Oligo(5-amino-*N*-acylanthranilic acids): Amide Bond Formation without Coupling Reagent and Folding upon Binding Anions

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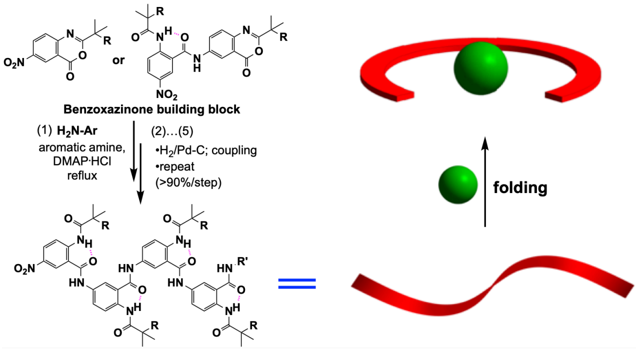
Supporting Information Placeholder



ABSTRACT: Oligomers of 5-amino-*N*-acylanthranilic acid, previously unknown aromatic oligoamides that cannot be obtained with known amide coupling methods, are synthesized based on a new, highly efficient amide-bond formation strategy that takes advantage of the ring-opening of benzoxazinone derivatives. These oligoamides offer multiple backbone NH groups as H-bond donors which, in the presence of iodide or chloride ion, are convergently arranged and H-bonded, which enforces a folded, crescent conformation. These aromatic oligoamides provide a versatile platform based on which anion-dependent foldamers, or anion binders with tunable affinity and specificity, are being constructed.

The creation of foldamers have attracted wide interest over the last two decades.[1] Foldamers are constructed to mimic biological folding, to interfere the interactions involving biomacromolecules, or to uncover behavior and functions not found in nature. Examples of foldamers include those with peptidomimetic[2-7] and abiotic[8-12] backbones. The majority of known foldamers are helical, although a few systems adopting non-helical conformations[13-16] are also known. Compared to the limited sets of residues that constitute each class of biomacromolecules, a much wider combination of building blocks, and covalent linkages that are only limited by one's imagination can be incorporated into the design of synthetic foldamers.[17]

We have developed several series of cavity-containing aromatic foldamers.[18] One representative class, as shown by general structure **A** (Figure 1a), are aromatic oligoamides consisting of *meta*-linked benzene residues.[19] The backbone amide hydrogens of **A** engage in highly stable, three-center intramolecular hydrogen bonds.[20] The rigidity and planarity of the aromatic residue and amide linkage, along with the H-bonded amide groups, lead to crescent or helical conformations containing inner cavities of ~9 Å across. The cavities of these foldamers, along with those of macrocycles sharing similar backbones,[18,21] are rich in amide oxygens and are thus electrostatically negative, based on which hosts for cationic species and molecules rich in H-bond donors have been generated.[22]

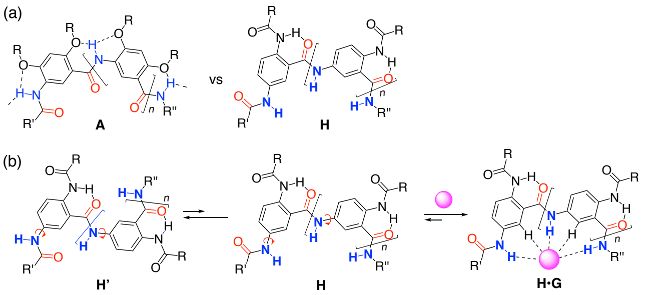


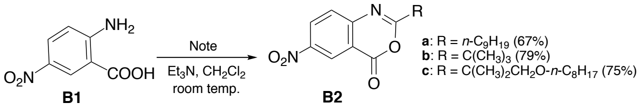
Figure 1. (a) Previously developed aromatic oligoamide foldamer A has a fully constrained backbone. Oligoamide H, with the orientation of its backbone amide groups (red) being inverted relative to those of A, has multiple amide NH groups (blue) available for H-bonding. (b) Instead of adopting multiple conformations as represented by **H'**, oligoamide **H**, upon binding a guest (red sphere) via H-bonding, will be driven to adopt a crescent conformation in which all backbone amide protons and "internal" aromatic protons, are convergently arranged.

