the unit cell are omitted for clarity. (a) View face-on to the aromatic rings showing the linearity of the hydrogen bonds in the AAAA-DDDD array. Annotated with NH...N hydrogen bond lengths; N...N distances shown in parentheses. (b) View along the edge of the complex showing the planarity of 4 and the slight twist of the pendant phenyl rings in 5.

Scheme 1. Synthesis of Quadruple N–H/C–H Hydrogen-Bond Donor 6^a



^aReagents and conditions: (i) $(\text{PhO})_2\text{PON}_3$, $^t\text{BuOH}$, Et_3N , 16 h, 100 °C, 33%. (ii) $\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2 then CS_2 , pyridine, 16 h, 130 °C, 83% over two steps. (iii) HgO , NH_3 , $\text{CHCl}_3/\text{MeOH}$, 1 h, rt, 91%. (iv) AcOH , NaPF_6 , 30 min, rt, 71%.

ophosphate salt **6** (Scheme 1, iii–iv). In principle, **6** can exist in several conformations and tautomers stabilized by different intramolecular hydrogen-bonding arrangements (e.g., **6** and **6'**, Scheme 1).

Characterization of NH...N/CH...N AAAA-DDDD Quadruple Hydrogen-Bond Array [5·6]. Addition of **6** to **5** in CD_2Cl_2 to form a 1:1 stoichiometry immediately led to considerable shifts in the $^1\text{H NMR}$ spectra of both components (Figure 3). The triazole C–H protons of **6** (H^a) are broadened and shifted downfield by ~ 1 ppm, consistent with very close positioning to, and polarization by, a region of high electron density (e.g., a heteroatom lone pair). Some protons of the pyridyl rings of **5** also undergo significant shielding (e.g., H^A) and deshielding (e.g., H^B) in the complex. Intermolecular NOE crosspeaks between H^B and H^b (Supporting Information, Figure S8) of **5** and **6** are consistent with the geometry of [5·6] being the anticipated edge-to-edge complex. A 1:1 stoichiometry complex was observed by electrospray ionization mass spectroscopy (ESI-MS) ($[\mathbf{5}\cdot\mathbf{6}]^+$ $m/z = 806.06$, see Supporting Information, Figures S10–S12).

The association constant of [5·6] proved to be too large to be measured directly in CD_2Cl_2 by $^1\text{H NMR}$ or UV/vis spectroscopy. However, a titration of **6** with **5** at 10^{-4} M concentrations in CH_3CN (298 K) showed a decrease in UV/vis absorption spectrum of **5** ($\lambda_{\text{max}} = 426$ nm), accompanied by a new species with a bathochromic shift ($\Delta\lambda$) of 11 nm (Figure 4). From these data the K_a of [5·6] in CH_3CN was determined to be $2.6 \times 10^4 \text{ M}^{-1}$ (see Supporting Information). This means that replacing two of the NH...N hydrogen bonds in [5·4] ($K_a = 1.5 \times 10^6 \text{ M}^{-1}$) with the two CH...N interactions in [5·6] ($K_a = 2.6 \times 10^4 \text{ M}^{-1}$) results in only a ~ 60 -fold decrease in the K_a value in CH_3CN .

Supramolecular Complexes Featuring Two Intercomponent NH...N Hydrogen Bonds and Zero, One, or Two CH...N Interactions. To further probe the contribution of the CH...N interactions to the overall stability of the hydrogen-bonding array, a series of binding constant measurements were

