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COMMUNICATION

Structure Dependent Guest Recognition with Flexible Ferrocene Based Aromatic Oligoamide β-Sheet Mimics

Ya-Zhou Liu,[a] Hu Wang,[a] Chieh-Kai Chan,[b] Xiao Mu,[a] Koen Robeyns,[a] Cheng-Chung Wang[b] and Michael L. Singleton*[a]

Abstract: A series of aromatic oligoamides incorporating an inherently flexible ferrocene dicarboxylic acid unit was synthesized. Solid state, solution, and computational studies on these systems indicated that the aromatic strands can adopt a *syn* parallel stacked conformation. This results in modular β-sheet like molecular clefts that display structure dependent recognition of small polar molecules. NMR and theoretical studies of the host-guest interaction support an in cleft binding mode and allowed the selectivity of the oligomers to be rationalized on the basis of minor changes in functional group presentation on the edge of the aromatic strands.

Curved β-sheet motifs are common in the active sites of many proteins, where they provide functionalized clefts important for specific recognition and catalysis.[1] Nevertheless, synthetic mimics of these curved β-sheet structures, of interest for mimicking the above functions, are rare,[2] and most work on β-sheets has remained focused on the synthesis and stability of extended structures.[3] Recently however, a new class of β-sheet mimics based on aromatic oligoamide foldamers[4] (AOF) has been reported that allows access to curved motifs. Several examples of extended and bent sheet-like structures comprised of stacked aromatic strands have been described.[5]

Unlike their aliphatic analogs, where the chains are held together primarily through hydrogen bonding, typically weaker π-π interactions have been implicated in stabilizing the stacked structures in AOF β-sheet mimics. As such, turn-units that direct the aromatic strands in a parallel fashion at distances suitable for π-stacking have been essential to the design of these molecules. Some examples used with AOF include proline,[6] 1,8-naphthalenes,[7] tertiary squaramides,[4b] and 4,6-dinitro-1,3-phenylenediamine,[4a,5] Figure 1A. Still, for these turns, long strands (larger π-surfaces) are needed to observe well-stacked structures and obtaining bent or cleft-like structures with short sequences remains a challenge.

To this end, ferrocene diacid is an intriguing candidate as a turn-unit. This scaffold has been used previously for promoting hydrogen bonding between aliphatic peptide sequences,[8] as well as for the design of hydrogen bonding receptors/sensors[9] and molecular machines.[10] For aromatic strands, the short distance between the cyclopentadienyl (Cp) rings (3.3 to 3.4 Å)[11] is well-suited for promoting stacking interactions between the strands. Indeed, syn stacked conformations are often the most stable forms for 1,1' aromatic functionalized ferrocenes.[12] On the other hand, ferrocene is a fluxional molecule and rotation of the Cp rings or about the C-C bonds of the 1 or 1' substituents, Figure 1B, has potential to generate a rich conformational landscape. Nevertheless, this flexibility may be advantageous, as it can permit the strands to move for optimal stacking interactions.

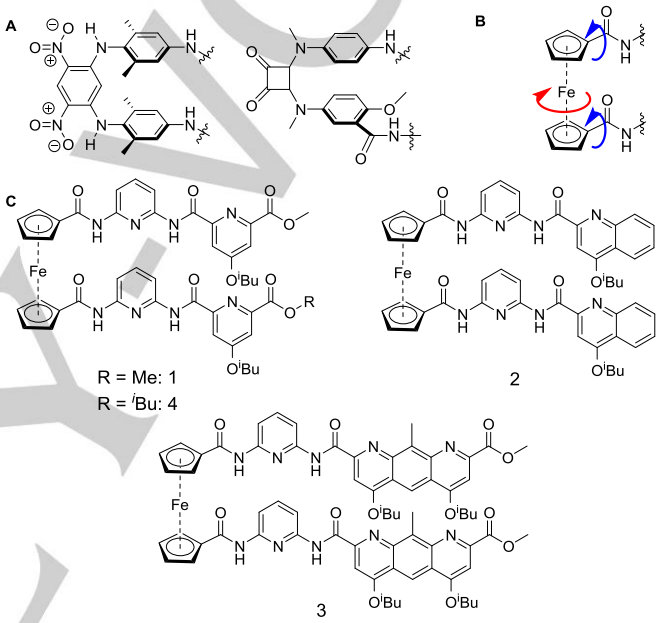

Figure 1. (A) Two examples of turn units previously used for β-sheet-like aromatic oligoamides. (B) Turn unit used in this work. (C) Structures of the pentamers **1**-**4**.