In contrast to electrostatically negative cavities which are featured by convergently placed electronegative atoms, electrostatically positive cavities need the same arrangement of (partially) positively charged atoms. While a number of macrocyclic scaffolds have been used to centripetally orient H-bond donors,[23] non-cyclic oligomers offering multiple H-bond donors that can be convergently placed are rare.[24] Such oligomers could provide versatile platforms for addressing major challenges in supramolecular chemistry, such as the binding, recognition, or transport of anions and polar molecules rich in H-bond acceptors.

Herein we report the design, synthesis, and study of a hitherto unknown series of aromatic oligoamides that fold upon binding anions. As shown in Figure 1a, inverting the orientation of the backbone amide groups of **A** leads to oligoamide **H** in which a six-membered intramolecular H-bond is introduced between each backbone amide oxygen and the amide proton of the adjacent acylamino sidechain. Such an intramolecular H-bond keeps the backbone amide oxygen atom from engaging in additional H-bonding and, more importantly, frees each backbone NH group to engage in H-bonding with other guest species.

Unlike that of **A**, the backbone of oligoamide **H** is partially constrained. Around each backbone amide group of **H**, the rotation of the aryl-CO single bond is limited by an intramolecular H-bond, while the rotation of the C(O)NH-aryl bond remains unhindered. It is thus expected that **H** will adopt multiple conformations which is entropically favorable (Figure 1b). Upon adding a guest, such as an anion that forms strong H-bonds[22c,25] with the backbone amide protons, the entropic barrier for adopting a single conformation is overcome by the enthalpic contribution from the multiple H-bonds between the guest and the oligoamide host. As a result, the equilibrium is shifted toward complex **H•G**, resulting in a folded comformation for **H**.

Scheme 1.



Note: For **B2a** and **B2b**: RCOCl (2.1 equiv). For **B2c**: (i) RCOCl (1.05 equiv); (ii) CH$_3$COCl (1.2 equiv)

In contrast to **A** and other oligoamides which can be synthesized based on established amide chemistry, oligoamides **H**, consisting of 5-amino-*N*-acylanthranilic acid residues, cannot be obtained by using known methods. It was reported that,[26] when being treated with acylating or coupling reagents, anthranilic acid and its *N*-acylated derivatives self-cyclize into derivatives having a (4*H*)-3, 1-benzoxazin-4-one (or benzoxazinone) core, which prevents amide coupling from happening.

Indeed, treating 5-nitro-anthranilic acid **B1** with two or more equivalents of decanoyl or trimethylacetyl chloride gave benzoxazinone derivatives **B2a** or **B2b** (Scheme 1). Similarly, compound **B2c** was obtained by converting **B1** into the corresponding 5-nitro-*N*-acylanthranilic acid which was then treated with acetyl chloride. The ^{1}H NMR spectra of **B2a-c** reveal the same benzoxazinone core (Figure S1). The identities of these compounds are also verified with ESI-MS spectra (Figure S2).

Single crystals of **B2b** were obtained from hexane/ethyl acetate (1/2, v/v) by slow evaporation of solvents at room temperature. The X-ray structure of **B2b** confirms that acid **B1** was converted into the benzoxazinone derivative by treating with trimethylacetyl chloride (Figure 2a).

