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Synthesis and Self-Association of Double-Helical AADD Arrays

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Abstract: The design and syntheses of four self-complementary oligomers that contain an underlying AADD hydrogen bond sequence are presented, and their self-association was examined in the solution and solid state. The molecular recognition between the two strands is highly sensitive to substitutions of their component heterocycles. Substitution with electron-donating and -withdrawing groups and the influence of preorganization has a large effect on the overall stabilities of the complexes studied. In particular, a wide range ($>10^5\,M^{-1}$) of stabilities with respect to substitutions at various positions in the AADD oligomers was demonstrated. In the most extreme case, the dimerization constant measured ($K_{dimer} \geq 4.5\times10^7\,M^{-1}$) is comparable to the most stable homodimers of neutral AADD arrays reported to date.

Keywords: double-helical structures · hydrogen bonds · NMR spectroscopy · substituent effects · supramolecular chemistry

Introduction

Arrays of hydrogen bonds have attracted wide interest as building blocks for stimuli-responsive polymers and assemblies with nanoscale dimensions.[1] The incorporation of these subunits as side chains in polymers can overcome the natural tendency of macromolecules to phase separate due to immiscibility and create blends that would not normally form.[2] Hydrogen-bond arrays with orthogonal sequences have also been employed to generate multiblock copolymer architectures.[3] Weakly interacting arrays or subunits must often be appended in large numbers, which may significantly change the target-polymer properties. Therefore, strongly interacting arrays are often desirable, because they may be used in lower-mole percentages to obtain the desired effect.[4] Designing these systems can be highly challenging due to a number of complications, such as intramolecular hydrogen bonding,[5] preorganization,[6] and secondary interactions[7] that can greatly affect the binding strength and fidelity[8] of the resulting complexes. Considering the contemporary and growing interest in supramolecular polymers and relatively few currently available designs of neutral hydrogen-bonded arrays, there is still a clear need for strongly binding, complementary and self-complementary building blocks that may act in a specific and orthogonal manner to those currently available.

Recently, we introduced a new type of hydrogen-bond array that self-assembles to form a double helical complex[9] from two complementary or self-complementary strands.[10] In a similar manner to traditional coplanar hydrogen-bond arrays, we have found that the stability of these complexes is highly dependent on both the number and, more importantly, the sequence of hydrogen-bond donors and acceptors in the array. The dependence is aptly demonstrated by the two complexes depicted on the left side of Figure 1.

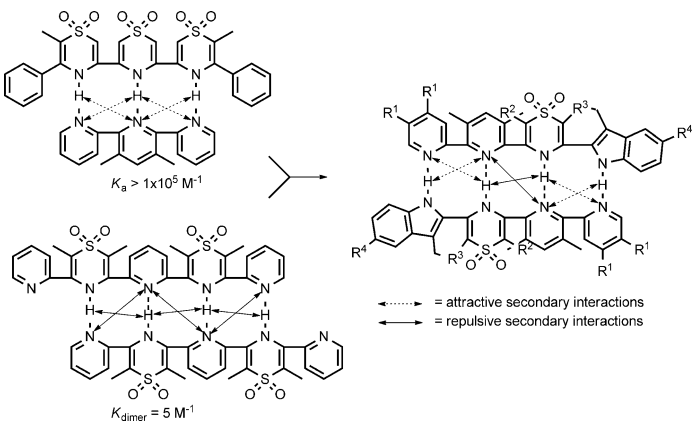

Figure 1. AADD array (right) as a hybrid of alternating ADADA and contiguous AAA–DDD sequences (left). K values were determined in $CDCl_3$ at room temperature.

The complex formed by the two contiguous arrays presenting AAA and DDD sequences is several orders of magnitude more stable than that produced by the dimerization of the alternating ADADA array pictured below it, even though it is stabilized by one less hydrogen bond. The effect is a consequence of strong secondary hydrogen-bond interactions between the two strands upon complex formation.

Based on these results, we considered whether the two designs could be amalgamated to generate a hybrid structure

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with both contiguous and alternating donor/acceptor elements, and how stable the resulting complexes would be. In view of the importance and wide utility of coplanar AADD arrays in the development of supramolecular polymers and materials,[11] we anticipate an array based on our double-helical design containing this sequence could be utilized in similar applications, if the dimerization constant is comparable. Herein, we describe the synthesis and characterization of a series of four AADD hydrogen-bond arrays that form self-complementary double-helical complexes exhibiting K_{dimer} values from 10^2 to $>10^7\,M^{-1}$.

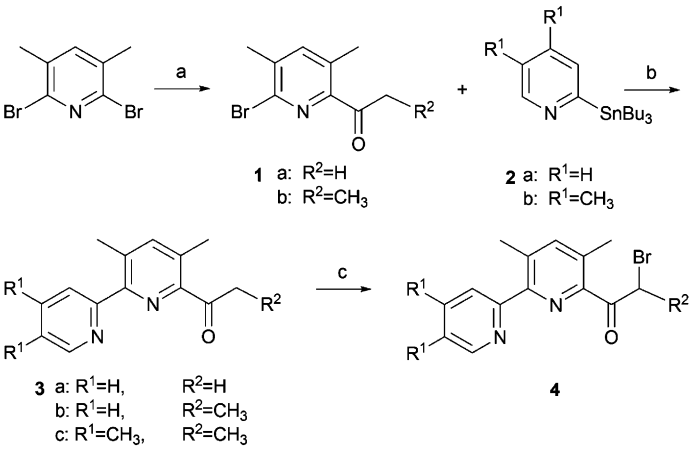
Results and Discussion

Design and synthesis: The four AADD arrays synthesized were chosen to elucidate the importance of several factors that were anticipated to affect dimer formation and stability. The presence or absence of a methyl substituent (R^2) on the thiazine donor was intended to indicate the importance of sterics in preventing any potentially undesired intramolecular hydrogen bonding with the adjacent pyridyl acceptor (Scheme 3). Similarly, the installation of a trimethylene tether between the two donor heterocycles (R^3) was anticipated to improve dimerization as a result of its preorganizing effect on the array's conformation. The installation of electron-donating R^1 ($-CH_3$) and electron-withdrawing R^4 ($-CO_2Et$, $-NO_2$) group were expected to improve the acceptor and donor character of their respective heterocycles.[10c]

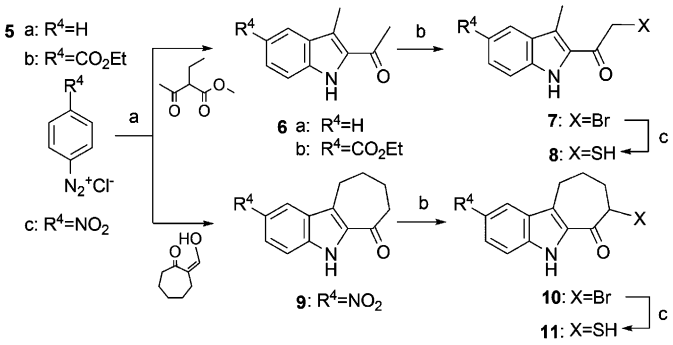
The final AADD arrays were generated by using a convergent approach, in which two halves of the molecule were synthesized and joined to provide a thioether intermediate that is further oxidized and cyclized to give the thiazinedioxide ring system.[12] The reaction scheme involves readily available and inexpensive starting materials and conversions are executed in moderate-to-excellent yields by using six linear steps.

