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AAA−DDD Triple Hydrogen Bond Complexes

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Abstract: Experiment and theory both suggest that the AAA−DDD pattern of hydrogen bond acceptors (A) and donors (D) is the arrangement of three contiguous hydrogen bonding centers that results in the strongest association between two species. Murray and Zimmerman prepared the first example of such a system (complex **3•2**) and determined the lower limit of its association constant (K_a) in $CDCl_3$ to be 10^5 M^{-1} by ^1H NMR spectroscopy (Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010−4011). The first cationic AAA−DDD pair (**3•4**$^+$) was described by Bell and Anslyn (Bell, D. A.; Anslyn, E. A. *Tetrahedron* **1995**, *51*, 7161−7172), with a $K_a > 5 \times 10^5$ M^{-1} in CH_2Cl_2 as determined by UV−vis spectroscopy. We were recently able to quantify the strength of a neutral AAA−DDD arrangement using a more chemically stable AAA−DDD system, **6•2**, which has an association constant of 2×10^7 M^{-1} in CH_2Cl_2 (Djurdjevic, S.; Leigh, D. A.; McNab, H.; Parsons, S.; Teobaldi, G.; Zerbetto, F. *J. Am. Chem. Soc.* **2007**, *129*, 476−477). Here we report on further AA(A) and DDD partners, together with the first precise measurement of the association constant of a cationic AAA−DDD species. Complex **6•10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$] has a $K_a = 3 \times 10^{10}$ M^{-1} at RT in CH_2Cl_2, by far the most strongly bound triple hydrogen bonded system measured to date. The X-ray crystal structure of **6•10**$^+$ with a BPh_4^- counteranion shows a planar array of three short (NH···N distances 1.95−2.15 Å), parallel (but staggered rather than strictly linear; N−H···N angles 165.4−168.8°), primary hydrogen bonds. These are apparently reinforced, as theory predicts, by close electrostatic interactions (NH−•−N distances 2.78−3.29 Å) between each proton and the acceptor atoms of the adjacent primary hydrogen bonds.

Introduction

Multipoint hydrogen bonding motifs are the cornerstones of the recognition processes of biology and increasingly feature in the design of sophisticated functional organic materials and synthetic supramolecular polymers.[1,2] Fused-ring heterocyclic systems are generally the scaffolds of choice for contiguous hydrogen bonding centers, as geometrically well-defined arrays of hydrogen bond donor (D) and acceptor (A) groups can be presented along the edges of each rigid planar (or near-planar) heteroaromatic unit. Unfortunately, accompanying solubility issues and the possibility of multiple tautomeric forms for some heterocycles can sometimes complicate the characterization of their binding properties. Few receptor pairs with AA−DDD or AAA−DDD hydrogen bonding motifs, which are predicted to result in particularly stable complexes because of favorable secondary electrostatic interactions,[3] have been prepared or studied[4,5] to date. Following the Jorgensen group's calculations[3] on the exceptionally strong binding in such hydrogen bond

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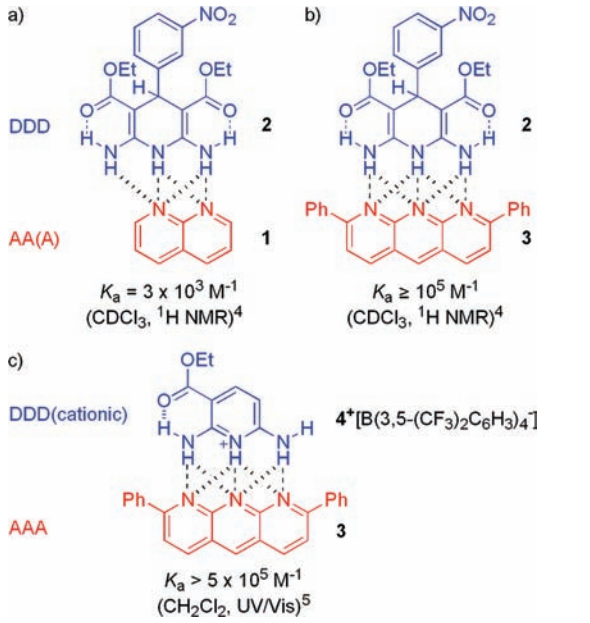

Figure 1. Early experimental examples of AA−DDD and AAA−DDD hydrogen bonding arrays: (a) AA−DDD complex **1•2**;[4] (b) AAA−DDD complex **3•2**;[4] (c) AAA−DDD(cationic) complex **3•4**$^+$[B(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_4^-$].[5] Primary hydrogen bonds shown with dashed lines; additional attractive secondary electrostatic interactions shown with hashed lines.

