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

Marcus Papmeyer, Clément A. Vuilleumier, Giovanni M. Pavan, Konstantin O. Zhurov, and Kay Severin*

Abstract: A facile and flexible method for the synthesis of a new AAA-DDD triple hydrogen bonding motif is described. The method allows accessing polytopic supramolecular building blocks with precisely oriented AAA and DDD groups in few steps. These building blocks have been used for the assembly of large macrocycles featuring four AAA-DDD interactions, and of a macrobicyclic complex showing 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^[1k] and several other AAA-DDD motifs^[1] and two AAAA-DDDD couples^[2] have been reported since then. 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 $K_a = 3 \times 10^{10} \text{ M}^{-1}$ 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 described very recently.^[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 so 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 the characterization of a new and easily accessible AAA-DDD motif. Importantly, our methodology allows preparing ditopic 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 via six AAA-DDD interactions.

A practical route for the synthesis of useful supramolecular building blocks with AAA/DDD motifs should display the following desirable characteristics: (i) facile synthesis and purification, (ii) high yields, (iii) access to building blocks with different geometry and solubility, and (iv) the method should allow the preparation of polytopic building blocks with multiple AAA/DDD units.

In our attempt to realize a synthetic protocol with these characteristics, we chose aromatic aldehydes for commencing the synthesis. Following a protocol developed by Meyer et al.,^[4] we first synthesized diamino-substituted dihydropyridines by 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 as DDD units,^[1k] but they are susceptible to tautomerization.^[1e,4,5] We therefore decided to add directly an oxidation step with DDQ, which gave the diaminopyridines **1a** and **1b** in good overall yields (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).

In order to synthesize the triple acceptor **3**, we adopted a cyclisation protocol originally introduced by Besson et al. for the preparation of pyrimidin-4(3H)-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 in the microwave yielded a mixture of the desired dipyrimidine-4,6(3H,7H)-dione **3** and a monocyclised pyrimidone intermediate. The latter could be converted to the product by repeating the two steps for a second cycle to give **3** in an overall 81% yield (Scheme 1). The syntheses of **2** and **3** are easily scalable and can be performed on a multi-gram scale.

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

With this straightforward synthesis in hand, we investigated the binding of the AAA-DDD couple **2** and **3** in dichloromethane. ¹H NMR titration experiments in CD₂Cl₂ gave binding isotherms that were linear until a 1:1 molar ratio was reached, followed by an abrupt change (see SI, Figure S1). Such a behavior is expected for an association constant higher than 10⁴ M⁻¹.^[8] In order to obtain a numerical value for the binding constant, isothermal titration calorimetry (ITC) was then employed (288 K, CH₂Cl₂). Interestingly, the titration data were best fitted assuming a 2:1 binding model involving a ternary complex (**2**·**3**)·**3** in addition to the expected dimer **2**·**3** (see SI, Figure S3 and S4). The association constant for dimer formation was $K_{a1} = 1.1(\pm 0.2) \times 10^7 \text{ M}^{-1}$. While this value is in the expected range for an AAA-DDD system, it is lower than the strongest interaction reported in literature ($3 \times 10^{10} \text{ M}^{-1}$).^[1d] Presumably, the weaker binding is due to the diminished basicity of the pyrimidone nitrogen atoms in acceptor **3** as compared to the 2,3-fused pyridine rings employed by Leigh and co-workers. For the complexation of the second AAA unit **3**, an association constant of $K_{a2} = 1.8(\pm 0.2) \times 10^5 \text{ M}^{-1}$ 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 since both compounds are non-fluorescent.

In order 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 methodology becomes evident. By applying our synthetic protocol to aromatic dialdehydes (isoterephthalaldehyde and

naphthalene-2,7-dicarbaldehyde), we were able to access the corresponding DDD-DDD building blocks **4** (yield: 85%) and **5** (yield: 63%), as well as the AAA-AAA building blocks **6** (yield: 43%) and **7** (yield: 61%, all yields are calculated starting from the corresponding aromatic bisaldehyde) (Scheme 2). The isolated 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]

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

Building blocks **4–6** are relatively rigid and the two AAA/DDD units are oriented in a divergent fashion. Due to the large degree of preorganization, we expected the formation of macrocyclic assemblies upon mixing of equimolar amounts of donors and acceptors. Based on the angle between the donor/acceptor sites (~120°), one could expect the formation of [3+3] macrocycles. 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 strongly bent AAA-DDD units.

Analysis of a CD₂Cl₂ solution containing equimolar amounts of **4** and **6** (both 5.0 mM) by ¹H NMR spectroscopy (298 K, 400 MHz) revealed upfield shifts of the signals of H_a and H_B pointing inside the macrocycle (for annotation see Scheme 2), as well as significant downfield shifts and broadening of the NH_B signals of **4** (Figure 1, top). This shift is 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 BARF⁻ anion, indicating a weak interaction between the cationic macrocycle

and the ‘non-coordinating’ anions. A similar shift was not observed for the simple dimer **2**·**3**.

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

Figure 1. (a) ¹H-NMR spectra (CD₂Cl₂, 298 K, 400 MHz) of acceptor **6** (5 mM, top), an equimolar mixture of **4** and **6** (5 mM respectively, middle), and donor **4** (5 mM, bottom). For lettering see Scheme 1. (b) ESI mass spectrum of a solution containing **4** and **6** showing peaks corresponding to the tetramer **4**₂·**6**₂.