Synthesis of the dipyridine fragment **4** was initiated by monolithiating 2,6-dibromo-3,5-lutidine[13] and acylating the resulting anion by using an appropriate dimethylamide to give **1** (Scheme 1). Palladium coupling with **2a/b** led to **3a–c** that are easily brominated to yield dipyridyl fragments **4a–c**.

Synthesis of the indole-containing fragments was straightforward by using a modification of the protocol that we previously employed.[14] The cyclic heptanoyl indole **9** was generated in a similar manner to that of the acyclic skatoles **6** by using a Japp–Klingemann–Fischer indole synthesis (Scheme 2).[15] These intermediates were then brominated and converted to their corresponding mercaptans by substitution with thioacetate and subsequent hydrolysis to give **8** and **11**. It is notable that the manipulations to produce both **8** and **11** from the initial diazonium salts can be executed without the aid of chromatography if desired, considerably simplifying their syntheses.



Scheme 1. Synthesis of the dipyridyl containing fragments of the AADD arrays. a) *t*BuLi/Et_2O (1.2 equiv), −78 °C, 0.5 h, *N*,*N*-dimethyl acetamide (1 equiv; **3a**) or *N*,*N*-dimethylpropionamide (**3b**), −78 °C, 1.5 h, 80–85 %; b) [$Pd(PPh_3)_4$] (3 mol %), toluene, reflux 18 h, 85–95 %; c) Br_2 (1.2 equiv) and HBr in acetic acid (2 equiv, 33 %; **3a**) or $AlCl_3$ in Et_2O (2 %; **3b**), 12–18 h, 70–82 %.

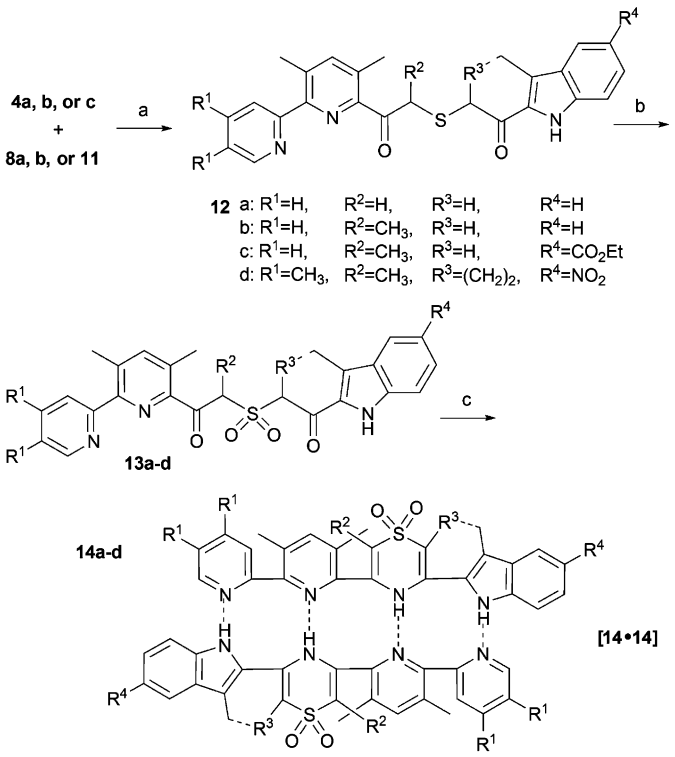


Scheme 2. Synthesis of the indole-containing fragments of the AADD arrays. a) (i) KOH, EtOH, H_2O, 0 °C to RT; (ii) HCOOH, reflux 2–20 h, 80–90 %; b) phenyltrimethylammonium tribromide (1 equiv), dry THF, 40 °C, 1–12 h, 75–80 %; c) (i) KSAc (1 equiv), DMF, 4–12 h; 90–95 %; (ii) cysteamine HCl (1 equiv), $NaHCO_3$ (1.2 equiv), MeCN, 24 h, 85–92 %.

The AADD arrays were assembled by connecting the two fragments to form thioethers **12** (Scheme 2). The thioethers were then oxidized to their analogous sulfones **13** and ultimately condensed with NH_4OAc to give the final products **14** (Scheme 3). Although the syntheses of only four arrays are presented herein, the synthetic approach is amenable to give derivatives incorporating a wide variety of R^1–R^4, should they be desired.

X-ray analysis of AADD complexes: Single crystals suitable for X-ray diffraction analysis were grown for all four of the AADD arrays synthesized. Of the four sets of crystals analyzed, satisfactory solutions were obtained for those containing **14a**±, **14c**§, and **14d**†.[16] The solid-state structures are instructive and shed light on the solution studies that follow.

The unsubstituted array **14a** crystallizes in space group $P2_1/c$ including two molecules per asymmetric unit (Figure 2). The two molecules form zigzag one-dimensional



Scheme 3. Final steps in the synthetic route to AADD arrays **14a–d**. a) 2,6-Lutidine (1 equiv), MeCN, 2–14 h, 80–85 %; b) urea hydrogen peroxide (4 equiv), trifluoroacetic anhydride (3 equiv), MeCN, 2–12 h, 80–95 %; c) NH_4OAc (6–10 equiv), AcOH, reflux 18–36 h, 70–90 %.

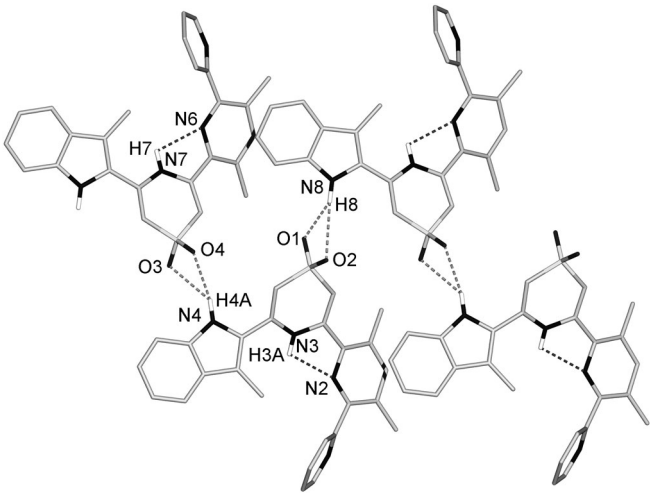


Figure 2. Stick representation of X-ray crystal structure of array **14a** with intermolecular and intramolecular hydrogen bonds indicated (dashed lines). All C–H hydrogen atoms have been removed for clarity.

tapes in the lattice through bifurcated hydrogen bonds between the sulfone oxygen atoms of one array and the indole proton of an adjacent molecule (O1···N8 = 2.92 Å, O1···H8 = 2.12 Å, O1···H8–N8 = 158°, O2···N8 = 3.47 Å, O2···H8 = 2.80 Å, O2···H8–N8 = 139°; O3···N4 = 3.16 Å, O3···H4A = 2.43 Å, O3···H4A–N4 = 139°, O4···N4 = 3.18 Å, O4···H4A = 2.46 Å, O4···H4A–N4 = 139°). Aside from this intermolecular interaction, the two molecules have very similar conformations and do not exhibit the double helical dimer character that might be expected. Instead, the two molecules both display an electrostatically favorable intramolecular contact between the N–H proton of their thiazine donor and the nitrogen atom of their lutidine acceptor (N2···H3A = 2.16 Å, N2···H3A–N3 = 112°; N6···H7 = 2.23 Å, N6···H7–N7 = 107°) resulting in interplanar angles between these two heterocycles of only 22 and 24° (N2-C12-C13-N3 and N7-C38-C37-N6 respectively). Presumably, this feature is a direct impediment to the dimerization motif anticipated.

