Hydrogen Bonds

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Molecularly Defined Nanostructures Based on a Novel AAA–DDD Triple Hydrogen-Bonding Motif

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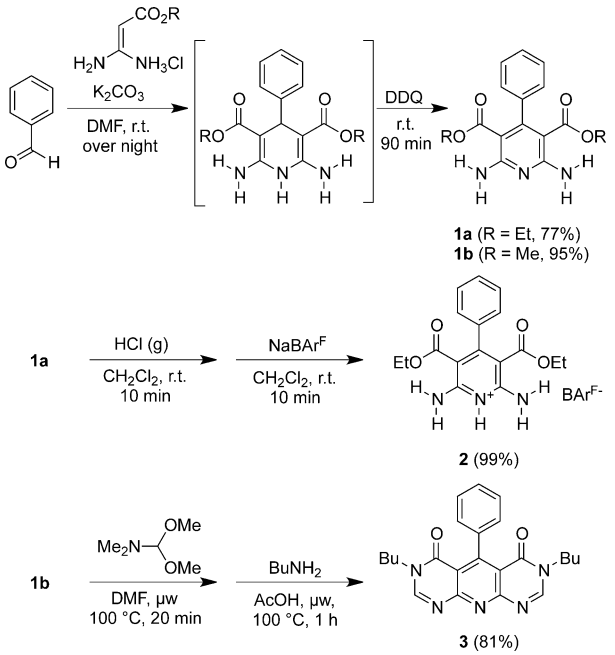
Abstract: *A facile and flexible method for the synthesis of a new AAA–DDD triple hydrogen-bonding motif is described. Polytopic supramolecular building blocks with precisely oriented AAA and DDD groups are thus accessible in few steps. These building blocks were used for the assembly of large macrocycles featuring four AAA–DDD interactions and a macrobicyclic complex with a total of six AAA–DDD interactions.*

The combination of a triple hydrogen-bond acceptor AAA with a triple hydrogen-bond donor DDD is known to give a highly stable complex in apolar organic solvents.[1] A first AAA–DDD complex was described in 1992 by Zimmerman and Murray,[1k] and several other AAA–DDD motifs[1] and two AAAA–DDDD pairs[2] have been reported since. The association constants of AAA–DDD complexes in apolar organic solvents such as chloroform typically exceed $10^5\,M^{-1}$. The extraordinary strength of these complexes is a result of the presence of multiple favorable secondary interactions.[3] For a system with a positively charged DDD donor, a remarkable value of $K_a = 3\times10^{10}\,M^{-1}$ has been measured.[1d] Given the high stability of AAA–DDD complexes, such a triple hydrogen-bonding motif is an ideal, yet largely unexplored, candidate for structural supramolecular chemistry. Molecularly defined nanostructures based on multiple AAA–DDD interactions are unknown, and a first example of a supramolecular polymer was only recently described.[1a] The difficulty of employing the AAA–DDD motif for the construction of more elaborate structures stems from the fact that polytopic building blocks with two or more AAA/DDD groups are difficult to access with the synthetic routes described thus far. Typical syntheses involve low-yielding steps, especially for the construction of the AAA part, and do not allow straightforward functionalization of the backbone. Below, we describe the synthesis and characterization of a new and easily accessible AAA–DDD motif. Importantly, our method enables the preparation of polytopic building blocks with precisely oriented AAA and DDD groups in few steps. The utility of such building blocks is demonstrated by the formation of large macrocycles. Furthermore, we report the synthesis of a macrobicyclic complex resulting from the self-assembly of five components by six AAA–DDD interactions.

A practical route for the synthesis of useful supramolecular building blocks with AAA/DDD motifs should 1) enable facile synthesis and purification, 2) provide the desired compounds in high yields, 3) provide access to building blocks with different geometry and solubility, and 4) enable the preparation of polytopic building blocks with multiple AAA/DDD units.

