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Extremely Strong and Readily Accessible AAA−DDD Triple Hydrogen Bond Complexes

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The development of multipoint hydrogen bonding motifs that form complexes with high stability and selectivity is important both for the understanding of biology and in the design of new materials.[1] There is a particular lack of building blocks that can be used to form acceptor, acceptor, acceptor−donor, donor, donor (AAA−DDD) hydrogen bonding patterns, believed to be the strongest contiguous triple hydrogen bond arrangement as a result of multiple favorable secondary electrostatic interactions.[2] Murray and Zimmerman provided the first experimental example of such a system when they reported that the K_a for complex **1·2** is $>10^5$ M^{-1} in $CDCl_3$, as evidenced by ^1H NMR spectroscopy (Figure 1).[3] They also found, however, that **1·2** is chemically unstable, and the presence of 1,8-bis(dimethylamino)naphthalene (proton sponge) was required to prevent hydride shift from C-4 of **2** to C-10 of **1** during their binding experiments.[3,4] No attempt to quantify the K_a beyond the limit measurable by NMR methods was reported and since these important and seminal studies relatively little progress[5] has been made in developing less reactive AAA−DDD systems. Here we report extremely high association constants for chemically stable AAA−DDD and AA−DDD complexes that feature the novel and readily accessible multiple hydrogen bond acceptors **3** and **4** (Figure 1).

We wondered whether the chemical stability of the Zimmerman AAA unit might be improved by extending the anthyridine aromatic framework. Accordingly, a pentacene analogue, **3**, was prepared in only two steps by the diiodination of 2,6-diaminopyridine followed by a double Suzuki coupling with 2-formylphenyl boronic acid and spontaneous cyclization and aromatization (Scheme 1). A modified approach yielded the equivalent AA system, **4**, the key step being flash vacuum pyrolysis (FVP) of an oxime (Scheme 1, step v). Single crystals suitable for X-ray analysis were obtained for each of **3** and **4** from saturated CH_2Cl_2/MeOH solutions. The solid state structures (Figure 2) confirmed the molecular geometries and provided data regarding the acceptor heteroatom separations for computer modeling of contiguous H-bond arrays with various prospective H-bond donors.

Experimentally, we first examined the ability of **3** to form complexes with DDD partners **2**[6] and **5** in $CDCl_3$ by ^1H NMR spectroscopy, using a standard titration method[7] under conditions where the self-association of each component was negligible (K_{dimer} < 20 M^{-1}). To assess the effect of the extended aromatic system on binding other than chemical reactivity, we also determined the K_a of **4·2** to compare with **6·2**[3] ($K_a = 3 \times 10^3$ M^{-1} in $CDCl_3$). Plots of the chemical shifts of the amino/hydroxyl groups of **2** or **5** versus the [DDD]/[AA or AAA] ratio for **4·2** and **3·5** showed typical 1:1 binding isotherms (Figure 3; confirmed by Job plots, see Supporting Information), and the data were computationally matched to the best-fitting association constant: **4·2**, $K_a = 8 \times 10^4$ M^{-1}; **3·5**, $K_a = 2.4 \times 10^4$ M^{-1}.[8] However, the Job plot for **3·2** showed a 2:1 complex at millimolar concentrations (see Supporting Information), and curve-fitting suggested at least one association constant beyond the range that could be reliably determined by our NMR experiments, consistent with the $K_a > 10^5$ M^{-1} previously reported[3] for **1·2**.