However, the addition of a methyl group (R^2) to the other three derivatives **14b–d** was intended to prevent such an unwanted interaction. In fact, none of these three structures exhibited an intramolecular hydrogen-bond analogous to **14a**. Instead, all three took up the expected double-helical dimer arrangement in the solid state.

Array **14c** crystallized in space group $P2_1/c$ including two molecules per asymmetric unit. Inspection of the lattice revealed a repeating dimer motif, in which the two unique molecules intertwine to form a hydrogen-bonded double helix with approximate C_2 symmetry (Figure 3). The two

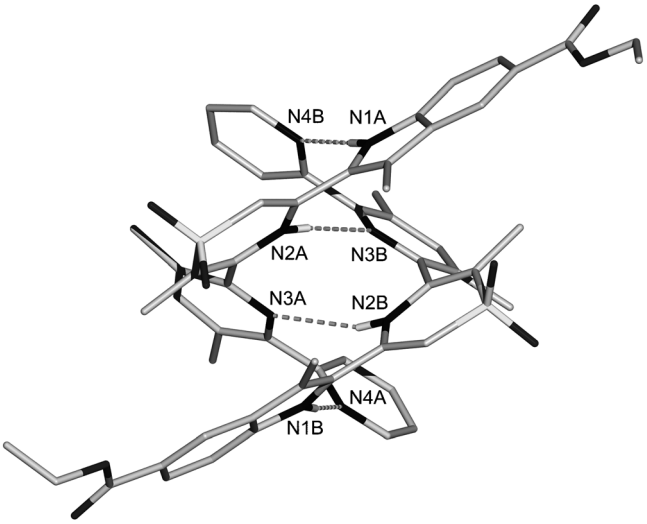


Figure 3. Stick representation of the X-ray crystal structure of dimer [**14c**·**14c**] with intermolecular hydrogen bonds indicated (dashed lines). All C–H hydrogen atoms have been removed for clarity.

molecules assemble in an antiparallel fashion that arranges their hydrogen-bond donors and acceptors in register to provide four primary hydrogen bonds between them (Table 1, rows 1–4). Adjacent heterocyclic rings in each molecule are twisted out of plane from one another to accommodate the four hydrogen bonds between the two strands (N1B-C12B-C13B-N2B = 33°; N2B-C17B-C18B-N3B = 60°; N3B-C24B-C25B-N4B = 40°; N1A-C12A-C13A-N2A = 37°; N2A-C17A-C18A-N3A = 56°; N3A-C24A-C25A-N4A = 45°). It is notable that the dihedral angle between the thiazine and lutidine rings in each strand is significantly larger (60 and 56°) than those between the other rings (< 46°). Wheth-

Table 1. List of primary and secondary hydrogen-bond distances and angles observed in the solid state structures of **14c** and **14d**.

Structure	Atoms	N···N [Å]	N*H*···*N* [Å]	N–H···N [°]
14c primary	N1B–H1B···N4A	3.00	2.10	178
	N2B–H2B···N3A	3.17	2.36	165
	N2A–H2A···N3B	3.11	2.24	175
	N1A–H1A···N4B	2.92	2.06	172
secondary	N1B–H1B···N3A	3.08	2.68	107
	N2B-H2B···N4A	3.32	2.75	127
	N2A–H2A···N4B	3.20	2.68	119
	N1A–H1A···N3B	3.12	2.71	111
14d primary	N4–H4···N1	2.88	2.18	172
	N3–H3···N2	2.97	2.15	175
secondary	N3–H3···N1	3.21	2.75	117
	N4–H4···N2	3.09	2.69	118

er this is a result of the steric repulsion caused by the two methyl substituents on the adjacent thiazine and lutidine rings, repulsive electrostatics between the two opposing thiazine donors (H2A···H2B = 2.57 Å) and lutidine acceptors (N3A···N3B = 3.11 Å), or both is impossible to distinguish based on the X-ray data only. Short secondary hydrogen-bond contacts also support the entwined hydrogen-bonded geometry (Table 1; rows 5–8).[17]

The solid-state structure of **14d** is similar to that of **14c**. In this case, the array crystallizes in space group *C*2/*c* with a single molecule per asymmetric unit. The molecules are arranged to form four identical double-helical dimeric complexes, each exhibiting C_2 symmetry, in the unit cell (Figure 4). The two molecules comprising each dimer are, again, positioned to allow four primary hydrogen bonds (Table 1, rows 9–10) and four secondary hydrogen bond contacts (Table 1, rows 11–12) to stabilize the complex geometry giving rise to noncoplanar orientations of the adjacent heterocyclic rings (N1-C7-C8-N2 = 42°; N2-C14-C15-N3 = 67°; N3-C18-C24-N4 = 23°) in each strand.

The major contrast between these two structures is a compression of the interplanar angles between the indole and thiazine rings (23° vs. 33 and 37°) and a concomitant expansion of the interplanar angle between the thiazine and lutidine rings (67° vs. 56 and 60°) of **14d** versus **14c**. Likely, this is a result of the trimethylene tether present in **14d** that greatly restricts the conformational freedom of the two donor heterocycles to a narrow range of interplanar angles.

^{1}H NMR spectroscopy characterization of AADD complexes: Our attempts to quantify the dimerization by typical spectrophotometric methods were unsuccessful. Dilutions examined by using UV/Vis spectroscopy revealed no useful measureable changes in the spectra (e.g., appearance of a charge-transfer band), nor an isosbestic point that could be identified. The limited fluorescence of the arrays prevented determination by that method as well. The self-associating behavior of the AADD arrays was therefore necessarily investigated by using ^{1}H NMR spectroscopy. The concentration-dependent chemical shifts of the thiazine and indole NH protons upon dilution of a concentrated solution in $CDCl_3$ at room temperature were plotted and successfully fitted to a simple 1:1 dimerization model in three of the four cases **14a**, **b**, and **c**.[18]

Examination of the concentration-dependent ^{1}H NMR chemical shifts of **14a** revealed behavior that may be rationalized by analogy to its X-ray crystal structure. The dilution of a sample of **14a** ($CDCl_3$, 298 K) exhibited no change in the chemical shift of the thiazine proton NH^a ($\delta = 9.80$ ppm) with respect to concentration. This indicates that in both the self-complexed and unassociated states, this proton is intramolecularly hydrogen bonded in a manner comparable to that observed in the solid state. However, the indole NH^b proton shifted downfield with increasing concentration (Figures 5 and 6) indicating an intermolecular hydrogen-bond interaction as a result of weak self-association ($K_{dimer} = 90\,M^{-1}$, $\Delta G = -11.1\,kJ\,mol^{-1}$). Inspection of molecular models based on the solid-state structure (i.e., intramolecularly hydrogen bonded) does permit the possibility