To study the balance between these factors and the applicability of ferrocene for generating functional β-sheet-like clefts, a series of AOF pentamers containing ferrocene dicarboxylic acid, Figure 1C, as a central unit was synthesized. Coupling of two equivalents of pyridine, quinoline, or diazaanthracene monomer acid chlorides[13] with the diaminopyridine functionalized ferrocene 1,1'-dicarboxylic acid trimer[14] gave the corresponding pentamers as red-orange solids in moderate to good yield after recrystallization.

The structures, determined by X-ray diffraction, for all three oligomers, Figure 2, show the central ferrocene unit connected to two aromatic strands in a parallel offset stacked arrangement with a largely eclipsed (torsion angle <8°) conformation for the Cp rings. Values measured for the distance between the planes of the aromatic strands are close to 3.4 Å, consistent with values observed in other stacked aromatic systems.[15] The head to head arrangement in the curved strands is expected to allow better overlap of the aromatic units, compensating for the parallel orientation of the dipole moments of the aromatic rings.[13b] This

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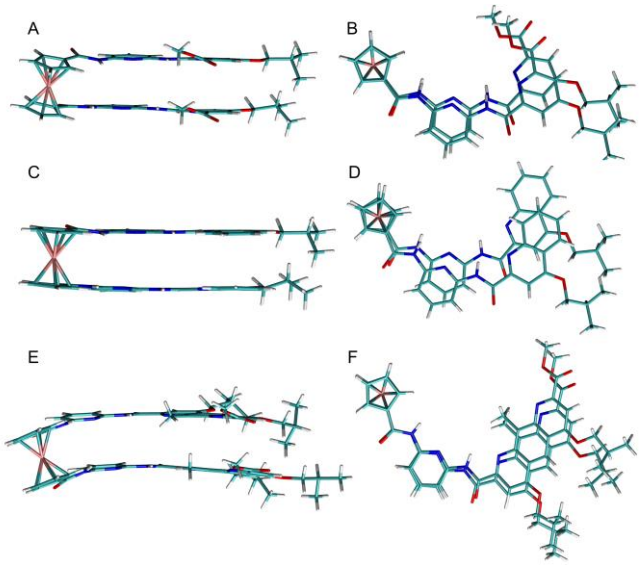

Figure 2. Side and top views of the X-ray structures of oligomers **1** (A&B), **2** (C&D), and **3** (E&F). Solvent molecules have been omitted for clarity.

unfavorable dipole alignment is further minimized in the solid state by the anti-parallel packing of neighboring molecules in the crystal lattice. The curvature of these sheet-like structures generates a molecular cleft lined by a number of hydrogen bond acceptor/donor sites coming from the amide N-H's and endocyclic nitrogens.

Despite the well-folded structure in the solid state, solution ^{1}H NMR studies show a high degree of mobility in the three oligomers. Independent of the solvent used, the Cp protons of **1**-**3** appear as only two signals indicating a fluxional process that equates the 2,5/2',5' and 3,4/3',4' protons on both rings. Even upon cooling to -90 °C in CD_2Cl_2 no splitting of the Cp resonances was observed with oligomers **1** and **2**. Because of the lower solubility of **3**, cooling only led to its precipitation from solution. Nevertheless, a number of observations suggest that the stacked conformation still has an important contribution to the overall conformational preferences in solution.

First, proton resonances for the aromatic strands in **1** – **3** are more upfield shifted than in the corresponding dimers. This is consistent with shielding from the neighboring strand, and is reported as evidence for the stacked conformations in *aryl* functionalized ferrocenes, as well as in aromatic β-sheet mimics.[6, 12c, 16] Additionally, using asymmetric oligomer **4**, the ^{1}H ROESY spectrum shows a weak correlation between the iso-butoxy methylene and the methyl group of the ester on the neighboring strand. This does not result from intermolecular contacts as ^{1}H NMR concentration studies show minimal changes in chemical shifts between 0.1 – 10 mM.

Computational studies also support that the stacked conformation is favorable. DFT minimized structures match well with the crystal structures of **1** – **3**. Calculations of open form or head to tail conformations, obtained by varying the dihedral angle of the Cp rings or amides respectively, found only higher energy structures. Indeed, Cp rotation from 0 – 180º, is strongly correlated to increased energy, suggesting important stabilizing interactions between the strands in the stacked structures.

