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Functionalized 1,8-Diazaiptycenes as Monomers for Aromatic Oligoamide Foldamers.

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Diversification of the structures and applications possible for foldamers relies on expansion of the building block library available for their synthesis. In this work, we describe the synthesis of a range of three dimensional heteroaromatic monomers, based on iptycene scaffolds, that are suitable for the synthesis of aromatic oligoamide foldamers. These units can be obtained in gram quantities in up to 80% yield through [4+2] cycloaddition between diester, diamine, and amino acid derivatives of 1,8-diazaanthracenes and a variety of dienophiles. X-ray structural studies of the monomers and an oligomer show that the new motif orients the two heterocyclic rings and attached groups at an angle of approximately 120° to each other, opening new geometric considerations for the design of this class of foldamer.

Foldamers, oligomeric molecules that adopt stable higher ordered structures in solution,[1] have attracted interest in the last decades for their unique structures and biological and materials applications.[2] The structures and thus potential applications of this class of molecules are derived from the properties inherent in the monomers used for their synthesis. For example, in the case of aromatic oligoamide foldamers (AOF),[3] figure 1A, the building blocks are based on heterocyclic or heteroatom functionalized aromatic units. When connected by amide bonds, conjugation and the collection of electrostatic interactions between the amide bonds and the heteroatoms on the monomers lead to strong conformational preferences around the amide. Extension of this design to oligomers gives rise to highly stable and predictable structures that have allowed the engineering of a range of complex molecular architectures.[4] The potential for new classes of aromatic monomers to allow novel exciting structural motifs and properties to be discovered, makes the development of new monomers important for advancing applications of these foldamers.

Common monomers used for the synthesis of AOF, figure 1A, have included various functionalized benzenes, pyridines, quinolines, naphthyridines, and diazaanthracenes, among others.[5] While side chain modifications have led to many derivatives of these units, they all share similar flat aromatic cores with the distance and angle between the amine/carboxy groups being the primary design features used to dictate the folded structures.

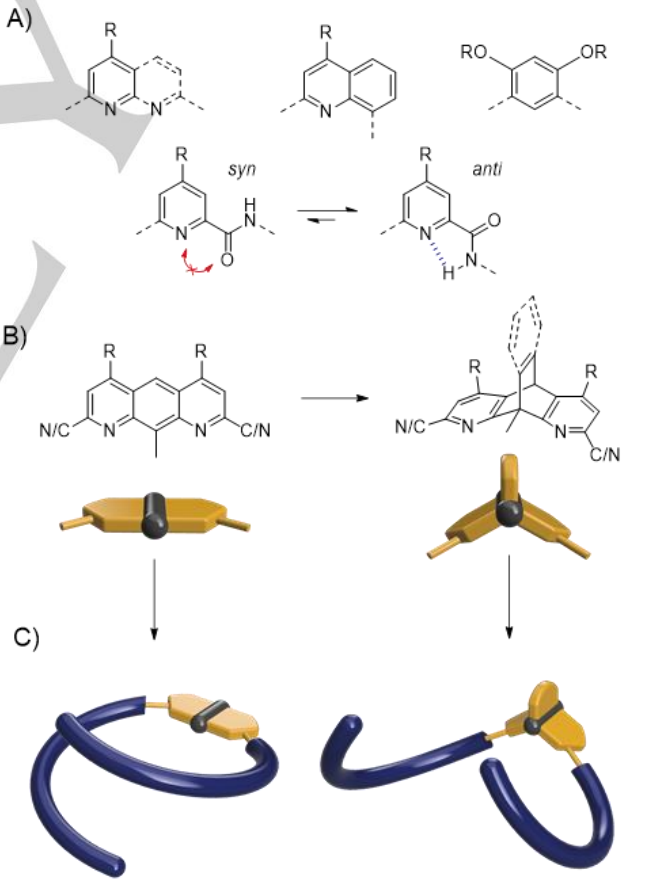

Figure 1. A) Examples of aromatic units for the construction of AOF and conformational preferences of the amide-aryl linkage. B) Synthetic strategy towards iptycene building blocks from diazaanthracenes with cartoon representations shown below. C) Cartoon representation of potential effects of iptycene units on AOF structures.