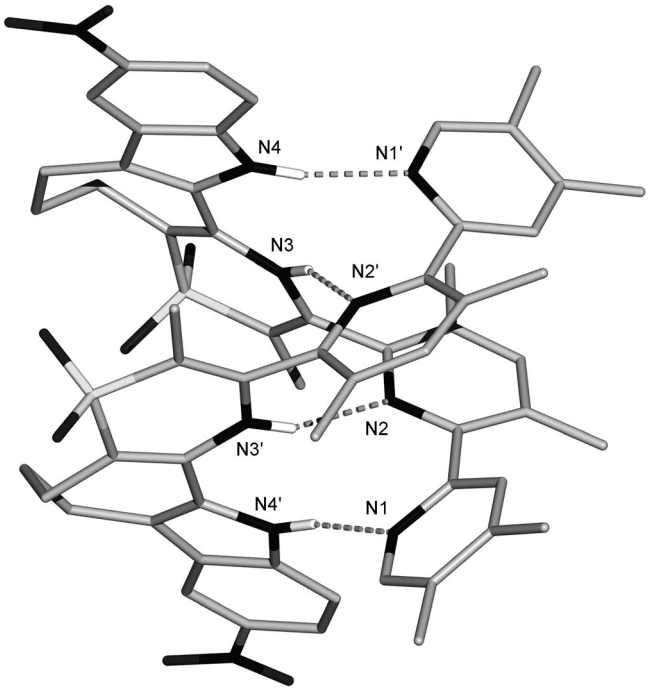


Figure 4. Stick representation of the X-ray crystal structure of dimer [**14d**·**14d**] with intermolecular hydrogen bonds indicated (dashed lines). All C–H hydrogen atoms have been removed for clarity.

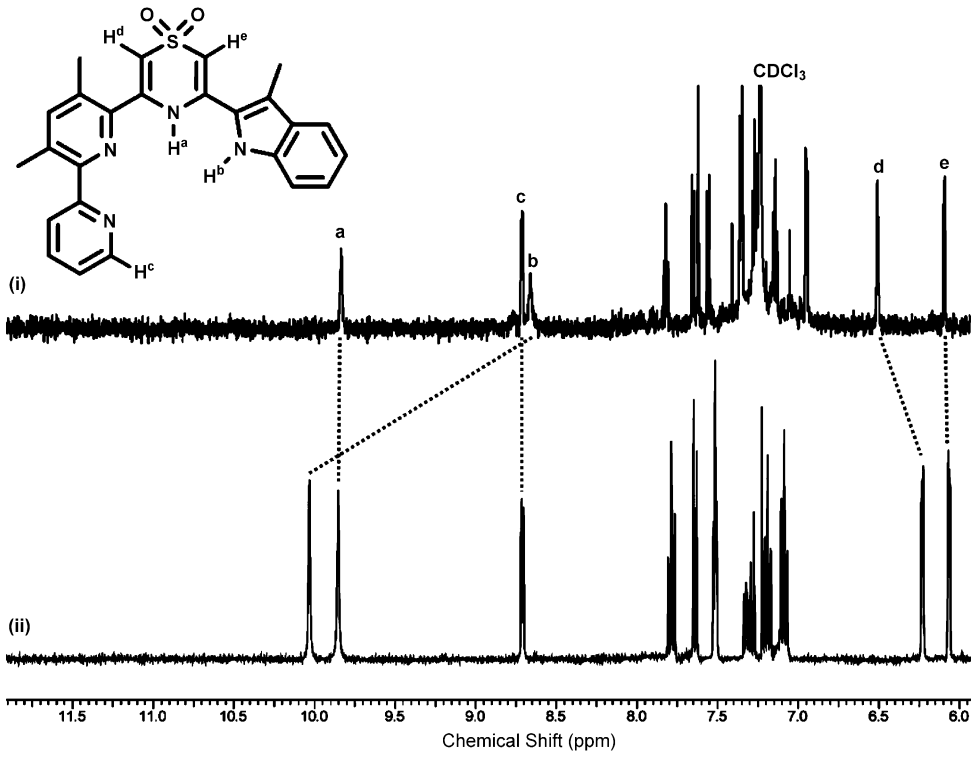


Figure 5. ^{1}H NMR spectra displaying the concentration dependent behavior of **14a** in $CDCl_3$. (i) 7×10^{-5} M at 298 K and (ii) 2×10^{-3} M solution at 298 K with no shift in the NH^a peak.

of an antiparallel 1:1 self-associated geometry involving hydrogen bonding between either the two indole and pyridyl termini of the oligomers or the indole donors and opposing sulfone acceptors. Regardless, the dimerization is weak and does not appear to produce the double helical geometry intended in solution.

The addition of a methyl group ($R^2=-CH_3$) in **14b–d** changed the solution behavior dramatically. Concentration of a solution of **14b** or **14c** ($CDCl_3$, 298 K) produced large downfield shifts of both the NH protons (NH^a and NH^b) in either array (Figure 6). Fitting of this data (by using N–H^b) to the same 1:1 dimerization model gave $K_{dimer}=1400$ and 5700 M^{-1} ($\Delta G=-17.9$ and -21.4 kJ mol^{-1}) for **14b** and **14c**, respectively. As can be inferred from these results, the installation of the methyl group provided an additional order of magnitude increase in the stability of the dimer and prevented unwanted intramolecular hydrogen bonding between the thiazine proton NH^a and the lutidine acceptor. The calculated uncomplexed chemical shifts of NH^a ($\delta_{free}=8.06$ (**14b**) and 7.72 ppm (**14c**)) derived from fitting of the dilution data were significantly upfield from that recorded for solutions of **14a** ($\delta=9.80$ ppm at all concentrations) and indicative of this lack of interaction in their free states. In fact, the δ_{max} (NH^a) calculated for self-association of **14b** and **14c** from the dilution data (9.90 and 10.16 ppm, respectively) are very similar to the value for **14a**; lending further support for this conclusion. Addition of a moderately electron-withdrawing substituent ($R^4=-COOEt$) to the indole ring in **14c** increased the dimer stability by a modest amount in comparison to **14b** ($\Delta\Delta G=-3.5$ kJ mol^{-1}) and with a similar magnitude to that observed in a related system that we have recently reported.[10c] Through-space contacts observed in a NOESY experiment with **14c** also corroborated a solution-state structure similar to that observed in the solid state (see the Supporting Information).

The structure of **14d** incorporates three modifications to the AADD design intended to further increase the stability of the homodimer. First, the two donor heterocycles of the array were restricted to a narrow range of interplanar angles by using a trimethylene tether ($R^3=-CH_2CH_2-$). Simple molecular models of the free array indicated that the dihedral angle H*N*-*C*-*C*-*N*H is expected to be $20\pm5°$, preorganizing the two NH groups in their approximate binding orientations with respect to one another.[19] Second, a more powerful withdrawing group was placed on the indole ring ($R^4=-NO_2$) to improve the hydrogen-bond donor character of the indole NH group. Finally, two methyl substituents were placed on the terminal pyridine acceptor ($R^1=CH_3$) in positions that would not sterically perturb the conformation of either the free or self-associated arrays, but improve the hydrogen-bond acceptor character of the heterocycle.