arrangements, the first experimental systems were realized[4] by Murray and Zimmerman who reported the association constants (K_a) of AA−DDD complex **1•2** to be $K_a = 3 \times 10^3$ M^{-1} (Figure 1a) and that of AAA−DDD system **3•2** to be $\geq 10^5$ M^{-1} (Figure 1b) in $CDCl_3$. Variations of the contiguous hydrogen bond acceptor−donor arrangements were consistent with cooperative secondary hydrogen bonding interactions playing a prominent role in the stabilization energy of these complexes.[6] However, AAA−DDD system **3•2** proved to be chemically reactive and required the presence of proton sponge (1,8-bis(dimethylamino)naphthalene) during the binding studies to prevent a hydride shift occurring from C-4 of **2** to C-10 of **3**. An attempt to simultaneously increase the chemical stability and binding affinity of a contiguous AAA−DDD pair was reported by Bell and Anslyn,[5] who described the properties of the AAA−DDD(cationic) complex **3•4**$^+$[B(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_4^-$] (Figure 1c). The cationic DDD species enhances the hydrogen bond donating ability of the donor unit while also providing some electrostatic stabilization of the DDD−AAA complex. The K_a of **3•4**$^+$[B(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_4^-$] was estimated from UV−vis titration experiments to be greater than 5×10^5 M^{-1} in CH_2Cl_2; however, no precise determination of the binding constant could be made because excited state proton transfer in the AAA−DDD(cationic) complex complicated the fluorescence spectra. Since these seminal studies, until recently,[7] relatively little progress[8] had been made in developing more robust and less chemically reactive AAA−DDD systems.

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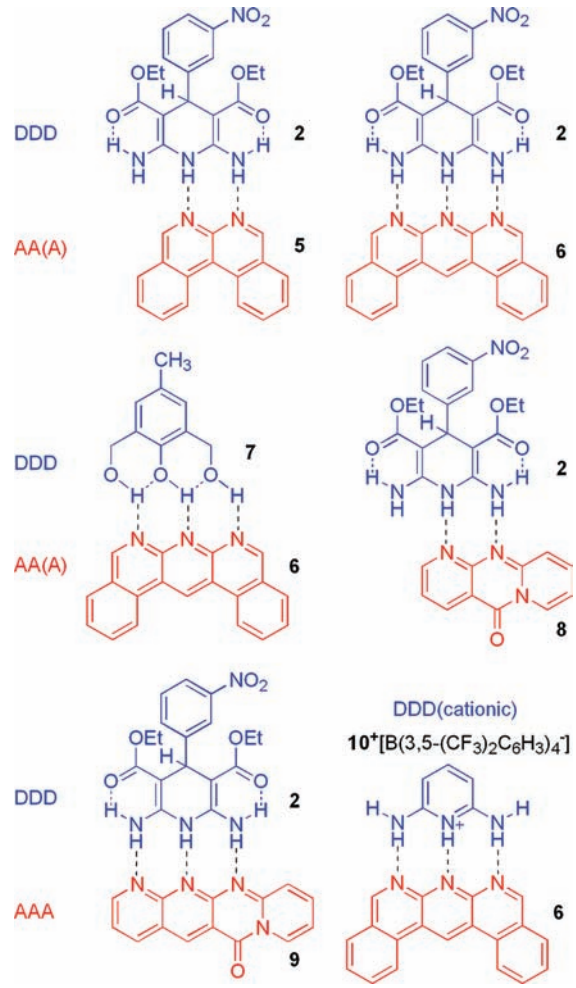

Figure 2. AA(A)−DDD systems featured in the present study.

In 2007 we made a preliminary report[7] on the synthesis and complexation studies of AA and AAA units **5** and **6** with DDD partners **2** and **7** (Figure 2). The extended aromatic system in **6** does not undergo the hydride transfer reaction that hindered the study of **3** and is also probably a slightly stronger hydrogen bond acceptor than the classic Zimmerman AAA system.[7] Here we extend the library of molecules with contiguous acceptor or contiguous donor sites, providing an account of the synthesis and complexation studies of six complementary pairs (Figure 2).

Synthesis. There are few known examples of heterocycles with multiple contiguous hydrogen bond sites in an AAA pattern. Caluwe and Majewicz introduced[9] methodology for the synthesis of 1,9,10-anthyridines (three pyridine rings fused together in a linear fashion through their 2,3/4,5 positions so that the three nitrogen atoms are all presented on the same edge of the molecule, e.g., **3**) but most examples of these heterocycles appear to be easily reduced to the corresponding 5,10-dihydroanthyridines (for example, by NaOEt/EtOH[9] and during the binding studies of **3** with DDD unit **2**[4]). Various aryl and heteroaromatic groups have been introduced[10] at the 5-position of **3** in an attempt to overcome the instability of the central ring, but binding studies with these modified systems have not, to our knowledge, been reported. We decided to extend the

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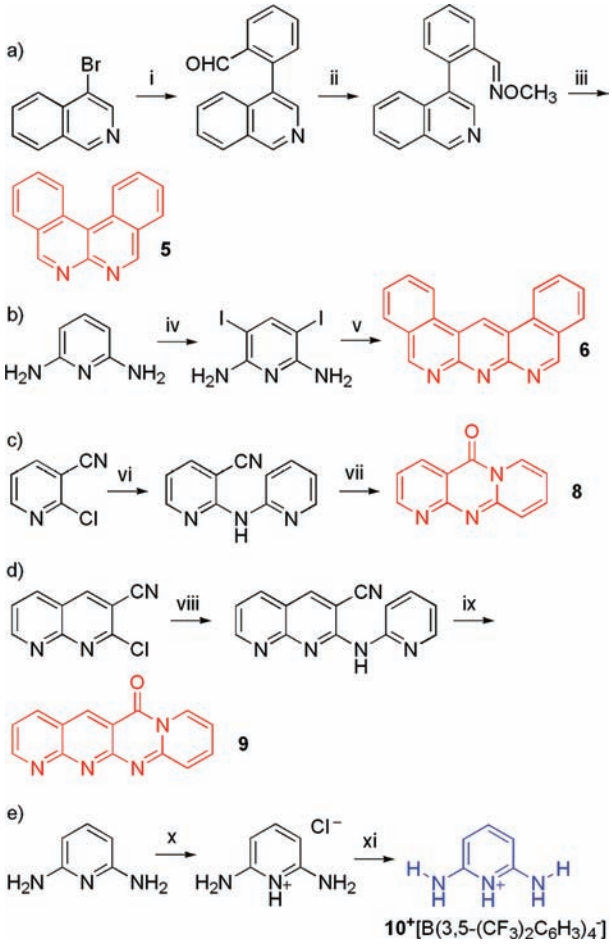
Scheme 1. Synthesis of AA and AAA units **5**, **6**, **8** and **9** and Cationic DDD Unit $\mathbf{10}^{+a}$