The formation of a single aggregate was confirmed by diffusion-ordered NMR spectroscopy (DOSY) (CD₂Cl₂, 298 K, 400 MHz, 1.0 mM). The analysis showed the presence of a defined assembly with a diffusion coefficient of $D = 3.98 \cdot 10^{-6} \text{ cm}^2/\text{s}$. Taken together, the data are good evidence that the combination of **4** and **6** gives exclusively the $[2+2]$ macrocycle **4**₂·**6**₂.

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

interactions.^[11] H-bonded tetramers are also found in G-quartets and their synthetic analogues.^[12, 13]

In order to obtain information about the kinetic stability of macrocycle **4**₂·**6**₂, we have recorded ¹H NMR spectra of solutions containing a constant amount of acceptor **6** (2.5 mM) and a variable amount of donor **4** (see SI, Figures S5–S8). When the amount of **6** was in excess compared to **4**, the exchange between free **6** and macrocycle **4**₂·**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 the donor **4** was larger than that of acceptor **6**. These data suggest that exchange reactions proceed via an associative mechanism. The cationic nature of the macrocycle **4**₂·**6**₂ inhibits the association of the doubly charged **4** due to unfavorable columbic interactions (→ slow exchange with excess **4**), whereas the neutral acceptor **6** can readily associate and exchange with complex **4**₂·**6**₂ (→ fast exchange with excess **6**). This assumption is corroborated by the ITC data described above, which show that one donor can coordinate to two acceptor units. The exchange between **4** and **4**₂·**6**₂ was also studied by exchange spectroscopy (EXSY) in CD₂Cl₂. We were able to derive an exchange rate constant of $k = 0.40 \text{ s}^{-1}$, which confirms 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 to study 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 CH₂Cl₂ molecules and 160 BAR^F counterions (computational details in the SI). This system underwent 400 ns of MD simulations in NPT periodic boundary conditions at 25 °C and 1 atm of pressure. During the MD, 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 and six $[1+1]$ macrocycles were also observed (see SI). Since the MD run is limited to a short time window (400 ns), this result should be regarded as a snapshot during the assembly process, rather than of a 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 CH₂Cl₂ solvent and BAR^F counterions allowed to calculate the free energy of formation for different size macrocycles. The self-assembly energies confirm the preferential formation of $[2+2]$ macrocycles in solution over smaller $[1+1]$ or larger $[3+3]$ macrocycles (see SI).

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

In addition to 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.

Starting from literature known 1,8-bis(pinacoliboryl)anthracene and the corresponding 4-bromophenylpyridine unit, we have synthesized the clip-shaped donor **8** (Figure 3a) employing standard Suzuki-coupling conditions. The tritopic acceptor **9** was obtained from the corresponding trialdehyde in a similar fashion as described above. The isolated yield for the hexa donor **8** was 62%, and **9** was obtained in 75% overall isolated 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 **8₃·9₂**. 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 ¹H NMR signals up to a ratio of **8**:**9** = 3:2 (see SI, Figure S11). Addition of more **8** leads 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 **8₃·9₂**, which is in slow exchange with excess of **8**. DOSY measurements (CD₂Cl₂, 298 K, 400 MHz, 1.0 mM) revealed the formation of a single, defined aggregate with a diffusion coefficient of $D = 1.57 \cdot 10^{-6} \text{ cm}^2/\text{s}$. This value is significantly smaller than the diffusion coefficient of the biggest macrocycle **5₂·7₂** ($3.40 \cdot 10^{-6} \text{ cm}^2/\text{s}$), in line with the expected size of complex **8₃·9₂**. The challenging direct detection of **8₃·9₂** by mass spectrometry ($M_w = 5.7 \text{ kDa}$) was unfortunately not successful: 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 presence of explicit CH₂Cl₂ solvent molecules and BARF[−] counterions. An MD simulation (400 ns) conducted under the same conditions as described for the macrocycles demonstrated that the **8₃·9₂** 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 benzene ring of **9**. The free energy of formation per AAA-DDD interaction was found negative ($\Delta G = -2.1 \text{ kcal/mol}$), albeit less favorable than what was observed for the [2+2] assembly **4₆** ($\Delta G = -7.9 \text{ kcal/mol}$). This difference is due to the increased conformational flexibility of the building blocks **8** and **9** when compared to **4** and **6**, which results in a less favorable entropic term. In fact, the enthalpic contributions per AAA-DDD interaction were found similar for the macrocycle (−15.3 kcal/mol) and for the macrobicyclic (−12.9 kcal/mol).

In summary, we have developed an easy and flexible method for the synthesis of supramolecular building blocks containing triple hydrogen bond donor or acceptor groups. A key advantage of our methodology 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 macrobicyclic complex from five components including a tritopic acceptor. It is likely that our methodology 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.

Figure 3. (a) Structure of the anthracene donor **8** and triple acceptor **9**. (b) Equilibrated structure of the cage **8₃·9₂** obtained from the MD simulations.

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Hydrogen Bonds

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Molecular Nanostructures Based on a Novel AAA-DDD Triple Hydrogen Bond Motif

Made to connect: a new synthetic methodology provides easy access to supramolecular building blocks with multiple AAA or DDD groups. The components assemble via stable AAA-DDD triple hydrogen bonds to give macrocycles or a macrobicyclic complex (shown).