Indeed, the solution behavior of **14d** upon dilution ($CDCl_3$, 298 K) is very different in comparison to **14a–c**. In this case, self-association appeared to be complete in all the solutions examined down to a minimum concentration practicably measurable by the 600 MHz NMR spectrometer employed in these studies (Figure 7).[20] Inspection of ^{1}H NMR spectra obtained at concentrations from 2.5 mM to as low as 1 μM revealed chemical shifts for protons NH^a and NH^b that were unchanged within this range. The sharp resonances and large downfield chemical shift values for these protons (10.85 (NH^a) and 13.60 ppm (NH^b)) indicate they are strongly hydrogen bonded, presumably as a result of dimer formation. Unfortunately, the absence of any variation in the proton chemical shifts in the concentration range examined precludes fitting of the data to the model used in determining the dimerization constants for **14a–c**. However, if we conservatively assume 10% dissociation at 1 μM then a lower limit of 4.5×10^7 M^{-1} ($\Delta G=-43.7$ kJ mol^{-1}) may be calculated for the dimerization of **14d** under these conditions.[11n,20] To further support the conclusion that **14d** is, in

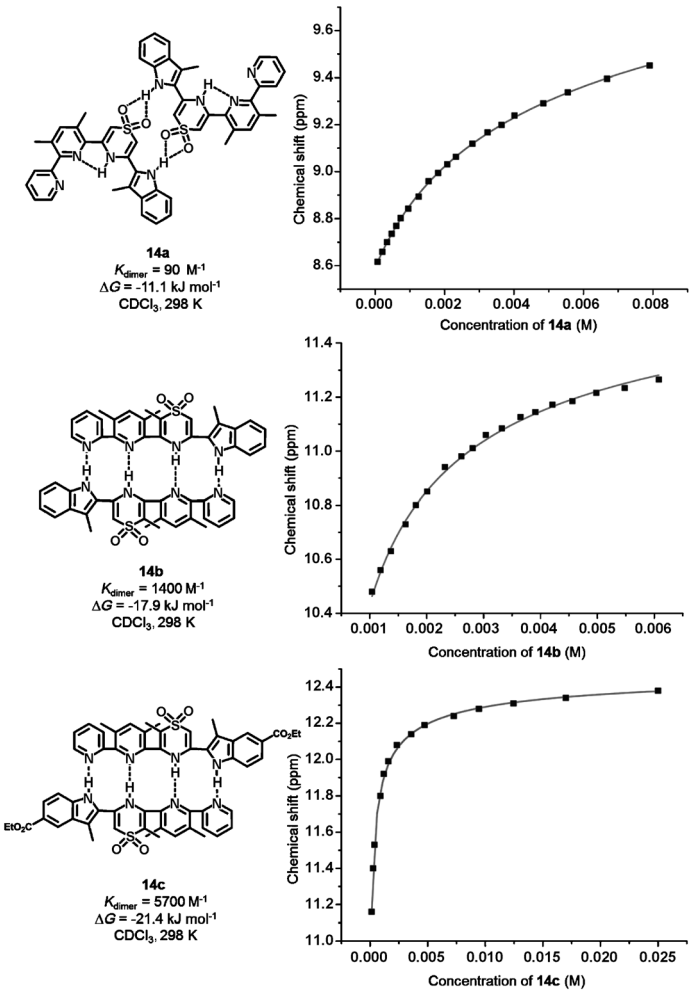


Figure 6. NMR spectroscopy dilution curves of arrays **14a–c** (following N–H^b) with their respective K_{dimer} values and free energies calculated from fitting of the data to a 1:1 dimerization model.[18] Note that in the case of **14a**, only one of two potential dimers is depicted.

fact, dimerized in solution a dilution was also performed in 2% (v/v) [D_6]DMSO/$CDCl_3$. Under these conditions, a typical 1:1 dilution curve that was fitted as in **14a–c** to give $K_{dimer} = 8.5 \times 10^4$ M^{-1} ($\Delta G = -28.1$ kJ mol^{-1}) was observed (see the Supporting Information). The dimerization constant exhibited by this array in $CDCl_3$ is comparable to the most stable examples of neutral AADD dimers reported in the literature to date. Given the limited increases in dimer stability expected from the incorporation of the electron withdrawing ($R^4 = -NO_2$) and donating ($R^1 = -CH_3$) groups to the underlying skeleton,[10c] a large proportion of this remarkable increase in stability ($\Delta\Delta G \geq -22.3$ kJ mol^{-1} in comparison to **14c**) must originate from preorganization by the trimethylene tether. Moreover, it raises the question of what further increases in K_{dimer} might be realized in this system, if either or both of the two other interplanar degrees of freedom were restrained in a similar manner.

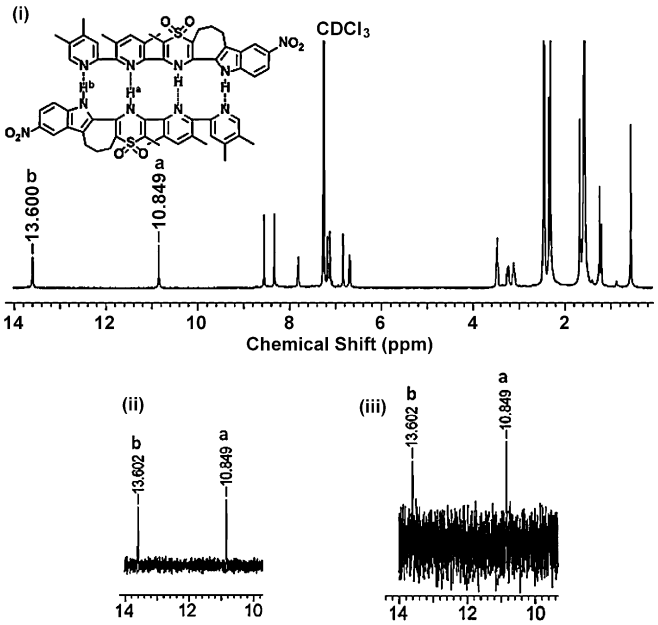


Figure 7. (i) 600 MHz ^{1}H NMR spectrum of **14d** at 2.5×10^{-3} M in $CDCl_3$; (ii) and (iii) downfield portion of the NMR spectra of **14d** (in ppm) at 100 μM and 1 μM dilutions, respectively.