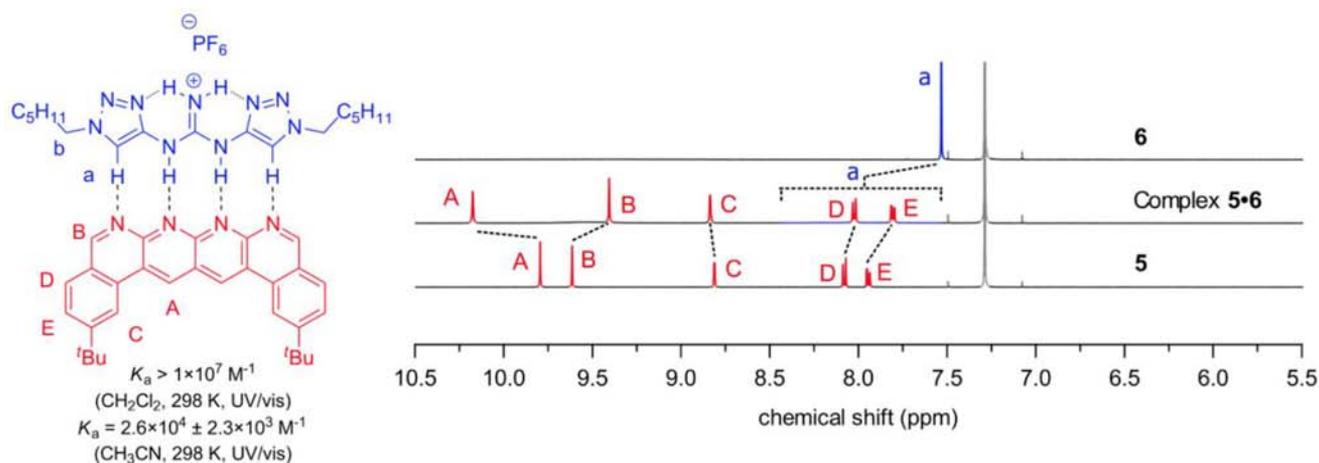


Figure 3. Partial ^1H NMR spectra (500 MHz, CD_2Cl_2 , 298 K) of **6** (top), complex **[5·6]** (middle), and **5** (bottom). Dashed lines show shifts upon formation of complex **[5·6]**. Residual CHCl_3 shown in gray.

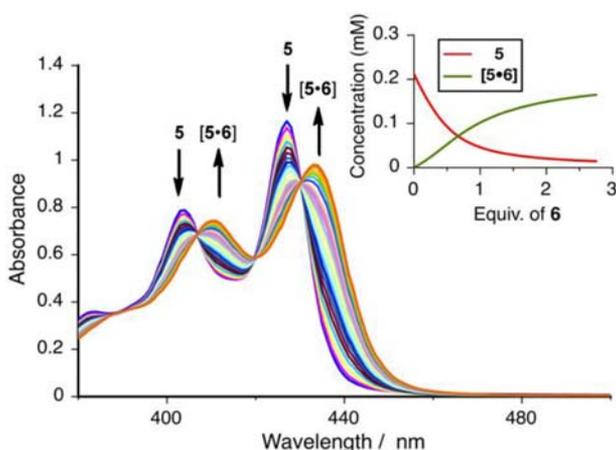


Figure 4. UV/vis titration of **5** with **6** in CH_3CN . UV/vis spectra (2.1×10^{-4} M) of **5** on addition of **6** (0–3 equiv), maintaining the concentration of **5** constant. Changes in absorbance reflect changes in the amount of **5** and **[5·6]** present during the titration experiment and differences in their UV/vis absorption. Inset: Profile of component stoichiometry from fitting software. For Job plot, see Supporting Information (Figure S4).

made between compounds with increasing numbers of contiguous acceptor sites (**11** with two acceptor sites, **12** with three, **5** with four) and donors containing two NH 's from a central guanidinium core plus either two additional contiguous NH groups (**4**), two additional contiguous CH groups (**6**), or no additional groups (**13**) able to interact with the acceptor pyridine sites (Figure 5). The rationale for the study is that, with each of **5**, **11**, and **12**, two pyridine sites would satisfy the hydrogen-bond requirements of the two NH groups of **4**, **6**, and **13**, but **11** has no further pyridine groups to engage in $\text{CH}\cdots\text{N}$ interactions, and **12** has only one. Although this comparison can give some indication of the ability of $\text{CH}\cdots\text{N}$ interactions to contribute to the strength of an extended hydrogen-bond array, there are many approximations implicit in the study. For example, the solvation of the different hydrogen-bond donors and acceptors will vary, and also the electrostatic interactions that enhance the hydrogen-bond-accepting ability of neighboring pyridine groups should be more pronounced in **5** than in **11** or **12**.¹³