[a] Reagents and conditions: (i) $Pd(PPh_3)_4$, K_2CO_3, dioxane/water (1:1), 80%; (ii) methoxyamine hydrochloride, EtOH, 96%; (iii) FVP (flash vacuum pyrolysis; furnace temperature = 700 °C, inlet temperature = 182 °C, pressure = 4.8×10^{-2} Torr, 10 min, 75%; (iv) *N*-iodosuccinamide, DMF, 86%; (v) 2-formylphenyl boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, dioxane/water (1:1), 80%; (vi) 2-aminopyridine, $Pd(OAc)_2$, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), K_2CO_3, toluene, 70%; (vii) polyphosphoric acid, 95%; (viii) 2-aminopyridine, $Pd(OAc)_2$, BINAP, K_2CO_3, toluene, 40%; (ix) polyphosphoric acid, 85%; (x) HCl gas, $CHCl_3$, 98%; (xi) NaB(3,5-$(CF_3)_2C_6H_3)_4$, CH_3CN, 75%.

aromatic framework of the 1,9,10-anthyridine skeleton in the form of the pentacene analogue 6,7,8-triaza-dibenzo[*a*,*f*]anthracene **6** and 1,6a,11,12-tetraaza-naphthacein-6-one **9** and their AA (naphthyridine) analogues **5** and **8**, each of which could be prepared in three or less synthetic steps (Scheme 1).

The synthesis of AA unit **5** was accomplished via a Suzuki coupling between 4-bromoisoquinoline and 2-formylphenyl boronic acid followed by formation of the subsequent oxime ether (Scheme 1a, steps i and ii). Flash vacuum pyrolysis (FVP, step iii)[11] then afforded compound **5** in 75% yield. AAA unit **6** was synthesized in two steps via iodination of the 3,5-positions of 2,6-diaminopyridine with *N*-iodosuccinimide,[12] followed by a one-pot double Suzuki coupling-cyclization-aromatization protocol with 2-formylphenyl boronic acid (80%, Scheme 1b). Palladium catalyzed cross-coupling of 2-aminopyridine with

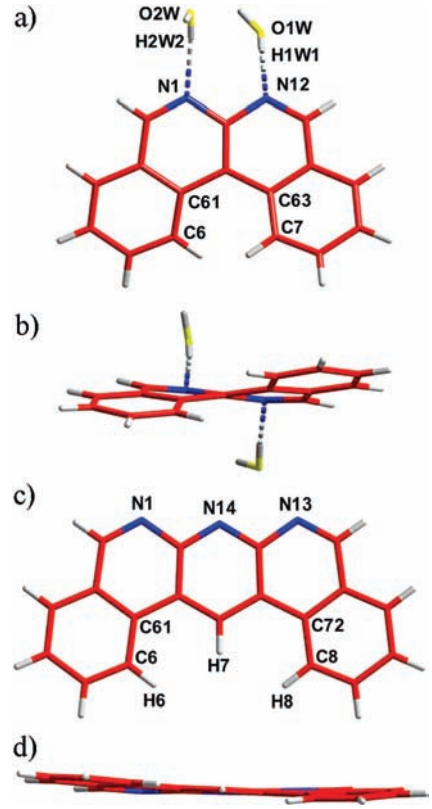


Figure 3. X-ray crystal structures of (a) $\mathbf{5}\cdot 2H_2O$ viewed from above the molecular plane, (b) $\mathbf{5}\cdot 2H_2O$ viewed edge on, showing the significant (~30°) helical twist to the molecule, (c) **6** viewed from above the molecular plane, and (d) **6** viewed edge on, showing the slight (~7°) helical twist to the molecule. Carbon atoms are shown in red; hydrogen white; nitrogen blue; oxygen yellow. Hydrogen bond lengths (Å) and angles (°): N1···H2W2 = 2.121, N1···H2W2−O2W = 175.5; N12···H1W1 = 2.094, N1···H1W1−O1W = 166.0.

commercially available 2-chloro-3-cyanopyridine or previously reported 2-chloro-3-cyano-1,8-naphthyridine[13] yielded the precursors to **8** (Scheme 1c) and **9** (Scheme 1d). Ring closure of these intermediates was achieved by heating in polyphosphoric acid to give the acceptor molecules **8** and **9** in good yields (84 and 85%, respectively) without the need for further purification.