In our attempt to realize a synthetic method with these characteristics, we chose aromatic aldehydes for commencing the synthesis. Following a procedure developed by Meyer and co-workers,[4] we first synthesized diamino-substituted dihydropyridines by the reaction of benzaldehyde with methyl- or ethyl 3,3-diaminoacrylate hydrochloride in the presence of K_2CO_3. Analogous dihydropyridines have been used by Zimmerman and Murray as DDD units,[1k] but they were susceptible to tautomerization.[1e,4,5] We therefore decided to directly add an oxidation step with DDQ, which gave the diaminopyridines **1a** and **1b** in good overall yields



Scheme 1. Synthesis of triply hydrogen-bond acceptor **2** and triple donor **3**.

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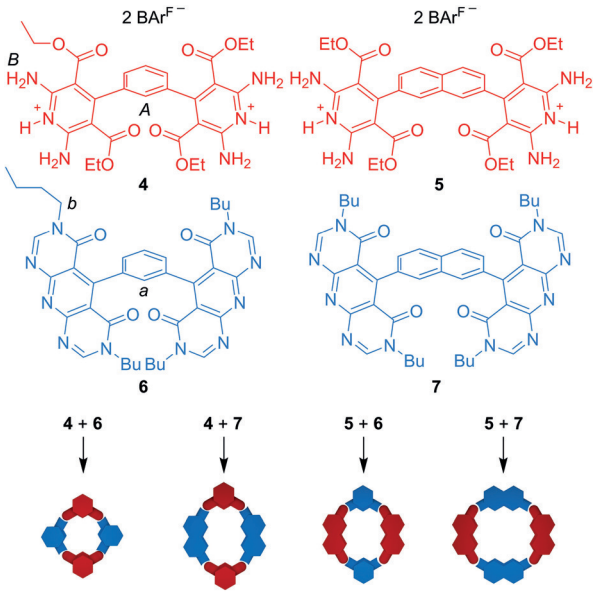
(Scheme 1). The triple donor **2** was then obtained by protonation of **1b** with HCl and ion exchange with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F$).

To synthesize the triple acceptor **3**, we adopted a cyclization method originally introduced by Besson et al. for the preparation of pyrimidin-4(3*H*)-ones starting from anthranilic acid derivatives.[6] Treatment of **1b**[7] with *N*,*N*-dimethylformamide dimethyl acetal and subsequent heating with butylamine in acetic acid under microwave conditions yielded a mixture of the desired dipyrimidine-4,6(3*H*,7*H*)-dione **3** and a monocyclized pyrimidone intermediate. The latter could be converted into the product by repeating the two steps for a second time to give **3** in an overall yield of 81 % (Scheme 1). The syntheses of **2** and **3** are easily scalable and can be performed on multigram scale.

With this straightforward synthesis in hand, we investigated the binding of the AAA–DDD couple **2** and **3** in dichloromethane. ^{1}H NMR titration experiments in CD_2Cl_2 gave binding isotherms that were linear until a 1:1 molar ratio was reached, followed by an abrupt change (see the Supporting Information, Figure S1). Such a behavior is expected for an association constant higher than $10^4\,M^{-1}$.[8] To obtain a numerical value for the binding constant, isothermal titration calorimetry (ITC) was then carried out (288 K, CH_2Cl_2). Interestingly, the titration data were best fitted assuming a 2:1 binding model involving a ternary complex (**2**·**3**)·**3** aside from the expected dimer **2**·**3** (Figures S3 and S4). The association constant for dimer formation was $K_{a1} = 1.1(\pm 0.2)\times 10^7\,M^{-1}$. Whereas this value is in the expected range for an AAA–DDD system, it is lower than the strongest interaction reported in the literature ($3\times 10^{10}\,M^{-1}$).[1d] Presumably, the weaker binding is due to the diminished basicity of the pyrimidone nitrogen atoms in acceptor **3** compared to the 2,3-fused pyridine rings employed by Leigh and coworkers. For the complexation of the second AAA unit **3**, an association constant of $K_{a2} = 1.8(\pm 0.2)\times 10^5\,M^{-1}$ was determined. It is worth noting that the formation of a 2:1 complex with a weaker second binding constant has also been observed for an AAAA–DDDD system.[2a] Unfortunately, it was not possible to investigate the association of **2** and **3** by fluorescence spectroscopy as both compounds are nonfluorescent.