Finally, the stacked confirmation appears important for the host-guest properties of the oligomers. While examples of cleft-like aromatic β-sheet mimics have been described, few functional systems able to bind small molecules, have been reported.[13b] As the cleft-like structures lined with polar groups can act as a binding site for small molecules,[17] we studied the host-guest properties of **1** and **2** with catechol, resorcinol, and benzoic acid through ^{1}H NMR titrations. Besides being structural motifs in a number of biologically important molecules,[18] the variation in

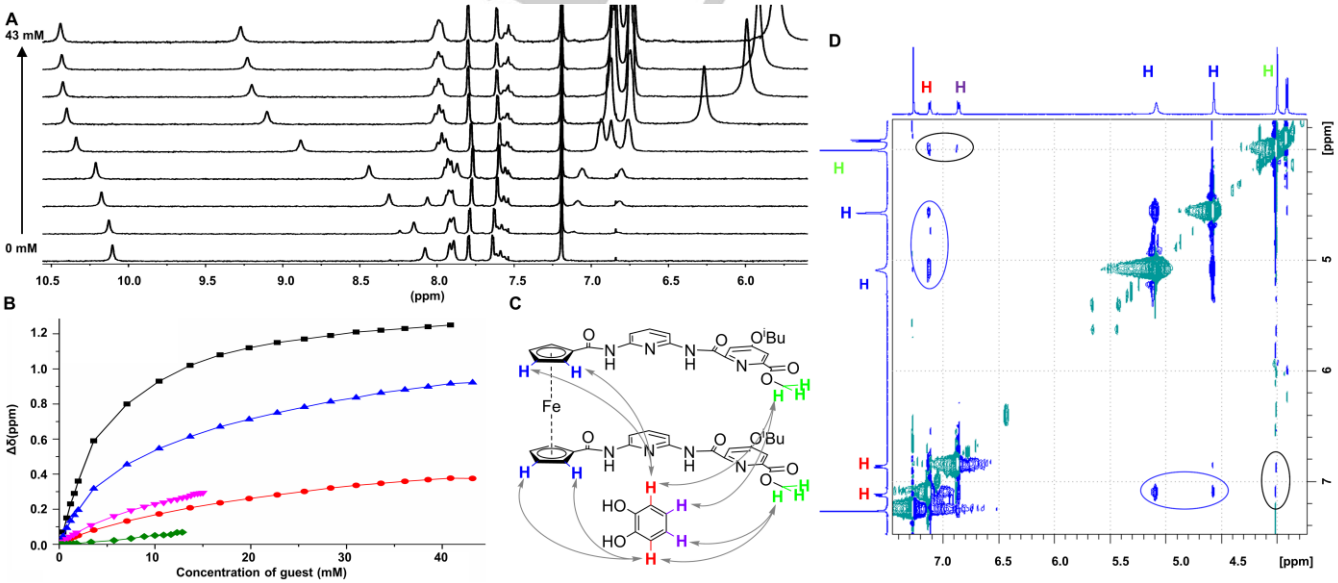

Figure 3. (A) Part of ^{1}H NMR titration experiment (300 MHz, 298 K) in chloroform-*d* of **1** (2 mM) in the presence of catechol (from 0 to 43 mM). (B) Chemical shifts of amide protons in **1** or **2** versus increasing guest concentrations. Black squares represent catechol ⊂ **1**; blue triangles represent benzoic acid ⊂ **2**; pink triangles represent resorcinol ⊂ **1**; red circles represent catechol ⊂ **2**; green squares represent resorcinol ⊂ **1**. (C) Structure of **1** with catechol, key protons are shown in colors, arrows represent observed interactions between the two molecules. (D) Part of 2D-NOESY spectrum of **1** (1 mM) with catechol (1 mM) in $CDCl_3$, blue and black circles show NOE correlations. Colors are the same as for C.