While anthranilic acid or its *N*-acyl derivatives cannot directly couple with other amines due to self-cyclization, benzoxazinone **C** and its derivatives do react with amines via two routes (Figure 3a).[27] One involves nucleophilic attack at carbon C-1, leading to ring-opening product **C'**; the other involves attacking C-2 to give quinazolinone **C''**. Steric factors determine the outcome of a reaction.[27] With bulky R and/or R', the desired ring-opening of **C** happens, forming product **C'** having an acylamino (RCONH-) sidechain and a new amide bond; with small or slim R and/or R' that do not impose significant steric hindrance, carbon C-2 is attacked to give **C''** with no amide bond.

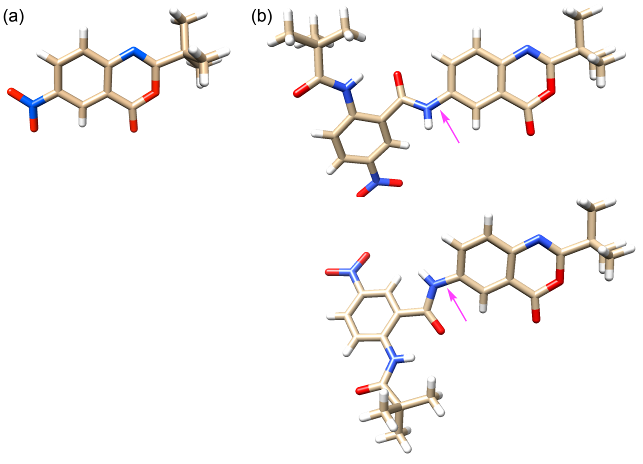


Figure 2. (a) X-ray structure of compound **B2b**. (b) X-ray structure of compound **2b'** reveal two conformations related by rotation around the single bonds as indicated by magenta arrows.

Compound **B2a** and **B2b** carrying an *n*-octyl and a *t*-butyl side chains, respectively, were treated with *n*-octylamine (Figure 3b). The reaction of **B2a** and *n*-octylamine afforded quinazolinone **B3** in 58% yield, while the reaction of **B2b** and *n*-octylamine led to the ring-opening product **1b** nearly quantitatively. The molecular weights of **B3** and **1b** are confirmed by mass spectra (Figure S3). ^{1}H NMR spectra (Figure S4) reveal two amide signals at 6.33 and 11.79 ppm for **1b**, with no amide signal observed with **B3**. Thus, to ensure the formation of the amide bond and the release of the acylamino side chain, as observed with amide **1b**, a bulky R group, like that of **B2b**, with a tertiary α-carbon should be present.

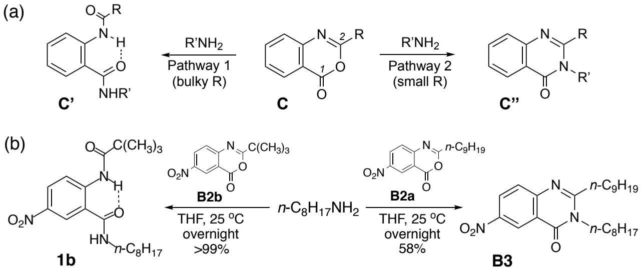
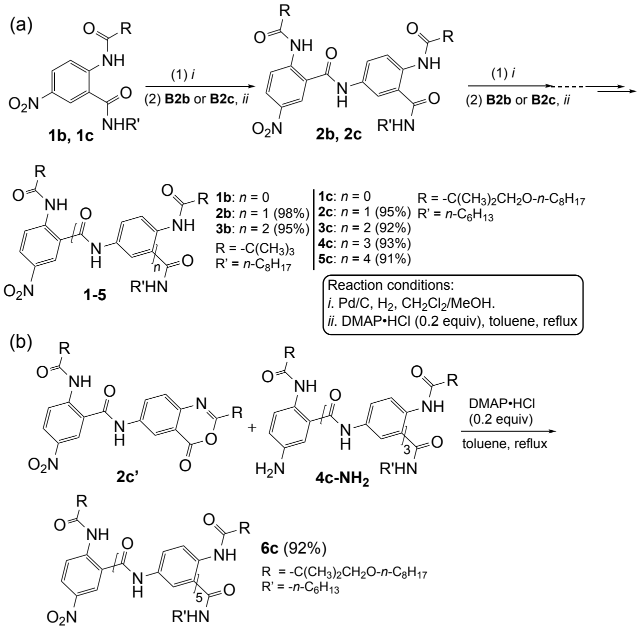