To utilize AAA–DDD interactions for the construction of more complex supramolecular assemblies, it is necessary to incorporate multiple AAA and/or DDD units in a single molecular building block. Here, the advantage of our new method becomes evident. By applying our synthetic procedure to aromatic dialdehydes (isoterephthaldehyde and naphthalene-2,7-dicarbaldehyde), we were able to access the corresponding DDD-DDD building blocks **4** (85 % yield) and **5** (63 %), as well as the AAA-AAA building blocks **6** (43 %) and **7** (61 %; all yields were calculated starting from the corresponding aromatic dialdehyde; Scheme 2). The yields of 43–85 % are considerably higher than those recently reported by Song and co-workers for the only other synthesis of ditopic AAA-AAA and DDD-DDD units.[1a]

Building blocks **4**–**6** are relatively rigid, and the two AAA/DDD units are oriented in a divergent fashion. Owing to the large degree of preorganization, we expected the formation of



Scheme 2. Self-assembly of different AAA/DDD building blocks to discrete [2+2] macrocycles.

macrocyclic assemblies to occur upon mixing of equimolar amounts of donors and acceptors. Considering the angle between the donor and acceptor sites (ca. 120°), the formation of [3+3] macrocycles was expected. However, it is known that AAA–DDD systems can tolerate a deviation from the ideal 180° bond angle.[1d] Therefore, the formation of [2+2] macrocycles seemed possible as well. The entropically favored formation of simple [1+1] dimers appeared unlikely because such assemblies would display more strongly bent AAA–DDD units.

Analysis of a CD_2Cl_2 solution containing equimolar amounts of **4** and **6** (5.0 mM) by ^{1}H NMR spectroscopy (298 K, 400 MHz) revealed upfield shifts of the signals of H_a and H_A, which point into the macrocycle (see Scheme 2), as well as significant downfield shifts and broadening of the NH_B signals of **4** (Figure 1 a). This shift was expected as the NH bonds become more polarized upon complex formation. Interestingly, a small upfield shift of 0.06 ppm was also observed for the signals of the BAr^{F-} anion, indicating a weak interaction between the cationic macrocycle and the "noncoordinating" anion. A similar shift was not observed for the simple dimer **2**·**3**.

Analysis of solutions containing **4** and **6** by high-resolution mass spectrometry with nanoelectrospray ionization gave a clean mass spectrum, with the two most prominent peaks corresponding to the ions $[\mathbf{4}_2\mathbf{6}_2(BAr^F)]^{3+}$ and $[\mathbf{4}_2\mathbf{6}_2(BAr^F)_2]^{2+}$ (Figure 1 b). Peaks corresponding to the [1+1] or [3+3] macrocycles were not detected at all.

The formation of a single aggregate was confirmed by diffusion-ordered NMR spectroscopy (DOSY; CD_2Cl_2, 298 K, 400 MHz, 1.0 mM), which confirmed the presence of a defined assembly with a diffusion coefficient of $D = 3.98\times 10^{-6}\,cm^2\,s^{-1}$. Taken together, the data are good evidence for the hypothesis that the combination of **4** and **6** exclusively gives the [2+2] macrocycle $\mathbf{4}_2$·$\mathbf{6}_2$.