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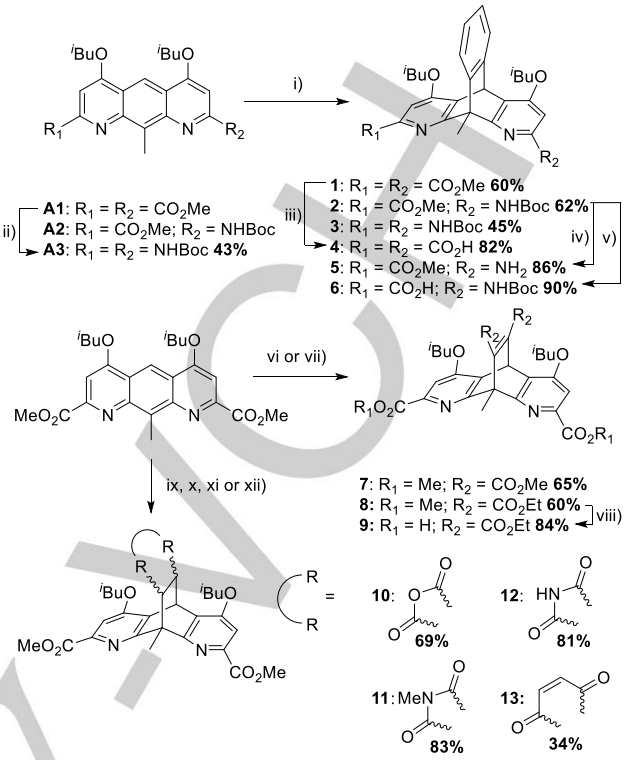
Adding a three dimensional character to aromatic monomers, while maintaining advantageous properties such as rigidity, can offer new ways to orient or control monomer direction. However, three dimensional aromatic monomers are rare and when reported have almost exclusively been used as end groups for controlling chirality in longer sequences.[5m,6] One intriguing option for new monomer units are iptycenes, figure 1B-C. The properties of these molecules have made them attractive for a number of applications in supramolecular chemistry and materials development.[7] The bridged bicyclo-octatriene core of these structures provides a rigidity similar to other aromatic monomers but orients the attached aromatic rings at an angle to each other, providing a new geometric consideration between the amine/carboxy groups that can be used in the design of AOF. Still, to be useful as monomers, the iptycenes must possess the inherent structural features needed for oligomerization and controlling conformational preferences, i.e. amino or carboxyl groups ortho to endo- or exocyclic hetereoatoms. Based on previous reports by Quast and Schön showing that diaazaanthracenes can serve as dienophiles in Diels-Alder reactions to give 9,10-alkyl bridged derivatives,[8] we reasoned that applying this strategy to 1,8-diazaanthracene monomers[5q&s] previously described for AOF synthesis could directly yield diacid, diamine, and amino acid iptycene units suitable for oligomer synthesis, thus giving access to this new class of building block.

As shown in scheme 1, the 1,8-diazaiptycene monomers are readily synthesized in moderate to good yield via Diels-Alder reaction between the 1,8-diazaanthracenes and various dienophiles. This affords a range of monomers with different functionalities through variation of the diazaanthracene or dieneophile derivatives used. For the starting diazaanthracene units, the diester derivative **A1** and the protected amino acid **A2** have been described previously.[5q&s] Synthesis of the 2,7-diamino derivative **A3** proceeds through initial aminolysis of **A1** using hydrazine hydrate in methanol. Oxidation of the resulting acylhydrazide with $NOBF_4$ in CH_2Cl_2 affords the bis acylazide derivative. Subsequent Curtius rearrangement in a 1:1 mixture of toluene and tert-butanol gives **A3** in an overall 43% yield across the three steps.