The DDD arrays used in these studies include commercially available 2,6-bis(hydroxyl-methyl)-p-cresol (**7**), the previously reported[4] 2,6-diamino-1,4-dihydropyridine unit **2**, and 2,6-diaminopyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ($\mathbf{10}^+[B(3,5\text{-}(CF_3)_2C_6H_3)_4^-]$). The cationic DDD unit ($\mathbf{10}^+$) with the weakly ion-pairing tetraaryl borate anion [B(3,5-$(CF_3)_2C_6H_3)_4^-$] (BARF[14]) was obtained in 75% yield (Scheme 1e) by protonation of 2,6-diaminopyridine with HCl gas followed by anion exchange with NaB(3,5-$(CF_3)_2C_6H_3)_4$ in acetonitrile.

The solid state structures of **5** and **6** were determined by X-ray diffraction analysis of single crystals obtained by slow evaporation of saturated solutions of the AA and AAA molecules in CH_2Cl_2/MeOH (Figure 3).[7] AA unit **5** crystallized as the dihydrate in space group *Pbca* (Figure 3a and b). A notable feature of the structure is that the spatial requirements of the

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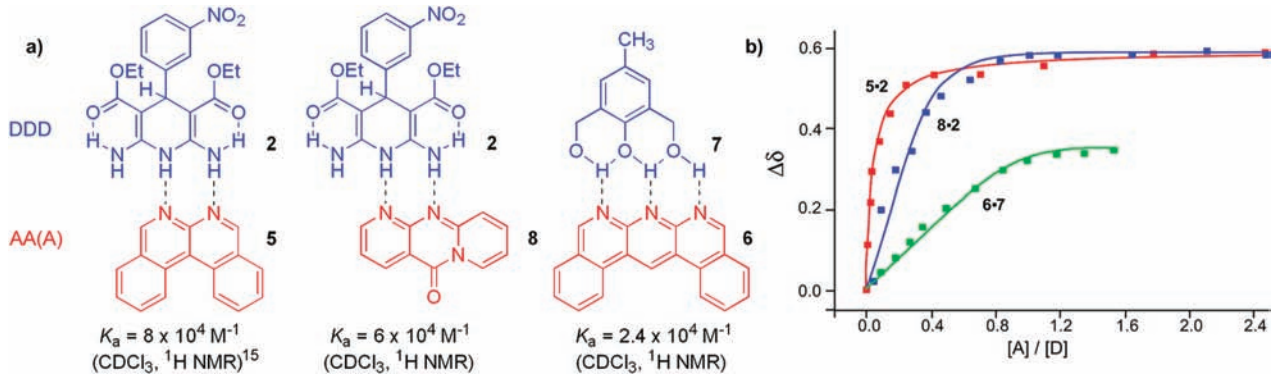

Figure 4. (a) Structures, association constants, and (b) binding isotherms of receptor pairs **5•2**, **8•2** and **6•7**. ^{1}H NMR titration analyses performed in $CDCl_3$ using the change in chemical shift ($\Delta\delta$) of the amino NH_2 groups of **2** (10^{-3} M) upon addition of **5** or **8** and the hydroxyl groups of **7** (10^{-3} M) upon addition of **6**. The lines indicate best-fitting K_a's for **5•2** (red), **8•2** (blue) and **6•7** (green).

hydrogen atoms attached to C6 and C7 require the quadruple-ring system to adopt a pronounced helical twist (C6−C61−C63−C7 torsional angle = 29.9°) to accommodate them. AAA system **6** (Figure 3c and d), which crystallized in space group $P2_1/c$, exhibits a greatly reduced twist (C6−C61−C72−C8 torsional angle = 6.9°) as the annulated phenyl rings are separated by the width of an additional six membered ring.

Association Constant Determinations for AA−DDD Complexes 5•2 and 8•2 and AAA−DDD Complex 6•7. The weaker complexes ($K_a < 10^5$ M^{-1}) in this study could be satisfactorily[15] measured by standard ^{1}H NMR titration methods[16,17] and these were used to determine the stabilities of complexes **5•2**, **8•2** and **6•7** (Figure 4). The titrations were carried out in $CDCl_3$ at 293 K under conditions where self-association of **2**, **5**, **6**, **7**, and **8** was negligible (as determined by ^{1}H NMR). Plots for the change in chemical shifts of amino (**2**) or hydroxyl (**7**) protons versus host to guest ratio for complexes **5•2**, **8•2** and **6•7** gave titration curves that fit[18] to a 1:1 binding isotherm, giving association constants of 8×10^4 M^{-1}, 6×10^4 M^{-1} and 2.4×10^4 M^{-1} respectively (Figure 4). The AAA−DDD complex **6•7** employs hydroxyl protons as the hydrogen bond donor source, which are significantly poorer donors than heterocyclic amine protons.[19] The three receptor pairs show exceptionally strong binding for supramolecular complexes held together with so few (**5•2** and **8•2**) or such weak (**6•7**) noncovalent interactions. The binding energies for AA−DDD pairs **5•2** and **8•2** are 1.8 and 2.0 kcal mol^{-1} more stable than the previously reported[4] AA−DDD system **1•2** (Figure 1a).

Association Constant Determinations for AAA−DDD Complexes 6•2, 9•2 and 6•10$^+$. ^{1}H NMR titration experiments with AAA−DDD complexes **6•2**, **9•2** and **6•10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$] gave binding isotherms that were steep, abruptly changing and close to their maximum values at a 1:1 ratio (see Supporting Information), typical of association constants outside the range that can be accurately measured by standard NMR methods.[16] These observations are consistent with the previous reports[4,5] on AAA−DDD systems. In addition, the titration data for **6•2** fitted a 2:1 stoichiometry at 10^{-3} M, confirmed by a Job plot with a maximum at a molar ratio of 0.65 at this relatively high concentration (see Supporting Information).