Conclusion

Four new double-helical AADD hydrogen bond arrays (**14a–d**) were designed and synthesized, and their self-complementary dimerization was examined. Intramolecular hydrogen bonding prevented one of the arrays (**14a**) from forming the entwined structure expected. The elimination of this intramolecular interaction through steric interference ($R^2 = -CH_3$) enabled the remaining three arrays (**14b–d**) to assume the double-helical complex geometry intended in both the solution and the solid state. The stabilities of these dimers, although demonstrably higher than the desmethylated example (**14a**), vary greatly depending on their pattern of further substitution. Installation of an electron-withdrawing group to the indole ring system increased K_{dimer} (**14c**) by a relatively small margin. A much greater increase in stability was observed (**14d**) upon introduction of a trimethylene tether between the two donor heterocycles that preorganizes them for binding. This modification and the incorporation of electron-withdrawing/donating substituents to polarize the hydrogen bond donor/acceptor subunits of the array further, produced a complex with an extremely high dimerization constant ($K_{dimer} \geq 4.5 \times 10^7$ M^{-1}) that parallels the most stable literature examples based on neutral hydrogen-bond interactions. These studies demonstrate that this type of binding motif can generate complexes with comparable interaction strengths to those observed in rigid coplanar arrays, but with very different topologies. We are currently investigating the integration of these building blocks into higher-order assemblies, such as supramolecular polymers and copolymers.

Acknowledgements

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[1] For examples of hydrogen bonds used to form polymers and nanoscale materials, see: a) B. Rybtchinski, *ACS Nano* **2011**, *5*, 6791–6818; b) T. Fenske, H.-G. Korth, A. Mohr, C. Schmuck, *Chem. Eur. J.* **2011**, *17*, 738–755; c) A. R. Stefankiewicz, A. De Ciana, J. Harrowfield, *CrystEngComm* **2011**, *13*, 7207–7211; d) A. Llanes-Pallas, K. Yoosaf, H. Traboulsi, J. Mohanraj, T. Seldrum, J. Dumont, A. Minoia, R. Lazzaroni, N. Armaroli, D. Bonifazi, *J. Am. Chem. Soc.* **2011**, *133*, 15412–15424; e) X. Feng, Y. Cheng, Q. Wu, J. Zhang, T. Xu, *J. Phys. Chem. B* **2011**, *115*, 3777–3783; f) D. Wang, Y. Su, C. Jin, B. Zhu, Y. Pang, L. Zhu, J. Liu, C. Tu, D. Yan, X. Zhu, *Biomacromolecules* **2011**, *12*, 1370–1379; g) D. Sahu, H. Padhy, D. Patra, D. Kekuda, C.-W. Chu, I.-H. Chiang, H.-C. Lin, *Polymer* **2010**, *51*, 6182–6192; h) V. Kozlovskaya, E. Kharlampieva, I. Drachuk, D. Cheng, V. V. Tsukruk, *Soft Matter* **2010**, *6*, 3596–3608; i) P. Shokrollahi, H. Mirzadeh, O. A. Scherman, W. T. S. Huck, *J. Biomed. Mater. Res. A* **2010**, *95A*, 209–221; j) I. Tanis, D. Tragoudaras, K. Karatasos, S. H. Anastasiadis, *J. Phys. Chem. B* **2009**, *113*, 5356–5368; k) G. Brinke, J. Ruokolainen, O. Ikkala, *Adv. Polym. Sci.* **2007**, *207*, 113–177; l) A. J. Wilson, *Soft Matter* **2007**, *3*, 409–425; m) Q. Zeng, D. Wu, C. Liu, H. Ma, J. Lu, S. Xu, Y. Li, C. Wang, C. Bai, *Cryst. Growth Des.* **2005**, *5*, 1041–1047; n) E. Kolomiets, J.-M. Lehn, *Chem. Commun.* **2005**, 1519–1521.

[2] a) X. Sun, F. Pi, J. Zhang, I. Takahashi, F. Wang, S. Yan, Y. Ozaki, *J. Phys. Chem. B* **2011**, *115*, 1950–1957; b) T. Park, S. C. Zimmerman, *J. Am. Chem. Soc.* **2006**, *128*, 11582–11590; c) I. A. van Casteren, R. A. M. van Trier, J. G. P. Goossens, H. E. H. Meijer, P. J. J. Lemstra, *Polym. Sci., Part B: Polym. Phys.* **2004**, *42*, 2137–2160; d) B. Zhu, Y. He, N. Yoshie, N. Asakawa, Y. Inoue, *Macromolecules* **2004**, *37*, 3257–3266; e) L. Zhang, S. H. Goh, S. Y. J. Lee, *J. Appl. Polym. Sci.* **1999**, *74*, 383–388; f) E. J. Moskala, S. E. Howe, P. C. Painter, M. M. Coleman, *Macromolecules* **1984**, *17*, 1671–1678.

[3] For examples of hydrogen bonds used to form block copolymers, see: a) H.-S. Sun, C.-H. Lee, C.-S. Lai, H.-L. Chen, S.-H. Tung, W.-C. Chen, *Soft Matter* **2011**, *7*, 4198–4206; b) N. V. Salim, Q. Guo, *J. Phys. Chem. B* **2011**, *115*, 9528–9536; c) A. Vora, B. Zhao, D. To, J. Y. Cheng, A. Nelson, *Macromolecules* **2010**, *43*, 1199–1202; d) H.-C. Lin, M.-D. Jiang, S.-C. Wu, L.-L. Jou, K.-P. Chou, C.-M. Huang, K.-H. Wei, *J. Polym. Sci. Part A* **2009**, *47*, 4685–4702; e) S.-W. Kuo, *Polym. Int.* **2009**, *58*, 455–464; f) S. H. Kim, F. Nederberg, R. Jakobs, J. P. K. Tan, K. Fukushima, A. Nelson, E. W. Meijer, Y. Y. Yang, J. L. Hedrick, *Angew. Chem.* **2009**, *121*, 4578–4582; *Angew. Chem. Int. Ed.* **2009**, *48*, 4508–4512; g) F. Ke, X. Mo, R. Yang, Y. Wang, D. Liang, *Macromolecules* **2009**, *42*, 5339–5344; h) E. He, C. Y. Yue, K. C. Tam, *Langmuir* **2009**, *25*, 4892–4899; i) D. Xiong, L. Shi, X. Jiang, Y. An, X. Chen, J. Lü, *Macromol. Rapid Commun.* **2007**, *28*, 194–199; j) T. Park, S. C. Zimmerman, *J. Am. Chem. Soc.* **2006**, *128*, 13986–13987; k) S. C. Lee, H. J. Lee, *Langmuir* **2006**, *22*, 488–495; l) J. Q. Zhao, E. M. Pearce, T. K. Kwei, H. S. Jeon, P. K. Kesani, N. P. Balsara, *Macromolecules* **1995**, *28*, 1972–1978; m) J. C. M. van Hest, D. A. P. Delnoye, M. W. P. L. Baars, M. H. P. van Genderen, E. W. Meijer, *Science* **1995**, *268*, 1592–1595.

[4] a) C. Tang, S.-M. Hur, B. C. Stahl, K. Sivanandan, M. Dimitriou, E. Pressly, G. H. Fredrickson, E. J. Kramer, C. J. Hawker, *Macromolecules* **2010**, *43*, 2880–2889; b) C. Tang, E. M. Lennon, G. H. Fredrickson, E. J. Kramer, C. J. Hawker, *Science* **2008**, *322*, 429–432; c) P. S. Corbin, L. J. Lawless, Z. Li, Y. Ma, M. J. Witmer, S. C. Zimmerman, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5099–5104.