Next, these units were converted into the corresponding triptycenes. Reaction of **A1** with in situ generated benzyne[9] in MeCN gives 1,8-diazatriptycene monomer **1** in 60% yield. In contrast to the bright yellow and fluorescent starting material, the product is obtained as a white solid with no strongly observable fluorescence, consistent with disruption of the extended aromatic system. This disruption is further evidenced by ^{1}H NMR. Notably the 10-position proton resonance shifts from 8-9 ppm in the starting diazaanthracene to around 6 ppm after the reaction. An upfield shift is also observed for the 9-position methyl group resonances (~3.3 ppm to ~2.5 ppm). Reaction of **A2** and **A3** under similar conditions proved equally efficient, furnishing the amino acid and diamino diazatriptycene monomers **2** and **3** in yields ranging from 45-62%. These reactions are easily scaled up allowing the monomers and their corresponding free acid or free amine derivatives (**4**-**6**) to be obtained in multi-gram quantities.



Scheme 1. Synthesis of triptycene and iptycene monomers. Reaction conditions: i) Caesium fluoride, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, CH_3CN, 55°C; ii) a) H_2NNH_2, MeOH, reflux; b) $NOBF_4$, CH_2Cl_2; c) anhydrous ^{t}BuOH, toluene, reflux ; iii) KOH, CH_2Cl_2:MeOH, r.t.; iv) Trifluoroacetic acid, CH_2Cl_2, r.t.; v) NaOH, dioxane, water, r.t.; vi) for 7, Dimethyl acetylenedicarboxylate, p-xylene, 110°C; vii) For 8, Diethyl acetylenedicarboxylate, p-xylene, 110°; viii) Lithium iodide, THF, reflux ; ix) for 10, , maleic anhydride, p-xylene, 140°C; x) for 11; N-methylmaleimide, p-xylene, 140°C; xi) for 12, maleimide, p-xylene, 140°C ; xii) for 13, benzoquinone, p-xylene, 80°C.

Formation of the triptycenes leads to a decrease of the symmetry of the parent **A1**-**A3**, to either Cs in the case of the diacids or diamines or C_1 in the case of the amino acid. This has the effect of making the new monomers either prochiral or chiral. Indeed, synthesis of a triptycene dimer via PyBOP coupling of chiral monomers **5** and **6**, scheme S1A, gives a nearly 1:1 mixture of diastereoisomers that, unfortunately, could not be separated by standard chromatography. To increase the potential utility of the monomers for oligomer synthesis, resolution of the two enantiomers of **2** was attempted. Classical resolution by diastereomeric salt formation has, so far, not yielded promising results. However, through screening the coupling of different chiral auxiliaries to free amine derivative **5**, (-)-camphanic acid was found to give diastereoisomers that can be partially separated by standard chromatography on silica gel. Once obtained, alcoholysis of the camphanic amide with $MeOH/H_2SO_4$ gives the free amine enantiomers (+)-**5** and (-)-**5**, Scheme S1B, in 67 % and 49 % yield respectively.

While the added benzene moiety in the triptycene scaffolds offers a highly stable and unreactive group, this synthetic approach to the monomers also gives the potential to incorporate additional functional groups in the bridging

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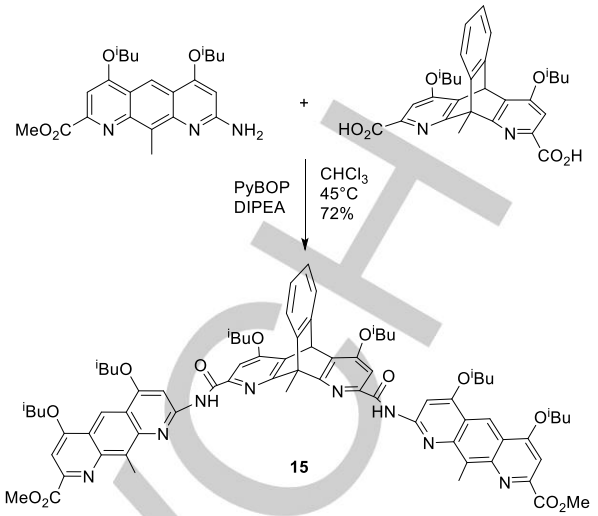
unit. To explore this idea, dimethyl acetylenedicarboxylate was used as the dienophile for reaction with **A1**. In p-xylene at 110°C, complete reaction with **A1** occurs overnight to give iptycene derivative **7** in 65% yield . Similar to the triptycene derivatives, the resonance corresponding to the 10-position proton in the starting material disappears and a new signal at 6.03 ppm is observed consistent with reaction occurring on the central ring of the diazaanthracene. Initial attempts at selective saponification of **7** gave complicated mixtures of products. To provide better selectivity between the ester groups, diethyl acetylenedicarboxylate was used as the dienophile for reaction with **A1**, giving the diethyl maleate iptycene derivative, **8**, with a yield similar to the methyl derivative (60%). Reaction of **8** with LiI in refluxing THF then allows selective deprotection of the methyl esters to give diacid **9**.