Compound **2** exists as a mixture of 1,4-dihydro and 3,4-dihydro tautomeric forms (Figure 5a) that are in slow exchange in $CDCl_3$ at room temperature, further complicating these binding experiments. An illustration of the efficacy of **6** as an AAA partner is provided by the observation that although ten equivalents of AAA partner **3** are reported[4] to fully convert **2** into the 1,4-dihydro DDD form at millimolar concentrations, only 0.5 equivalents of **6** were required to convert the initial 67:33 ratio of the 1,4-dihydro:3,4-dihydro forms of **2** to greater than 98:2 (Figure 5).

UV−vis titrations (see Supporting Information) of these AAA−DDD complexes at 10^{-5} M concentrations (CH_2Cl_2, 293 K) also gave sharply changing isotherms, indicating that still more dilute concentrations (and thus a more sensitive spectrophotometric method) would be required to precisely measure their binding strength.

The K_a values for complexes **6•2**, **9•2** and **6•10**$^+$ were successfully determined using titrations based on fluorescence spectroscopy at nanomolar concentrations.[17] Compounds **6** and **9** fluoresce with quantum yields of 0.94 for **6** and 0.25 for **9** in CH_2Cl_2, determined by standard methods.[20] Fluorescence titrations were performed in CH_2Cl_2 at 293 K by adding a solution of **2** (1×10^{-8} M) to **6** or **9** (initial concentrations 1×10^{-9} M) and monitoring the increase in fluorescence intensity at 410 nm (for **6•2**) and 517 nm (for **9•2**) upon excitation at 395 and 480 nm. The complexes are extremely strongly bound, with a K_a value for **6•2** of 2×10^7 M^{-1} (Figure 6a)[7] and 7×10^6 M^{-1} for

(15) Although the K_a value of 8×10^4 M^{-1} for **5•2** was reproducible at this concentration (close to the limit at which ^{1}H NMR titrations are accurate), and the error in data-fitting was <5%, the ^{1}H NMR titration binding isotherm (Figure 4b) is sufficiently steep and close to its maximum value at a 1:1 ratio that the K_a may be an underestimate and the value not as accurate as the others reported in this paper.

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(17) Repetitions of the binding experiments for each of the reported complexes gave K_a's within 10% of the values shown (the error in data-fitting for each run was <5%). See also ref 15.

(18) GAs-Fit: A program that uses an evolutionary algorithm to solve the standard equations for titration methods, suitable even for large binding constants (http://gasfit.djurdjevic.org.uk). In tests, for data in the K_a 10^2−10^5 M^{-1} range, GAs-Fit gave similar results to the binding constant determination program available from the group of H.-J. Schneider (http://www.uni-saarland.de/fak8/schneider/Links/download.html).

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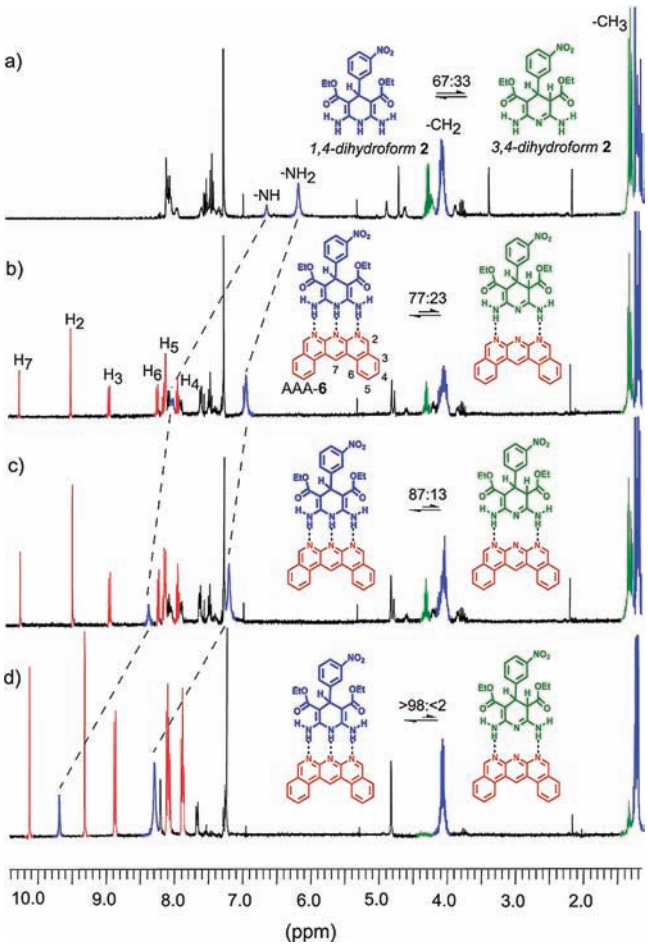

Figure 5. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) spectra of (a) **2**, (b) **2** + 0.13 equiv of **6**, (c) **2** + 0.25 equiv of **6**, and (d) **2** + 0.5 equiv of **6**. Experiments carried out at 1×10^{-3} M concentration of **2**.