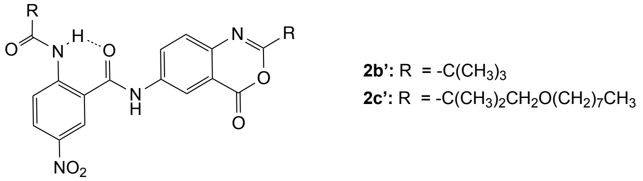
Figure 3. (a) Two outcomes for the ring-opening reactions of (4H)-3, 1-benzoxazine-4-one C with a nucleophile such as an amine. (b) Treating n-octylamine with compounds B2a and B2b, respectively, gives products B3 and 1b.

Based on the observation made with **B2b**, the synthesis of oligoamides having the backbone of general structure **H** was probed (Scheme 2a). Treating **B2b** and the amine derived from **1b** in the presence of 4-dimethylaminopyridine hydrochloride (DMAP•HCl) gave dimer **2b** in 98% yield. Reducing **2b** to its corresponding amine followed by coupling with **B2b** gave trimer **3b** in 95% yield. However, coupling **B2b** to the amine from trimer **3b** led to a poorly soluble product, presumably the corresponding tetramer, that defied characterization. Dimer **2c** to pentamer **5c** carrying sidechains having a quaternary α-carbon and an *n*-octyloxy tail were obtained >90% yields by stepwise coupling of **B2c** to the amine precursors under the same conditions. Oligoamides **2c** to **5c** showed good solubility in solvents including chloroform and DMSO.

Scheme 2.



Dimeric **2b'** and **2c'**, each having a benzoxazinone moiety, were also prepared (Scheme S4) and charcterized (Figure S5). The solid-sate structure of **2b'** confirms the presence of the benzoxazinone moiety (Figure 2b), in which two conformations related by ~180° rotation around the single bond between the benzoxazinone unit and the rest of the molecule, are revealed.



Under the same conditions for coupling **B2b** or **B2c**, treating **2c'** and tetramer amine **4c-NH₂** gave hexamer **6c** in 92% yield (Scheme 2b). The synthesis of **2b**, **3b**, and **2c**-**6c** indicates that our strategy, which involves repetitive coupling of benzoxazinone monomers **B2b** and **B2c**, or oligomers **2c'** and **4c-NH₂**, to a growing oligomer chain, represents a new, highly efficient method for forming amide bonds. This method, which involves refluxing without any coupling reagent, is straightforward and convenient for synthesizing these new aromatic oligoamides.

The interaction of the obtained oligoamides with anions was explored by titrating **4c** or **6c** with tetra-*n*-butylammonium (n-Bu_4N^+) chloride or iodide in $CD_3CN/CDCl_3$ (1/9, v/v). The signals of the backbone amide protons of **4c** exhibit downfield shifts with 0 to 2.0 equivalents of n-$Bu_4N^+Cl^-$ or n-$Bu_4N^+I^-$ (Figure S6), based on which association constants (K_a) of 863 ± 40 M^{-1} and 399 ± 8 M^{-1} for the binding of chloride and iodide, respectively, with **4c**, are obtained based on a 1:1 binding model. Titrating hexamer **6c** with n-$Bu_4N^+Cl^-$ and n-$Bu_4N^+I^-$ in DMSO-d_6/$CDCl_3$ (1/19, v/v) (Figure S7) gave K_a's of $(2.24 \pm 0.24) \times 10^3$ M^{-1} and $(2.34 \pm 0.12) \times 10^3$ M^{-1}, respectively, based on a 1:1 binding model. In contrast, titrating **4c** with tetra-*n*-butylammonium tetraphenyl borate (n-$Bu_4N^+Ph_4B^-$), which cannot form H-bond, did not lead to any shift in the amide proton resonances (Figure S8). These results demonstrate that **4c** and **6c** indeed bind anions like chloride and iodide.