Under similar conditions, a range of other dienophiles can also be applied with this strategy to give other derivatives. Reaction of **A1** with malonic anhydride or maleimides gave dihydroiptycene derivatives **10**-**12** in good to excellent yield (69-83%). Similarly, Diels-Alder reaction with quinone gave monomer **13** in moderate yield. Partial tautaumerization of this species also occurred during the reaction giving 11,14-dihydroxytriptycene derivative **14** as an additional product.

Changes to the geometry of the monomers are evident in the crystal structures for **1** and **8**, figure 2A-B. Relative to the starting A1 unit,[5q] for which the N-heterocyclic rings are coplanar (180°), or the previously reported photodimer of A1 (132°),[5q] for **1** and **8** the angle between the planes of these rings (φ) has decreased to 122° and 118° respectively. This leads to variation on the distance and angles between the carboxyl groups in the different derivatives that should have an important effect on the geometry of oligomers. To further study this idea, trimer **15** was synthesized by



Scheme 2. Synthesis of triptycene-based trimer **15**.

coupling of triptycene diacid **4** with two equivalents of amine deprotected **A2**, scheme **2**.

The X-ray structure of the trimer, figure 2C-D, shows the expected curved conformation resulting from electrostatic interactions between the different units and the amides; the two diazaanthracenes are oriented in the same direction. However, rather than being coplanar, as is the case for most short AOF sequences, the central triptycene leads to an angle of ~70° between the planes of these groups resulting in a concave and a convex face.