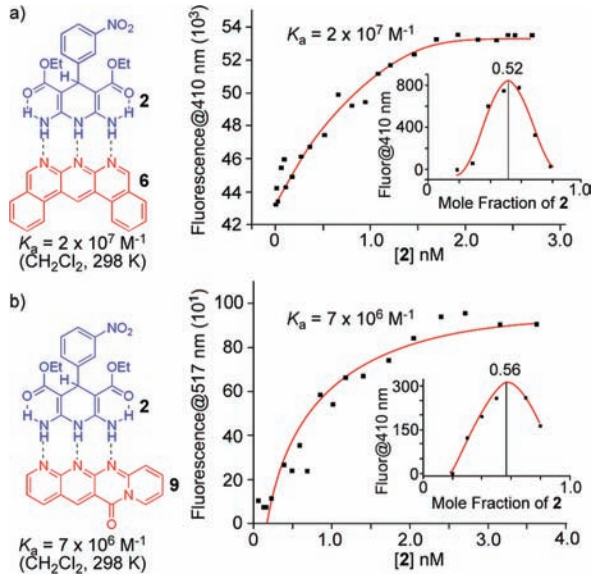

Figure 6. Change in the fluorescence intensities upon addition of aliquots of **2** to (a) **6** at 410 nm ($\lambda_{excitation}$ = 395 nm) and (b) **9** at 517 nm ($\lambda_{excitation}$ = 480 nm) in CH_2Cl_2 at 293 K. The red lines show the best fitting. (Insets) Job plots under the same conditions as the titration experiments.

9•2 (Figure 6b). Both sets of data fit to a 1:1 isotherm, while Job plot experiments confirmed the 1:1 stoichiometry for both complexes at this concentration (see insets in Figure 6). No

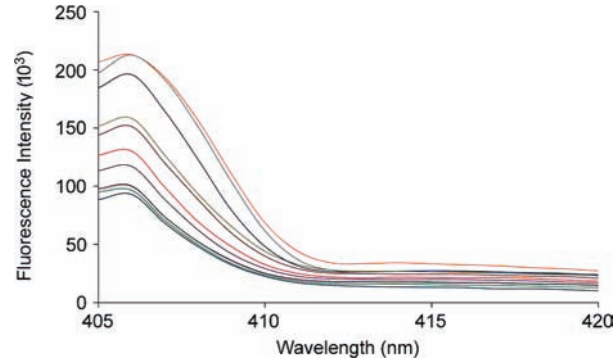

Figure 7. Fluorescence spectra of **6** (ca. 1×10^{-10} M) upon addition of **10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$] (0→ 2.5 equiv), maintaining the concentration of **6** constant, in CH_2Cl_2 at 293 K upon excitation at 395 nm.

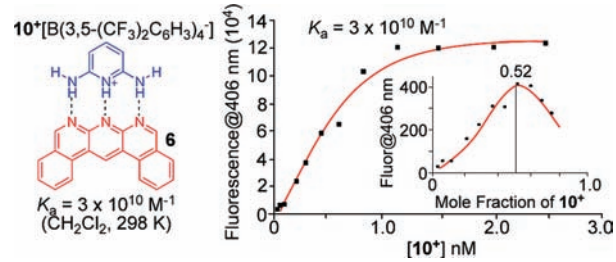

Figure 8. Fluorescence intensities of **6** (1×10^{-10} M) at 406 nm in CH_2Cl_2 at 293 K ($\lambda_{excitation}$ = 395 nm) upon addition of **10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$] (0→2.5 equiv.), maintaining the concentration of **6** constant, using a 1:1 complexation model. (Inset) Job plot under the same conditions as the titration experiment.

hydride shifts or excited state proton transfer phenomena were observed during the association constant measurements of any of these complexes.

To precisely measure the association constant of the cationic AAA−DDD pair **6•10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$], fluorescence titrations were performed in CH_2Cl_2 at 293 K by adding a solution of **10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$] (1×10^{-9} M) to **6** (ca. 1×10^{-10} M), while keeping the concentration of **6** constant, and monitoring the increase in fluorescence intensity at 406 nm upon excitation at 395 nm (Figure 7). The experimental data fit to a 1:1 isotherm,[21] confirmed by Job plot experiment showing a 1:1 binding (maximum molar ratio = 0.52). Complex **6•10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$] is the strongest triple hydrogen bonded complex measured to date with a $K_a = 3 \times 10^{10}$ M^{-1} in CH_2Cl_2 at 293 K (Figure 8). Treatment of **6•10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$] with solid K_2CO_3 deprotonates the pyridinium salt to generate 2,6-diaminopyridine. ^{1}H NMR titrations show no discernible complexation between **6** and 2,6-diaminopyridine in CD_2Cl_2 at millimolar concentrations (K_a < 10 M^{-1}) and so protonation/deprotonation offers a simple means to switch between the extremely strongly bonded complex **6•10**$^+$[B(3,5-$(CF_3)_2C_6H_3)_4^-$] and the uncomplexed, nonprotonated, components.

Single crystals of the **6·10**$^+$cationic AAA−DDD system were obtained by slow diffusion of diisopropyl ether into a concentrated acetonitrile solution of **6·10**$^+$[BPh_4^-]. The tetraphenylborate anion was used to lower the solubility of the AAA−DDD complex and promote crystallization. X-ray diffraction analysis of an amber colored single crystal revealed that the cationic AAA−DDD system crystallized in space group *Cc* as

(21) Hunter, C. A. *AllMaster14 host-guest titration fitting software*; University of Sheffield: Sheffield, U.K. 2008.