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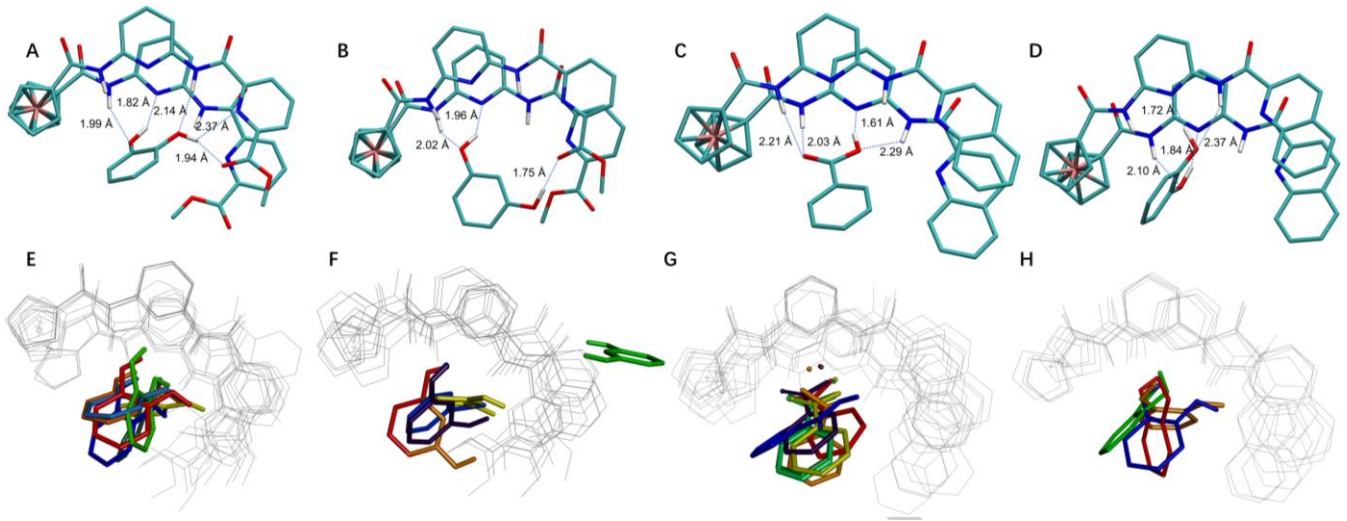

Figure 4 DFT optimized structures for the host-guest systems, (A-D) Lowest energy structures of A) **1** with catechol, B) **1** with resorcinol, C) **2** with benzoic acid and D) **2** with catechol, potential hydrogen bonds are indicated with blue dashed lines. (E-H) Overlays of the lowest energy geometries for E) **1** with catechol, F) **1** with resorcinol, G) **2** with benzoic acid and H) **2** with catechol. For the overlay models, host molecules are shown in wire frame and guests in stick style; side chains and protons not involved in forming hydrogen bonds are hidden for clarity.

donor/acceptor sites on the guests provides a way to study different possible modes of binding in the hosts.

NMR titrations of **1** or **2** with different guests, Figures 3A and S11, show shifts for several proton resonances with increasing guest concentrations. In **1**, the signals corresponding to the amide between the pyridines (10.12 ppm) and the amide next to the ferrocene (8.09 ppm) shift downfield by 0.32 and 1.19 ppm respectively, suggesting their participation in hydrogen bonding. Similar changes, though less pronounced, (Δδ of 0.07 and 0.39 ppm) are observed for the amides in **2**. For both, small upfield shifts are also observed for all of the remaining protons in the oligomers Less marked changes occur with resorcinol as the guest. The ferrocene amides remain almost unchanged, shifting only 0.09 and 0.03 ppm for **1** and **2** with increasing guest concentration while the pyridine amides shift more, (0.29 and 0.06 ppm). With benzoic acid, no significant changes were observed for any of the proton resonances in **1**. However, with oligomer **2**, increasing the concentration of benzoic acid results in similar changes as observed with catechol, i.e. downfield shifting of the amides (Δδ of 0.08 and 0.95 ppm).

Plots of changes in amide chemical shift versus guest concentration fit to 1:1 binding isotherms.[19] Association constants of 238 M^{-1} and 41 M^{-1} were found for catechol with **1** and **2**, respectively. By contrast, the binding constants for resorcinol are substantially lower. For **1**, K_a was found to be 80 M^{-1}, while for **2** no good fit could be modeled. A similar 1:1 binding (K_a = 108 M^{-1}) was found for the interaction of **2** with benzoic acid, while surprisingly no interaction was observed between this guest and **1**. This structure dependent binding is intriguing, especially given the high similarity between the core structures of **1** and **2**.

Additionally, the presence of the two strands in the oligomers also appears important for the interaction with the guests. Indeed, for the interaction of the single stranded pyridine dimer **5** (See SI) with catechol the association constant was found to be 115 M^{-1}, while no interaction was found with resorcinol.