[5] a) J. Taubitz, U. Luning, *Aust. J. Chem.* **2009**, *62*, 1550–1555; b) T. Rehm, C. Schmuck, *Chem. Commun.* **2008**, 801–813; c) M. F. Mayer, S. Nakashima, S. C. Zimmerman, *Org. Lett.* **2005**, *7*, 3005–3008.

[6] a) G. Cooke, V. M. Rotello, *Chem. Soc. Rev.* **2002**, *31*, 275–286; b) S. C. Zimmerman, P. S. Corbin, *Struct. Bonding (Berlin)* **2000**, *96*, 63–94; c) B. Gong, Y. Yan, H. Zeng, E. Skrzypczak-Jankunn, Y. W. Kim, J. Zhu, H. Ickes, *J. Am. Chem. Soc.* **1999**, *121*, 5607–5608; d) P. S. Corbin, S. C. Zimmerman, *J. Am. Chem. Soc.* **1998**, *120*, 9710–9711; e) K. M. Doxsee, M. Feigel, K. D. Stewart, J. W. Canary, C. B. Knobler, D. J. Cram, *J. Am. Chem. Soc.* **1987**, *109*, 3098–3107.

[7] a) B. Kuhn, J. E. Fuchs, M. Reutlinger, M. Stahl, N. R. Taylor, *J. Chem. Inf. Model.* **2011**, *51*, 3180–3198; b) J. Pranata, S. G. Wierschke, W. L. Jorgensen, *J. Am. Chem. Soc.* **1991**, *113*, 2810–2819; c) W. L. Jorgensen, J. Pranata, *J. Am. Chem. Soc.* **1990**, *112*, 2008–2010.

[8] a) T. Park, S. Nakashima, E. J. Todd, S. C. Zimmerman, *J. Am. Chem. Soc.* **2005**, *127*, 18133–18142; b) E. M. Todd, J. R. Quinn, T. Park, S. C. Zimmerman, *Isr. J. Chem.* **2005**, *45*, 381–389.

[9] For examples of double-helical complexes, see: a) N. Saito, R. Terakawa, M. Shigeno, R, Amemiya, M. Yamaguchi, *J. Org. Chem.* **2011**, *76*, 4841–4858; b) Y. Haketa, H. Maeda, *Chem. Eur. J.* **2011**, *17*, 1485–1492; c) Y. Furusho, E. Yashima, *Macromol. Rapid Commun.* **2011**, *32*, 136–146; d) D. Hu, Z. Yang, G. Zhang, M. Liu, J. Xiang, T. Liang, J. Ma, G. Yang, *CrystEngComm* **2011**, *13*, 6021–6023; e) Z.-Q. Wu, Y. Furusho, H. Yamada, E. Yashima, *Chem. Commun.* **2010**, *46*, 8962–8964; f) Q. Gan, F. Lie, B. Kauffmann, J. Xiang, I. Huc, H. Jiang, *Chem. Commun.* **2010**, *46*, 297–299; g) H. Yamada, K. Maeda, E. Yashima, *Chem. Eur. J.* **2009**, *15*, 6794–6798; h) H. Goto, Y. Furusho, K. Miwa, E. Yashima, *J. Am. Chem. Soc.* **2009**, *131*, 4710–4719; i) Y. Furusho, E. Yashima, *J. Polym. Sci. Part A* **2009**, *47*, 5195–5207; j) F. Reviriego, A. Sanz, P. Navarro, J. Latorre, E. Garcia-Espana, M. Lui-Gonzalez, *Org. Biomol. Chem.* **2009**, *7*, 3212–3214; k) H. Ito, Y. Furusho, T. Hasegawa, E. Yashima, *J. Am. Chem. Soc.* **2008**, *130*, 14008–14015; l) H. Goto, Y. Furusho, E. Yashima, *J. Am. Chem. Soc.* **2007**, *129*, 9168–9174; m) H. Zeng, X. Yang, A. L. Brown, S. Martinovic, R. D. Smith, B. Gong, *Chem. Commun.* **2003**, 1556–1557; n) S. J. Coles, J. G. Frey, P. A. Gale, M. B. Hursthouse, M. E. Light, K. Navakhun, G. L. Thomas, *Chem. Commun.* **2003**, 568–569; o) J. Keegan, P. E. Kruger, M. Nieuwenhuyzen, J. O'Brien, N. Martin, *Chem. Commun.* **2001**, 2192–2193; p) J. Sánchez-Quesada, C. Seel, P. Prados, J. de Mendoza, *J. Am. Chem. Soc.* **1996**, *118*, 277–278.

[10] a) H.-B. Wang, B. P. Mudraboyina, J. Li, J. A. Wisner, *Chem. Commun.* **2010**, *46*, 7343–7345; b) J. Li, J. A. Wisner, M. C. Jennings, *Org. Lett.* **2007**, *9*, 3267–3269; c) H.-B. Wang, B. P. Mudraboyina, J. A. Wisner, *Chem. Eur. J.* **2012**, *18*, 1322–1327.

[11] For examples of neutral AADD arrays, see: a) G. Gröger, W. Meyer-Zaika, C. Bottcher, F. Grohn, C. Ruthard, C. Schmuck, *J. Am. Chem. Soc.* **2011**, *133*, 8961–8971; b) H. Sun, H. H. Lee, I. Blakey, B. Dargaville, T. V. Chirila, A. K. Whittaker, S. C. Smith, *J. Phys. Chem. B* **2011**, *115*, 11053–11062; c) P. Zhang, H. Chu, X. Li, W. Feng, P. Deng, L. Yuan, B. Gong, *Org. Lett.* **2011**, *13*, 54–57; d) Q. Tang, Z. Liang, J. Liu, J. Xu, Q. Miao, *Chem. Commun.* **2010**, *46*, 2977–2979; e) E. Greco, A. E. Aliev, V. G. H. Lafitte, K. Bala, D. Duncan, L. Pilon, P. Golding, H. C. Hailes, *New J. Chem.* **2010**, *34*, 2634–2642; f) E. M. Todd, S. C. Zimmerman, *Tetrahedron* **2008**, *64*, 8558–8570; g) V. G. H. Lafitte, A. E. Aliev, P. N. Horton, M. B. Hursthouse, K. Bala, P. Golding, H. C. Hailes, *J. Am. Chem. Soc.* **2006**, *128*, 6544–6545; h) E. C. Spencer, J. A. K. Howard, P. K. Baruah, G. J. Sanjayan, *CrystEngComm* **2006**, *8*, 468–472; i) Y.-P. Zhao, C.-C. Zhao, L.-Z. Wu, L.-P. Zhang, C.-H. Tung, Y.-J. Pan, *J. Org. Chem.* **2006**, *71*, 2143–2146; j) P. Prabhakaran, V. G. Puranik, G. J. Sanjayan, *J. Org. Chem.* **2005**, *70*, 10067–10072; k) X.-Z. Wang, X.-Q. Li, X.-B. Shao, X. Zhao, P. Deng, X.-K. Jiang, Z.-T. Li, Y.-Q. Chen, *Chem. Eur. J.* **2003**, *9*, 2904–2913; l) C. Schmuck, W. Wienand, *Angew. Chem.* **2001**, *113*, 4493–4499; *Angew. Chem. Int. Ed.* **2001**, *40*, 4363–4369; m) R. F. M. Lange, G. M. van, E. W. Meijer, *J. Polym. Sci. Part A* **1999**, *37*, 3657–3670; n) F. H. Beijer, R. P. Sijbesma, H. Kooijman, A. L. Spek, E. W. Meijer, *J. Am. Chem. Soc.* **1998**, *120*, 6761–6769; o) R. P. Sijbesma, F. H. Beijer, L. Brunsveld,

B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe, E. W. Meijer, *Science* **1997**, *278*, 1601–1604.