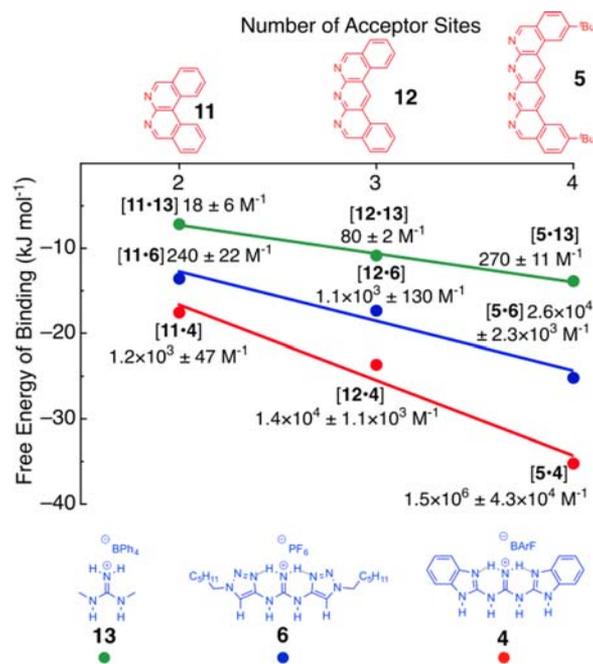


Figure 5. Plot of free energy of acceptor–donor binding vs the number of hydrogen-bonding sites on the acceptor with the appropriate acceptor compounds shown as axis labels. Association constants (determined from three repetitions) and their errors (standard deviation of repetitions) are shown next to each point. The error in data-fitting for each run was <1%. Conditions: 10^{-2} – 10^{-4} M, CH_3CN , 298 K, see Supporting Information for details.

Despite the limitations of the study, the results show some interesting trends (Figure 5). The simple guanidinium derivative **13**, which can only form two $\text{NH}\cdots\text{N}$ hydrogen bonds with any of the partners, forms relatively weak complexes in CH_3CN , with the association constant increasing by only an order of magnitude across the series **11**→**12**→**5** ($K_a = 18$ – 270 M^{-1}). In contrast, bis-triazole **6**, which can form up to two $\text{CH}\cdots\text{N}$ interactions in addition to the two $\text{NH}\cdots\text{N}$ hydrogen bonds, binds AAAA partner **5** ($K_a = 2.6 \times 10^4 \text{ M}^{-1}$) 2 orders of magnitude more strongly than it binds the 1,8-naphthyridine derivative **11** ($K_a = 240 \text{ M}^{-1}$). The peripheral triazole CH hydrogen-bonding groups clearly play a significant role in affecting the stability of the multipoint hydrogen-bond array,

although the effect is much smaller than that of NH hydrogen-bond donors (the binding constant for four-NH donor **4** increases 3 orders of magnitude across the series **11**→**12**→**5** in CH₃CN ($K_a = 1.2 \times 10^3$ – 1.5×10^6 M⁻¹).

The significant difference in binding strength between [**11**·**6**] ($K_a = 270$ M⁻¹), which features two NH···N hydrogen bonds, and [**5**·**6**] ($K_a = 2.6 \times 10^4$ M⁻¹), which has two NH···N hydrogen bonds plus two CH···N interactions in an aligned AAAA-DDDD array, suggests that CH···N interactions involving triazole groups probably benefit from secondary electrostatic interactions from adjacent hydrogen bonds in a similar manner to conventional hydrogen bonds involving NH donors.