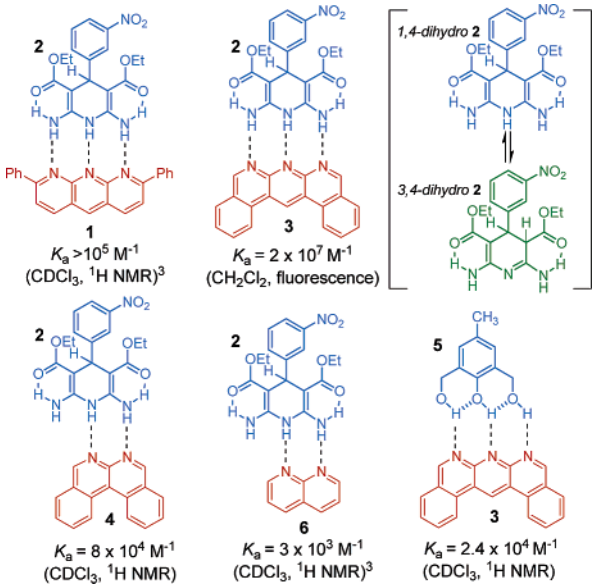
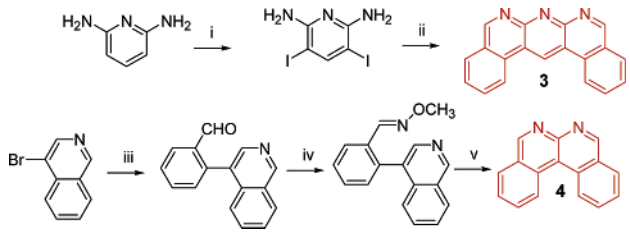


Figure 1. AAA−DDD (**1·2**,[3] **3·2**, and **3·5**) and AA−DDD (**4·2** and **6·2**[3]) heterocomplexes and their 1:1 stability constants (K_a's) in $CDCl_3$ or CH_2Cl_2 at room temperature. Repetitions of the binding experiments for each of **3·2**, **3·5**, and **4·2** gave K_a's within 10% of the values shown (the error in data-fitting for each run was <1%). Inset: In the absence of an additional H-bonding partner, **2** exists in a 2:1 ratio of 1,4-dihydro/3,4-dihydro tautomers at millimolar concentrations in $CDCl_3$ at room temperature.[3]

Scheme 1. Synthesis of AAA and AA Systems **3** and **4**[a]



[a] Reagents and conditions: (i) *N*-Iodosuccinamide, DMF, 86%; (ii) 2-formylphenyl boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, dioxane/water (1:1), 80%; (iii) 2-formylphenyl boronic acid, $Pd(PPh_3)_4$, K_2CO_3, dioxane/water (1:1), 80%; (iv) $MeONH_2$·HCl, EtOH, 96%; (v) FVP (furnace temperature = 700 °C, inlet temperature = 182 °C, $p = 4.8 \times 10^{-2}$ Torr, 10 min), 75%.

Some of the results and observations from the ^1H NMR binding experiments deserve further comment. First, hydroxyl groups are much poorer H-bond donors than amides, anilines, or pyrrole-like NH's,[9] and the hydroxyl protons of **5** are also involved in

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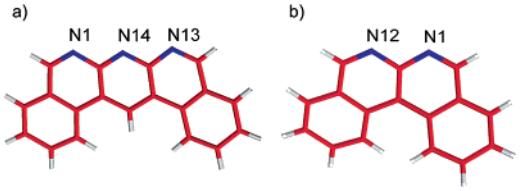

Figure 2. X-ray crystal structures of (a) **3** and (b) **4** (C red, N blue, H white). Nitrogen−nitrogen distances: (a) N13−N14 2.294 Å; N1−N14 2.290 Å and (b) N1−N12 2.300 Å (see Supporting Information).

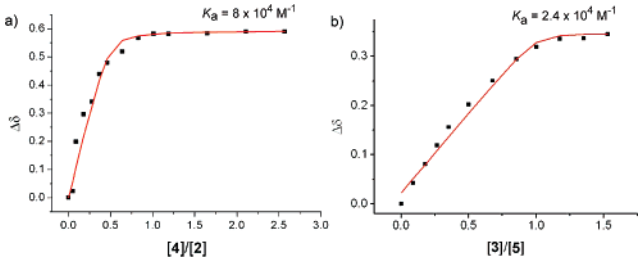

Figure 3. Binding isotherms using the change in chemical shift ($\Delta\delta$) of (a) the amino NH_2 groups of **2** (10^{-4} M) upon addition of **4** and (b) the hydroxyl groups of **5** (10^{-3} M) upon addition of **3**. The red lines indicate best-fitting K_a's.[8]