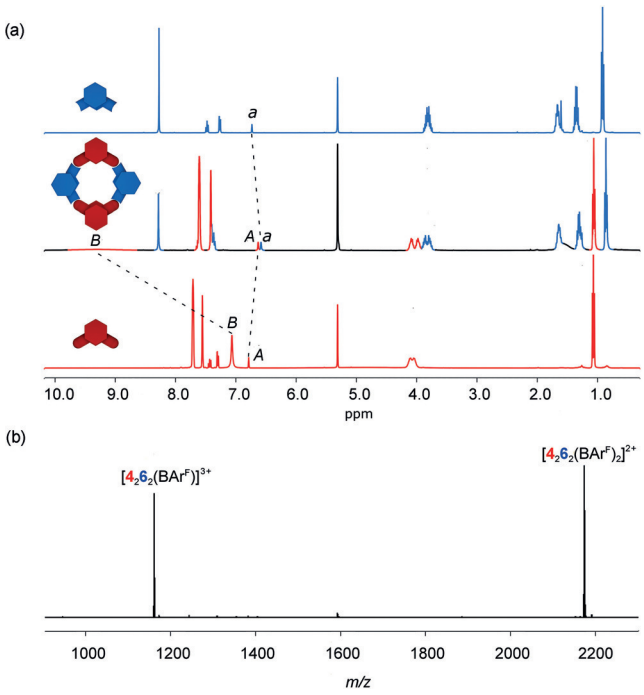


Figure 1. a) ^{1}H NMR spectra (CD_2Cl_2, 298 K, 400 MHz) of acceptor **6** (5 mM, top), an equimolar mixture of **4** and **6** (5 mM each, middle), and donor **4** (5 mM, bottom). For the proton assignment, see Scheme 2. b) ESI mass spectrum of a solution containing **4** and **6** showing peaks corresponding to the tetramer $\mathbf{4}_2\cdot\mathbf{6}_2$.

Similar results were obtained for solutions containing the donor–acceptor combinations **4**+**7**, **5**+**6**, and **5**+**7**. In all cases, we were able to observe dominant peaks for the [2+2] macrocycles by mass spectrometry (Figures S28–S33). DOSY spectra revealed the presence of a single large species with diffusion coefficients of 3.74×10^{-6} ($\mathbf{4}_2\cdot\mathbf{7}_2$), 3.56×10^{-6} ($\mathbf{5}_2\cdot\mathbf{6}_2$), and 3.40×10^{-6} cm^2s^{-1} ($\mathbf{5}_2\cdot\mathbf{7}_2$). These values indicate that the relative size of the macrocycles follows the order $\mathbf{4}_2\cdot\mathbf{6}_2 < \mathbf{4}_2\cdot\mathbf{7}_2 \approx \mathbf{5}_2\cdot\mathbf{6}_2 < \mathbf{5}_2\cdot\mathbf{7}_2$, which is in agreement with the size increase for assemblies based on the larger naphthyl-derived monomers **5** and **7** compared to the phenyl-based building blocks **4** and **6**.

The assemblies described above are first examples of macrocycles based on AAA–DDD interactions. Until now, the synthesis of H-bonded cyclic tetramers has relied on AD–DA,[9] AAD–DDA,[10] or self-complimentary AADD interactions.[11] H-bonded tetramers are also found in G quartets and their synthetic analogues.[12,13]

To obtain information on the kinetic stability of macrocycle $\mathbf{4}_2\cdot\mathbf{6}_2$, we recorded ^{1}H NMR spectra of solutions containing a constant amount of acceptor **6** (2.5 mM) and a variable amount of donor **4** (Figures S5–S8). When the amount of **6** was in excess compared to **4**, the exchange between free **6** and macrocycle $\mathbf{4}_2\cdot\mathbf{6}_2$ was found to be fast on the NMR time scale. However, slow exchange between monomer and macrocycle was observed when the concentration of donor **4** was larger than that of acceptor **6**. These data suggest that exchange reactions proceed by an associative mechanism. The cationic nature of macrocycle $\mathbf{4}_2\cdot\mathbf{6}_2$ inhibits the association of doubly charged **4** owing to unfavorable columbic interactions (→slow exchange with excess **4**), whereas the neutral acceptor **6** can readily associate and exchange with complex $\mathbf{4}_2\cdot\mathbf{6}_2$ (→fast exchange with excess **6**). This assumption is corroborated by the ITC data described above, which showed that one donor can coordinate to two acceptor units. The exchange between **4** and $\mathbf{4}_2\cdot\mathbf{6}_2$ was also studied by exchange spectroscopy (EXSY) in CD_2Cl_2. We were able to derive an exchange rate constant of $k = 0.40\ s^{-1}$, which confirmed the slow exchange between the dicationic building block and the tetracationic macrocycle.