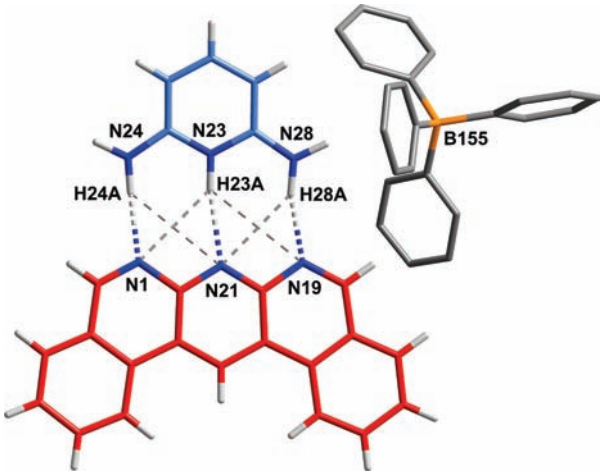

Figure 9. X-ray crystal structure of AAA−DDD(cationic) complex **6·10**$^+$[BPh_4^-].[22] Carbon atoms of the AAA unit are shown in red, those of the DDD unit pale blue and those of the anion gray; hydrogen atoms are white (omitted from the anion for clarity); nitrogen blue; boron orange. Primary and secondary hydrogen bonding interactions are denoted by dotted and dashed lines, respectively. Selected primary hydrogen bond lengths (Å) and angles (°): N1···H24A = 1.96, N1···H24A−N24 = 168.7; N21···H23A = 2.15, N21···H23A−N23 = 168.8; N19···H28A = 1.95; N19···H28A−N28 = 165.4. Selected secondary hydrogen bond lengths (Å) and angles (deg): N1···H23A = 2.85, N1···H23A−N23 = 135.1; N21···H24A = 3.24, N21···H24A−N24 = 133.0; N21···H28A = 2.78, N21···H28A−N28 = 140.3; N19···H23A = 3.29, N19···H23A−N23 = 127.9.

3(**6·10**$^+$[BPh_4^-])•5CH_3CN (Figure 9).[22] The structure shows a planar array of three short (N<u>H</u>···<u>N</u> distances 1.95, 1.95, and 2.15 Å, compared to 2.03−2.21 Å typically found in the crystal structures of other contiguous hydrogen bond arrays[1,2]), parallel (but staggered rather than strictly linear; N−H···N angles 165.4−168.8°), primary hydrogen bonds. These are apparently reinforced by close electrostatic interactions (N<u>H</u>−·−<u>N</u> distances 2.78−3.29 Å) between each proton and the acceptor atoms of the adjacent primary hydrogen bonds. Although only the strongest types of hydrogen bonds (of virtually covalent bond strength) tend to have 180° bond angles,[23] the offset arrangement observed in the crystal structure of **6·10**$^+$[BPh_4^-] is slightly surprising as the primary hydrogen bond lengths and the secondary interaction distances are not minimized by such an arrangement. Strictly linear motifs are a common feature in the X-ray crystal structures of other contiguous hydrogen bond arrays (ADA−DAD, AAD−DDA and AADD−DDAA systems)[1,2] although "propeller-twisted" pairings[24] are apparent in both DNA[24a] and some synthetic systems.[24b−d] However, the staggered coconformation of **6•10**$^+$ is not reproduced by various B3LYP/6-31G* level calculations using the Gaussian03 program[7,25] and may simply be a consequence of crystal packing forces.

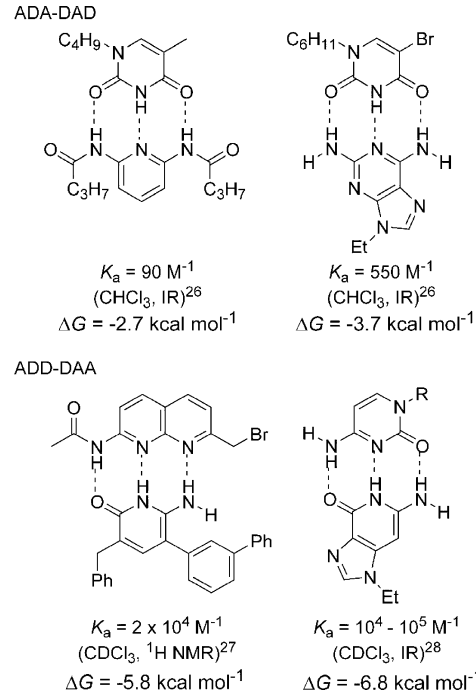

Figure 10. Some literature examples of DAD−ADA and AAD−DDA triple hydrogen bond complexes.

Contribution of Secondary Interactions to Complex Strength. Current dogma[6] is that secondary electrostatic interactions between adjacent hydrogen bonding sites play an important role in determining the stability of contiguous hydrogen bond arrays and rare experimental examples of AAA−DDD systems add new data to the field. Experimentally determined K_a values (Figure 10) for triple hydrogen bond complexes in halogenated solvents ($CHCl_3$, $CDCl_3$ or CH_2Cl_2) range from 90−550 M^{-1} (−2.7 to −3.7 kcal mol^{-1}) in neutral ADA−DAD type complexes (which feature only repulsive secondary interactions), to 1.2 × 10^4 - 10^5 M^{-1} (−5.8 to −6.8 kcal mol^{-1}) for the AAD-DDA type (which are stabilized by two attractive secondary interactions but have an equal number of repulsive secondary interactions).[26−28] Neutral AAA−DDD complexes **6•2** and **9•2** contain four attractive secondary interactions each and exhibit K_a's of 2 × 10^7 and 7 × 10^6 M^{-1} in CH_2Cl_2 that correspond to binding energies of −9.9 and −9.3 kcal mol^{-1}, respectively.