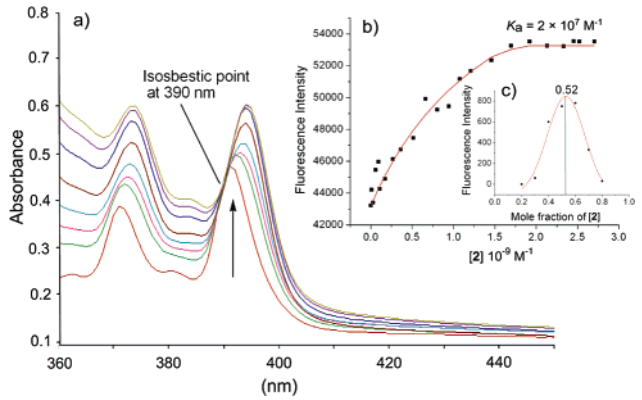

Figure 4. (a) UV/vis spectra in CH_2Cl_2 at 293 K upon the addition of **2** (0→1.2 equiv) to **3** (1×10^{-5} M). The arrow indicates the change in absorption at 390 nm with increasing **2**. (b) Fluorescence intensity at 410 nm in CH_2Cl_2 at 293 K upon the addition of **2** (0→3 equiv) to **3** (1×10^{-9} M). (c) Job plot under similar conditions to (b).

intramolecular H-bonding. It is therefore somewhat remarkable that the K_a ($CDCl_3$, room temperature) for **3·5** is sub-millimolar.[10] Second, the use of **2** in the binding experiments is complicated by its tautomerism (see Figure 1 inset). Murray and Zimmerman reported[3] that 10 equiv of **1** was required to fully convert **2** into the 1,4-dihydro form involved in DDD H-bonding. In contrast, in our NMR titration experiments only 0.5 equiv of **3** proved sufficient to convert the initial 2:1 ratio of the 1,4-dihydro/3,4-dihydro forms of **2** to >98:2 (see Supporting Information). A further indication of the powerful hydrogen bond accepting ability of these new heterocycles is seen in the direct comparison of the AA−DDD complexes in $CDCl_3$ at room temperature; **4·2** is at least 20 times more strongly bound than **6·2** (Figure 1).

We next investigated the binding in complex **3·2** by UV/vis and fluorescence spectroscopy. Upon addition of **2** to **3** (ca. 10^{-5} M, CH_2Cl_2, 293 K), the absorption intensity at 395 nm increased with a clear isosbestic point at 390 nm, suggesting a 1:1 binding mode in this concentration range (Figure 4a). Fluorescence titrations (**3** has a fluorescence quantum yield of 0.94 in CH_2Cl_2, while **2** is nonfluorescent) were performed in CH_2Cl_2 at 293 K by adding a solution of **2** (10^{-8} M) to **3** (initial concentration 1×10^{-9} M) and monitoring the increase in fluorescence intensity at 410 nm (Figure 4b). Curve-fitting gave a K_a for **3·2** of 2×10^7 M^{-1}. A Job plot confirmed the 1:1 stoichiometry (Figure 4c).

Geometry optimization and frequency calculations were carried out on **3·2**, both in vacuum and in CH_2Cl_2 solution, at the B3LYP/6-31G* level using the Gaussian03 program[11] (see Supporting Information). In the isolated molecules approximation the binding free energy was underestimated by ~10%, while in solution it was overestimated by ~25%. Both types of calculations showed an extremely large electrostatic contribution to complex formation. The simulations also suggest that the AAA−DDD complex is near planar, particularly in solution: a tilt angle of ~5° between the planes of **2** and **3** in CH_2Cl_2 (~21° in vacuum) provides the optimum H-bonding arrangement and the strongest AAA−DDD interaction.

In conclusion, heterocycles **3** and **4** are novel, readily accessible, and chemically stable AA and AAA hydrogen bonding units that form extremely strong supramolecular complexes with DDD partners. The importance of secondary electrostatic interactions in contiguous multipoint hydrogen bonding arrays is well-illustrated by comparison of the relative binding strengths of AAA−DDD complex **3·2** ($K_a = 2 \times 10^7$ M^{-1} in CH_2Cl_2 at room temperature) and the previously reported[12] ADA−DAD complex between 1-butylthymine and 2,6-dibutyramidopyridine (K_a = 90 M^{-1} in $CDCl_3$ at room temperature).

Supporting Information Available: Experimental procedures and spectral data for **3** and **4** and complexes **3·2**, **3·5**, and **4·2**, details of X-ray analysis of **3** and **4**, including cif files, and additional experimental details on computational and complexation studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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