To complement our experimental studies, we employed all-atom molecular dynamics (MD) simulations, which have proven to be an effective technique for studying supramolecular systems.[14] The entire simulation work was carried out with AMBER 12.[15] Initially, 160 monomers **4** and **6** (80 + 80) were dispersed in a simulation box containing CH_2Cl_2 molecules and 160 BAr^{F-} counterions (for computational details, see the Supporting Information). This system underwent 400 ns of MD simulations in NPT periodic boundary conditions at 25 °C and 1 atm of pressure. During the MD simulation, spontaneous self-assembly of the monomers occurred. Two [2+2] macrocycles were formed, one of which is depicted in Figure 2. Some short oligomeric species

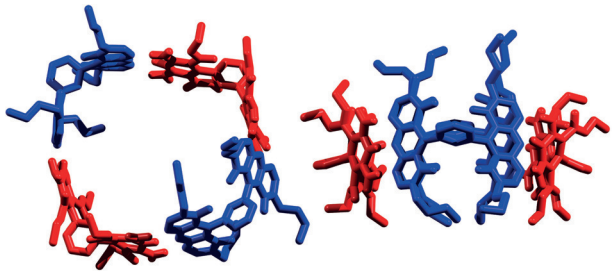


Figure 2. Structure of a [2+2] macrocycle formed from building blocks **4** and **6** during MD simulation viewed from the top (left) and from the side (right).

and six [1+1] macrocycles were also observed (see the Supporting Information). As the MD run is limited to a short time window (400 ns), this result should be regarded as a snapshot of the assembly process, rather than as the full equilibration of the self-assembling system. Nevertheless, this explorative MD simulation demonstrates that self-assembly of [2+2] macrocycles may occur very rapidly in solution. MD simulations of [1+1], [2+2], and [3+3] macrocycles, as well as of the single monomers **4** and **6**, in explicit CH_2Cl_2 solvent with BAr^{F-} counterions were employed to calculate the free energy of formation for macrocycles with different sizes.[16,17] The self-assembly energies confirm the preferential formation of [2+2] macrocycles in solution over smaller [1+1] or larger [3+3] macrocycles (see the Supporting Information).

Aside from molecularly defined macrocyclic assemblies, we have examined the formation of a macrobicyclic complex based on AAA–DDD interactions. Multipoint hydrogen bonding has been employed extensively for the construction of hydrogen-bonded cages.[18] However, to the best of our knowledge, there is no example of a cage-like assembly relying on AAA–DDD interactions.

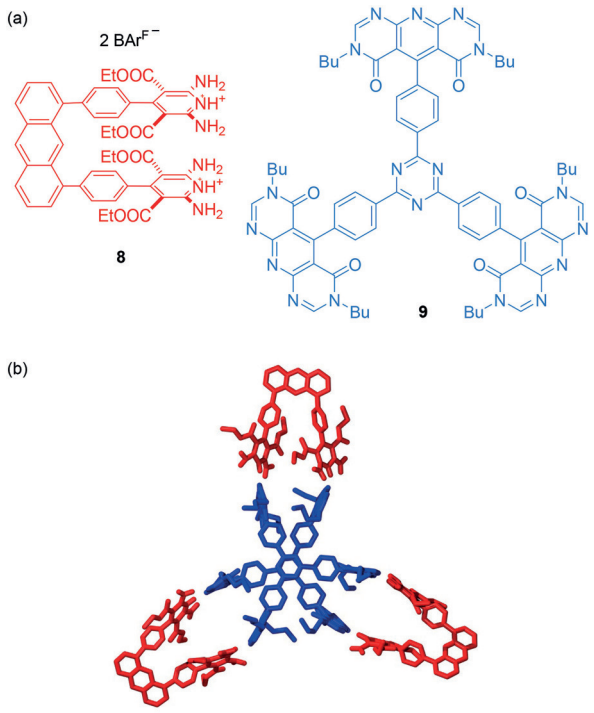


Figure 3. a) Structure of anthracene donor **8** and triple acceptor **9**. b) Equilibrated structure of the macrobicyclic complex $\mathbf{8}_3\cdot\mathbf{9}_2$ obtained in the MD simulations.