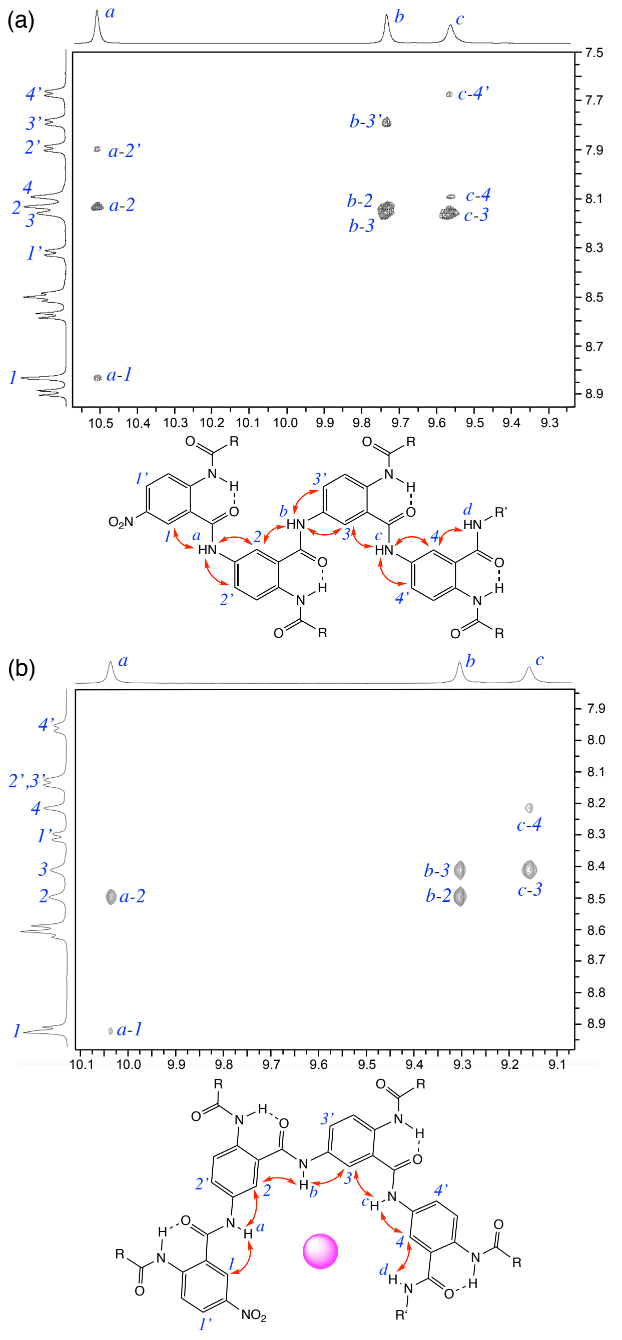


Figure 4. Partial NOESY spectra of (a) **4c** (5 mM) and (b) **4c** (5 mM) and tetrabutylammonium iodide (5 mM) in $CDCl_3$ containing 5% DMSO-d_6 (500 MHz, 25 °C, mixing time = 0.4 s). The observed NOEs are indicated by double-headed arrows.