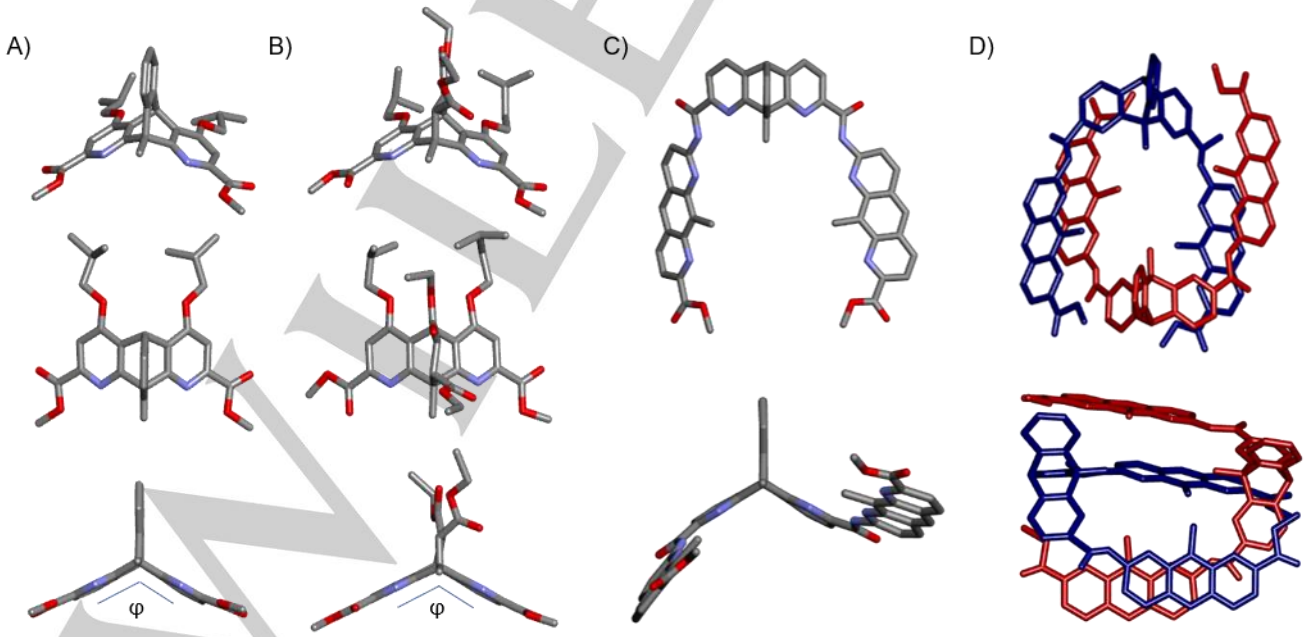


Figure 2. Solid-state structures of A) **1**; B) **8**; C) Views of trimer **15** and D) an intercalated dimer of **15**. Isobutoxy sidechains in D) and hydrogen atoms and solvent molecules for all structures have been omitted for clarity.

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Two different sets of crystals of **15**, obtained from $CHCl_3$/MeOH, show different types of association between trimers in the unit cell. In both cases, aromatic stacking between neighboring molecules is prevalent. However, in one structure, figure 2C, this occurs between discrete monomeric units and, in the other, Figure 2D, two trimers intercalate forming a dimer that then interacts with neighboring dimers, figure S5. Signals for a dimer species could also be seen in the HR ESI MS spectrum, which showed overlapping signals, figure S1. for both the singly charged **15** and the doubly charged dimeric $\mathbf{15}_2$. Numerous instances of self-association of aromatic oligoamides, for example multiple helix formation, are described in the literature for AOF.[5e,p,q,r & 10] However, concentration studies on **15** by ^{1}H NMR in $CDCl_3$ from 1 - 60 mM, figure S6, show only small (<~0.1 ppm) upfield shifts for some of the signals at high concentration. Such changes can be consistent with undefined aggregation in fast exchange. Still, their weak magnitude and the high symmetry of the species suggests that the monomeric form of **15** likely dominates in solution.

In conclusion, we have synthesized a range of new diester, diamine, and amino acid 1,8-diazaiptycene derivatives suitable for use in AOF synthesis and demonstrated their use in the synthesis of a short oligomer. Beyond the novel geometric considerations that these monomers can bring to AOF design, the potential to use reversible Diels-Alder reactions for modification of the monomer structures can open new ways for controlling large scale conformational changes or stimuli induced self-assembly in synthetic oligomers. Studies on these topics are currently underway in our group and will be reported in due course.

Acknowledgements

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Keywords: aromatic oligoamides • diazaiptycenes • Diels-Alder reaction • foldamers • triptycenes

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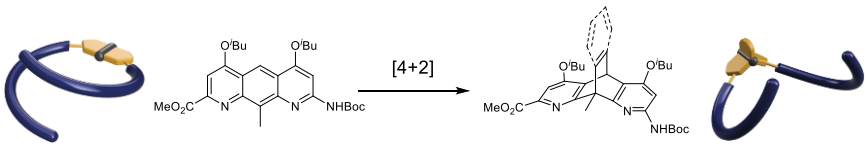

Fourteen 1,8-diazaiptycene monomer derivatives

Diels-Alder reaction using 1,8-diazaanthracenes as the diene provides a facile route to three-dimensional aromatic monomers, based on 1,8-diazaiptycene scaffolds, suitable for the synthesis of aromatic oligoamide foldamers. These units can be obtained in gram quantities This structural motif adds an additional bend angle between the amine or carboxy groups that can bring new geometric considerations into the design of this class of foldamer.

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