Starting from literature-known 1,8-bis(pinacolboryl)anthracene and the corresponding 4-bromophenylpyridine unit, we synthesized the clip-shaped donor **8** (Figure 3a) by employing standard Suzuki coupling conditions. The tritopic acceptor **9** was obtained from the corresponding trialdehyde in a similar fashion as described above. Sextuple donor **8** was isolated in 62%, and **9** was obtained in 75% overall yield over two steps. The good yields demonstrate once more the utility of our new synthetic strategy for the preparation of polytopic building blocks.

Based on simple geometric considerations, we reasoned that the building blocks **8** and **9** would aggregate to give the macrobicyclic complex $\mathbf{8}_3\cdot\mathbf{9}_2$. The NMR data were in full accordance with this hypothesis. When increasing amounts of **8** were added to a solution containing **9**, we observed differences for the chemical shifts of some ^{1}H NMR signals up to a ratio of **8**/**9** = 3:2 (Figure S11). The addition of more **8** led to the appearance of a second set of signals corresponding to free **8**. These results indicate the formation of a kinetically rather inert complex of the stoichiometry $\mathbf{8}_3\cdot\mathbf{9}_2$, which is in slow exchange with excess **8**. DOSY measurements (CD_2Cl_2, 298 K, 400 MHz, 1.0 mM) revealed the formation of a single, defined aggregate with a diffusion coefficient of $D = 1.57 \times 10^{-6}$ cm^{2}s^{-1}. This value is significantly smaller than the diffusion coefficient of the biggest macrocycle $\mathbf{5}_2\cdot\mathbf{7}_2$ (3.40×10^{-6} cm^{2}s^{-1}), which is in line with the expected size of complex $\mathbf{8}_3\cdot\mathbf{9}_2$. The challenging direct detection of $\mathbf{8}_3\cdot\mathbf{9}_2$ by mass spectrometry (M_w = 5.7 kDa) was unfortunately not successful as only smaller fragments were observed.

A molecular model of the macrobicyclic complex was built from three monomers of **8** and two monomers of **9** and then relaxed in the presence of explicit CH_2Cl_2 solvent molecules and BAr^{F-} counterions. An MD simulation (400 ns) conducted under the same conditions as described for the macrocycles demonstrated that the $\mathbf{8}_3\cdot\mathbf{9}_2$ assembly is stable (Figure 3b). At equilibrium, the MD simulation shows a side-on binding mode of donor **8**, with the AAA units of **9** being nearly perpendicular to the central aryl ring of **9**. The free energy of formation per AAA–DDD interaction was to be found negative ($\Delta G = -2.1$ kcal mol^{-1}), but less favorable than that of the [2+2] assembly $\mathbf{4}_2\cdot\mathbf{6}_2$ ($\Delta G = -7.9$ kcal mol^{-1}). This difference is due to the increased conformational flexibility of the building blocks **8** and **9** compared to **4** and **6**, which results in a less favorable entropy term. In fact, the enthalpic contributions per AAA–DDD interaction were found to be similar for the macrocycle (-15.3 kcal mol^{-1}) and the macrobicycle (-12.9 kcal mol^{-1}).

In summary, we have developed a facile and flexible method for the synthesis of supramolecular building blocks containing triple hydrogen-bond donor or acceptor groups. A key advantage of our process is the possibility to access polytopic building blocks with precisely oriented AAA/DDD groups in few steps. This finding paves the way for the utilization of the highly stable AAA–DDD interaction in structural supramolecular chemistry. As representative examples, we have prepared tetrameric macrocycles from bent, ditopic building blocks, and a macrobicyclic complex from five components, including a tritopic acceptor. It is likely that our method can be extended to a wide variety of polytopic compounds, as well as to Janus-type building blocks containing AAA and DDD groups. These compounds should enable the formation of novel cage structures, crystalline molecular networks, and novel supramolecular polymers. Studies in this direction are ongoing in our laboratory.

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