Switching “On” and “Off” NH···N/CH···N AAAA-DDDD Complex Formation. As the hydrogen-bond donors **4** and **6** are protonated salts, in order to induce preorganization and display the desired recognition motif, the interaction can be switched “off” by the addition of an appropriate base (Figure 6). Addition of 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene

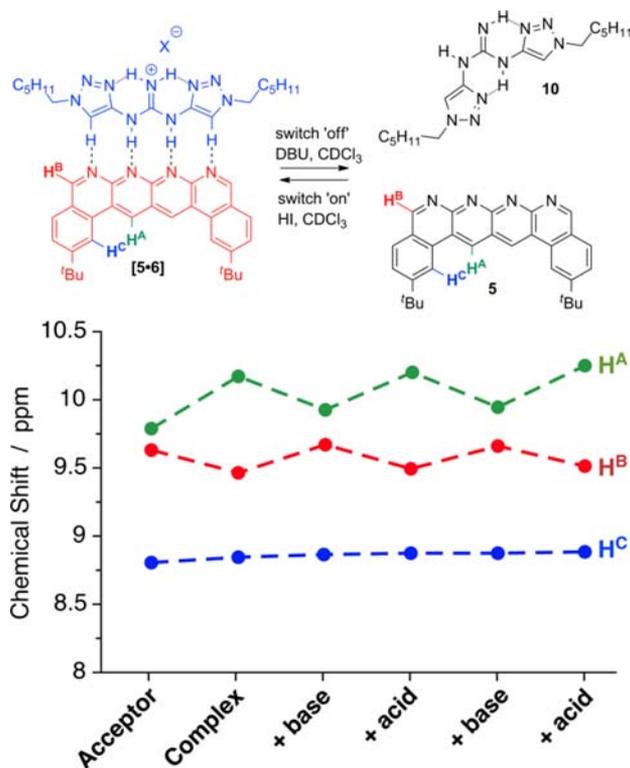


Figure 6. Switching “off” and “on” of the AAAA-DDDD [**5**·**6**] complex by deprotonation by DBU and reprotonation with HI. Counterion X⁻ = PF₆⁻ before the first switching event. The figure shows the change in ¹H NMR chemical shift of various protons of **5** before and after several switching events (1 mM, CDCl₃, 298 K, 400 MHz).

(DBU) to a solution of [**5**·**6**] in CDCl₃ deprotonated the guanidinium group and disrupted the strong association of **5** and **6**, as evidenced by shifts of H^A and H^B in the ¹H NMR spectrum to positions consistent with the uncomplexed building block (Figure 5). Reprotonation with 1 equiv of HI¹⁴ in CD₃CN smoothly re-formed [**5**·**6**] (Figure 6 and Supporting Information, Figure S6). In this way complex [**5**·**6**] could be switched “off” and “on” repeatedly by successive additions of base and acid.

CONCLUSIONS

The first X-ray crystal structure of an AAAA-DDDD complex, [**5**·**4**], shows that, in contrast to the staggered arrangement present in the only X-ray structure of an AAA-DDD system reported to date,^{4d} it has a close-to-linear array of four short intercomponent NH···N hydrogen bonds in the solid state. Changing the two benzimidazole groups of the DDDD unit to triazole groups replaces two of the NH···N hydrogen bonds with CH···N interactions (complex [**5**·**6**]), but reduces the association constant in CH₃CN by only 2 orders of magnitude ($K_a = 2.6 \times 10^4$ M⁻¹ in CH₃CN; $K_a > 1 \times 10^7$ M⁻¹ in CH₂Cl₂), suggesting that the CH···N interactions can be considered part of a AAAA-DDDD quadruple hydrogen-bonding array. The NH···N/CH···N AAAA-DDDD motif can be repeatedly switched “on” and “off” through successive additions of acid and base. The switching “on” and “off” of a strong hydrogen-bonding array may prove useful for the design of supramolecular polymers, gels, nanofibers, fibrils, and materials that can be assembled or disassembled in response to a simple stimulus.¹⁵

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all compounds, details of X-ray analysis, and complexation studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(13) The pyridine groups in **5** would be expected to be stronger hydrogen-bond acceptors than those in **11** or **12** (and those in **12** should be stronger than in **11**) because of the electrostatic interactions of the additional neighboring pyridine groups.

(14) HI was used as the acid as I^- is a relatively poor hydrogen-bond acceptor and so would not be expected to decrease the stability of the AAAA-DDDD complex, even as its concentration increases over multiple switching events.

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