(22) Crystal data for 3[**6·10**$^+$·BPh_4^-]·5CH_3CN: $C_{154}H_{132}B_3N_{23}$, M = 2337.26, amber needles 0.15 × 0.05 × 0.05 mm^3, monoclinic, space group Cc; a = 36.323(12) Å, b = 10.166(3), c = 34.552(10) Å; α = 90, β = 99.372(9), γ = 90°; V = 12588(6) $Å^3$, ρ_{calcd} = 1.233 Mg/m^3, μ = 0.573 mm^{-1}, Z = 4; λ = 1.54178 Å, T = 173(2) K, 79150 data (21718 unique, R_{int} = 0.0798), R = 0.0884 for 6199 observed data, wR_2 = 0.2881, S = 1.048 for 1643 parameters. Residual electron density 0.592 and −0.353 $eÅ^{-3}$. Data was collected using a Rigaku MM007 High brilliance RA generator (Cu Kα radiation, confocal optics) and Saturn92 CCD system. Intensities were corrected for Lorentz-polarization and for absorption. The structures were solved by direct methods. Hydrogens bound to carbon atoms were placed in chemically reasonable positions. Structural refinements were performed with full-matrix least-squares based on *F2* by using the program: Sheldrick, G. M. *SHELXTL 6.14*; Bruker AXS: Madison, WI, 2004.

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Thus in this series each incremental increase of two cooperative secondary interactions increases the stability of the neutral triple hydrogen bonded complex by roughly 3 kcal mol^{-1}.

Various empirical methods have been formulated in order to more precisely predict the binding energy data of hydrogen bonding complexes.[29,30] Schneider has developed an additive approach for estimating ΔG of association by attributing energy values of 1.9 kcal mol^{-1} for primary hydrogen bonds and 0.7 kcal mol^{-1} for cooperative secondary interactions.[29] Applying this method to an AAA−DDD type system, with three primary hydrogen bonds and four secondary interactions, gives a predicted value for the stability of such a complex to be 8.4 kcal mol^{-1} ($K_a = 5 \times 10^6\ M^{-1}$). Experimentally **9•2** is 0.6 kcal mol^{-1} more stable and **6•2** is 1.4 kcal mol^{-1} more stable than this predicted value. Zimmerman has formulated an alternative empirical method to calculate the ΔG of linear arrays of hydrogen bonds.[30] This approach takes into account different types of noncovalent interactions, such as differentiating between NH···N, NH···O, and CH···O hydrogen bonds, intramolecular hydrogen bonds that must be broken to form new intermolecular bonds, cooperative and repulsive secondary electrostatic interactions, and the loss of rotational and translational entropy when two species are complexed into a static geometry with restricted molecular motion. Evaluation of **6•2** employing this formula gives −7.7 kcal mol^{-1}, which is 2.2 kcal mol^{-1} less than the experimentally determined value. Both the Schneider and Zimmerman predictive tools are based on measurements made in $CHCl_3$ or CCl_4 whereas the data for **6•2** were obtained in CH_2Cl_2, however one would not expect this to fully account for the difference between the experimental and predicted values. One contributing reason for the disparity could be that both models are largely based on data extracted from DNA−base pairs that are rather more flexible and much weaker than the strong, rigid AAA−DDD systems reported here. The experimental data for AAA−DDD hydrogen bond complexes may prove useful for parametrizing these methods at the extremes of strongly binding hydrogen bonding motifs.

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Conclusions

Short and efficient synthetic routes to chemically stable AA and AAA hydrogen bonding units have enabled the binding constants of some supramolecular complexes of the AA−DDD and AAA−DDD type to be measured. Neutral AAA−DDD complexes **6•2** and **9•2** have K_a's of $2 \times 10^7\ M^{-1}$ and $7 \times 10^6\ M^{-1}$, respectively, in CH_2Cl_2 at room temperature, as determined by fluorescence spectroscopic titrations. The binding constant of a cationic AAA−DDD system **6•10**$^+$ was determined to be $K_a = 3 \times 10^{10}\ M^{-1}$ under the same conditions, a remarkable value for a triple hydrogen bond system and $\sim 10^8\times$ greater than the typical value for triple hydrogen bonded DNA base pairs. The X-ray crystal structure of **6•10**$^+$ shows short hydrogen-heteroatom distances for both the primary hydrogen bonds and the secondary electrostatic interactions between each proton and the acceptor atoms of the adjacent primary hydrogen bonds, responsible for the exceptional strength of the AAA−DDD motif according to the classic Jorgensen model. The binding between **6** and **10**$^+$ can be switched off by deprotonation of the pyridinium salt with K_2CO_3, providing a simple means of controlling this exceptionally strong molecular recognition event. This may prove useful in the construction of stimuli-switchable supramolecular polymers, noncovalent adhesives and other functional organic materials.

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Supporting Information Available: Experimental procedures and spectral data for all compounds, details of X-ray analysis of **6•10**$^+$ including cif file and additional experimental and complexation studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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