To better understand how the guests interact with the oligomers, we turned to a combination of solution studies and computational modeling. NOESY NMR studies of **1** with catechol in $CDCl_3$ support binding of the guest into the cleft of the host, Figure 3D. Correlations between the aromatic protons of the catechol and both the Cp and methyl ester protons were observed. Similar studies for the other host-guest combinations were inconclusive due to the weak binding affinity and/or overlap of the host/guest signals. Nevertheless, given the similar changes observed during the titration with catechol and benzoic acid, we suggest that they bind in a similar fashion with both **1** and **2**, while with resorcinol other binding modes may be involved. This is supported by computational studies.

To look at guest binding, 100 guest geometries, both in and outside of the cleft, were randomly generated using molclus,[20] and then optimized at the PM6+[21] level with MOPAC[22] resulting in 43 different geometries. Of these, the 20 lowest energy were then further optimized by DFT using Gaussian 09.[23] Overlays of the lowest energy geometries for the host-guest systems are shown in Figure 4A-H and S13. For catechol and benzoic acid, the guest was found bound inside of the clefts of the oligomers. Geometries where the guest was outside of the cleft were higher in energy by >23 kJ/mol.

For the lowest energy structure of **1** with catechol, one guest hydroxyl group forms hydrogen bonds with both a ferrocene amide NH and a pyridine endocyclic nitrogen, while the second hydroxyl appears to interact mostly with the carbonyl of a methyl ester. This latter interaction may explain the difference in affinity of **1** vs **2** for catechol. Indeed, the lowest energy structure for **2** with catechol shows both guest hydroxyl groups forming OH-N hydrogen bonds with the pyridine nitrogens, while the catechol oxygens form hydrogen bonds with the nearby amides. For almost all structures the shortest NH-O distances are observed for the interaction with the ferrocene amide, fitting well with the larger experimental shifts observed for this proton resonance in the presence of the guest. This is similarly true for the lowest energy structure of **2** with benzoic acid. In this case, this interaction results in the aromatic portion of the guest being in close proximity to the 8-position C-H of the quinoline unit. In **1**, this space is occupied by the esters, likely explaining the lack of affinity between **1** and benzoic acid.

The calculated structures with resorcinol suggest that different binding modes are possible. The lowest energy geometries for **1** and **2**, Figure 4F and S13, showed guest binding both inside and outside the clefts. Energy differences between these conformations are about 11 and 4 kJ/mol for resorcinol with **1** and **2**, respectively. Multiple guest binding equilibria may explain the difficulties fitting the titration data with **2**.

In conclusion, a series of aromatic oligoamides containing ferrocene as a turn-unit was synthesized. Despite the flexible nature of the central unit, the oligomers show stable stacked structures in the solid state. Still, in solution, the molecules are fluxional. Nevertheless, spectroscopic and theoretical studies suggest that the stacked structure may be one of the important conformations that exist in solution. The resulting clefts are functional hosts for binding small molecules and thus mimic this aspect of biological curved β-sheets. Interestingly, even with these relatively short oligomers, subtle changes in monomer composition are able to invert guest preferences from oligomer **1** to **2**. The increased flexibility in these oligomers and their ability to interact with guests is intriguing for the possibility to switch between multiple conformations, e.g. sheet to helix. Such conformational changes are of interest for sensing and information storage.[24] Studies on stabilizing different conformations and the exchange between them are ongoing in our lab and will be reported in due course.

Acknowledgements

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Keywords: Ferrocene • Aromatic Oligoamides • Foldamers • Structural Stability • Host-Guest Chemistry

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

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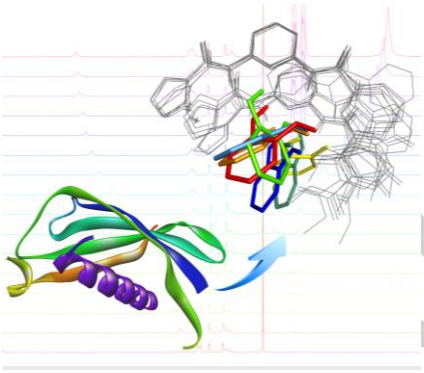
Ferrocene was found to be an efficient turn-unit in the development of a series of curved aromatic oligoamide β-sheet mimics. Solid state, NMR, and computational results support a stacked conformation of the strands giving cleft-like structures able to bind small molecules. Spectroscopic and theoretical studies allowed the binding modes and structure dependent selectivity to be rationalized based on minor changes in the cleft surface.



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