The conformational change of tetramer **4c** upon binding anions was probed by comparing the 2D (NOESY) spectrum of **4c** in the absence and presence of one equivalent of n-$Bu_4N^+I^-$. In $CDCl_3$ containing 5% DMSO-d_6, the NOESY spectrum of free **4c** reveals three NOEs involving each of amide protons *a*, *b*, and *c* and its neighboring aromatic protons (Figure 4a). Among the NOEs, those involving protons *a* and *1*, *b* and *2*, and *c* and

3, along with that between protons *d* and *4* (Figure S9), are expected because of the presence of the intramolecular H-bond between each backbone amide carbonyl group and the adjacent NH group of the sidechain. In addition, two NOEs involving amide proton *a*, *b*, or *c,* and the two "outer" (protons *1'-3'*) and "inner" (protons *1-3*) aromatic protons are observed, consistent with the expected rotation of each (CO)NH-aryl single bond in **4c** (Figure 4a). These observed NOEs indicate that, due to the rotation of the (CO)NH-aryl bonds, oligoamide **4c** most likely adopes random conformations roughly represented by the zigzagged structure in Figure 5a.

Like that of free **4c**, the NOESY spectrum of **4c** with 1 equiv. of n-$Bu_4N^+I^-$ (Figure 4b) also contains NOEs between protons *a* and *1*, *b* and *2*, *c* and *3*, along with *d* and *4* (Figure S10), consistent with the presence of the intramoleculart H-bonds. The NOEs involving amide protons *a*, *b*, and *c*, and the "outer" proton *2*', *3*', and *4*', which are observed with free **4c**, are absent in the presence of n-$Bu_4N^+I^-$. In contrast, a strong NOEs involving each of these amide protons and the "inner" aromatic proton *2*, *3*, or *4* is detected. Similar to n-$Bu_4N^+I^-$, mixing n-$Bu_4N^+Cl^-$ with **4c** also results in significant weakening or disappearance of NOEs involving the backbone amide and outer aromatic protons, while NOEs involving backbone amide protons and "inner" aromatic protons are strengthened (Figure S11). The observed NOEs between the amide and inner aromatic protons in the presence of iodide or chloride ion indicate that anion-binding and anion-induced folding is a general behavior of **4c** and, similarly, its homologous oligoamides.

The fact that only NOEs between amide protons *a*, *b*, and *c* and inner aromatic protons *1*, *2*, *3*, and *4* are evident in the presence of iodide or chloride ion demonstrates that, upon binding an anion, oligoamide **4c** adopts a conformation in which its backbone amide NH groups point convergently, i.e., being placed on the same side as the inner aromatic protons. This is consistent with the adoption of the crescent conformation shown in Figure 4b. The entropic cost for adopting such a conformation is compensated by the enthalpic contribution from the multiple H-bonding interactions between the anion guest and the backbone amide and aromatic protons.

The NOESY spectra of hexamer **6c** in DMSO-d_6/$CDCl_3$ (1/19, v/v) without and with iodide (Figures S12-14) revealed changes in NOEs similar to those observed with **4c**, suggesting that, hexamer **6c** has a crescent backbone, i.e., folds into an overall helical conformation upon binding iodide.

A new, highly efficient amide bond formation strategy has been established. Repetitive coupling of readily available building blocks derived from 5-aminoanthranilic acid led to oligo(5-amino-*N*-acylaminoanthranilic acids) with defined lengths in high yields. These are hitherto unknown aromatic oligoamides due to the unavailability of methods for their synthesis. The stepwise coupling of monomeric or oligomeric units allows oligoamides of defined lengths to be prepared under simple conditions that involve refluxing without any coupling reagent. Initial studies indicate that the resultant aromatic oligoamides, with multiple amide NH groups, undergo anion-dependent folding. Given their ready synthetic availability and tunable oligomer length, these novel aromatic oligoamides with multiple H-bond donors, provide a new, versatile platform for developing guest-dependent foldamers or binders of anions and other polar guests, with adjustable affinity and specificity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supporting figures, synthetic procedures, experimental conditions, analytical data, additional NMR spectra, and mass spectra can be found in the Supplementary Information, which is available free of charge on the ACS Publications website.

Accession Codes

CCDC 2018977 (for **2b'**) and 2018978 (for **B2b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the National Science Foundation (CHE-1905094 to BG).

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