[12] a) C. R. Johnson, I. Sataty, *J. Med. Chem.* **1967**, *10*, 501–503; b) V. Baliah, T. Rangarajan, *J. Org. Chem.* **1961**, *26*, 970–971.

[13] D. M. Lyubov, G. K. Fukin, A. V. Cherkasov, A. S. Shavyrin, A. A. Trifonov, L. Luconi, C. Bianchini, A. Meli, G. Giambastiani, *Organometallics* **2009**, *28*, 1227–1232.

[14] B. Rajur, A. Y. Merwade, L. D. Basanagoudar, *Synth. Commun.* **1992**, *22*, 421–428.

[15] M. C. Hillier, J.-F. Marcoux, D. Zhao, E. J. J. Grabowski, A. E. McKeown, R. D. Tillyer, *J. Org. Chem.* **2005**, *70*, 8385–8394.

[16] Single crystals of **14a** were grown by slow diffusion of diisopropyl ether into concentrated chloroform solution of the array. Diffraction data were collected by using $Mo_{K\alpha}$ radiation. The crystals were small and poorly diffracting, merohedrally twinned, therefore, further refinements could not improve the final R value. Crystal data: $C_{25}H_{22}N_4O_2S$; $M=442.53\,g\,mol^{-1}$; monoclinic; $a=10.515(3)$, $b=20.231(5)$, $c=20.630(6)$ Å; $\alpha=90$, $\beta=97.150(3)°$ $\gamma=90°$; $V=4355(2)$ Å^3; $T=173(2)$ K; space group $P2_1/c$; $Z=8$; 37669 reflections measured; 7421 were independent ($R_{int}=0.0583$); final $R=0.0983$ [$I>2\sigma(I)$] and $wR=0.2371$ [$I>2\sigma(I)$]; final $R=0.1073$ (all data) and $wR=0.2451$ (all data); GOF on $F^2=1.397$. Single crystals of **14c** were grown by slow diffusion of diisopropyl ether solvent into concentrated chloroform solution of the array. Diffraction data were collected by using $Mo_{K\alpha}$ radiation. Crystal data: $C_{61}H_{60}Cl_3N_9O_8S_2$; $M=1217.65\,g\,mol^{-1}$; monoclinic; $a=12.8276(8)$, $b=20.8609(13)$, $c=23.0123(13)$ Å; $\alpha=90$, $\beta=106.135(2)$, $\gamma=90°$; $V=5915.4(6)$ Å^3; $T=150(2)$ K; space group $P2_1/n$; $Z=4$; 138863 reflections measured; 12569 were independent ($R_{int}=0.1264$); final $R=0.0644$ [$I>2\sigma(I)$] and $wR=0.1442$ [$I>2\sigma(I)$]; final $R=0.1318$ (all data) and $wR=0.1781$ (all data); GOF on $F^2=1.023$. Single crystals of **14d** were grown by slow diffusion of diisopropyl ether solvent into concentrated chloroform solution of the array. Diffraction data were collected by using $Mo_{K\alpha}$ radiation. Crystal data: $C_{32}H_{31}Cl_6N_5O_4S$; $M=794.38\,g\,mol^{-1}$; monoclinic; $a=26.009(5)$, $b=12.919(3)$, $c=23.029(5)$ Å; $\alpha=90$, $\beta=113.26(3)$, $\gamma=90°$; $V=7109(2)$ Å^3; $T=150(2)$ K; space group $C2/c$; $Z=8$; 12073 reflections measured; 6287 were independent ($R_{int}=0.0296$); final $R=0.0617$ [$I>2\sigma(I)$] and $wR=0.1774$ [$I>2\sigma(I)$]; final $R=0.0872$ (all data) and $wR=0.2071$ (all data); GOF on $F^2=1.079$. B. P. Mudraboyina, unpublished results: the solution obtained from the data collected for **14b** was of insufficient quality for publication, but has been included in the Supporting Information to further support the discussion. The solution was of adequate quality to illustrate a complex topology for this array in the solid state that is very similar to that observed for **14c** and **14d**.

[17] a) B. A. Blight, A. Camara-Campos, S. Djurdjevic, M. Kaller, D. A. Leigh, F. M. McMillan, H. McNab, A. M. Z. Slawin, *J. Am. Chem. Soc.* **2009**, *131*, 14116–14122; b) J. R. Quinn, S. C. Zimmerman, J. E. D. Bene, I. Shavitt, *J. Am. Chem. Soc.* **2007**, *129*, 934–941; c) T. J. Murray, S. C. Zimmerman, *J. Am. Chem. Soc.* **1992**, *114*, 4010–4011.

[18] A. P. Bisson, F. J. Carver, D. S. Eggleston, R. C. Haltiwanger, C. A. Hunter, D. L. Livingstone, J. F. McCabe, C. Rotger, A. E. Rowan, *J. Am. Chem. Soc.* **2000**, *122*, 8856–8868.

[19] MM3 forcefield in CAChe version 5.04 for Windows from Fujitsu Ltd.

[20] a) X. Li, Y. Fang, P. Deng, J. Hu, T. Li, W. Feng, L. Yuan, *Org. Lett.* **2011**, *13*, 4628–4631; b) J. Zeng, W. Wang, P. Deng, W. Feng, J. Zhou, Y. Yang, L. Yuan, K. Yamato, B. Gong, *Org. Lett.* **2011**, *13*, 3798–3801; c) H. Zeng, R. S. Miller, R. A. Flowers, B. Gong, *J. Am. Chem. Soc.* **2000**, *122*, 2635–2644.

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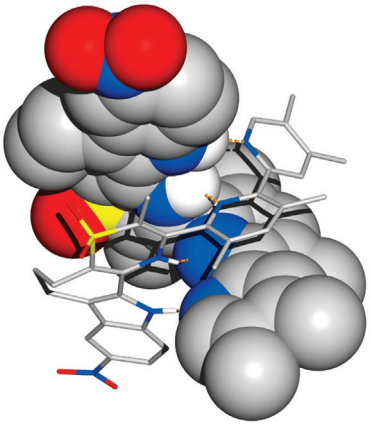
Hydrogen bonding with a twist: Four hydrogen bond-donor/acceptor arrays containing a self-complementary AADD sequence were synthesized. The self-association of the arrays into a double-helical complex topology was investigated in nonpolar solution and the solid state. The results revealed a lower limit of $4.5\times10^{7}\,\text{M}^{-1}$ ($CDCl_3$) for the K_{dimer} of the most stable example examined (see figure).



Hydrogen Bonds

B. P. Mudraboyina,
*J. A. Wisner** ..... ▮▮▮▮–▮▮▮▮

Synthesis and Self-Association of Double-Helical AADD Arrays