Synthesis and Supramolecular Characterization of Cyclic β-Aminoketones

By

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Biochemistry

Submitted in partial fulfillment
of the requirements for the degree of

Bachelor of Science (Honors)

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Abstract

This thesis describes the synthesis and supramolecular characterization of cyclic β-aminoketones, specifically 1-aza-adamantanetriones (AATs) and N-substituted-4-piperidones. These types of molecules contain a donor-σ-acceptor framework able to experience hyperconjugation between the nitrogen’s lone pair of electrons and the π* orbital of the carbonyl via the saturated spacer; this through-bond interaction (TBI) affects various electronic properties of these molecules including the development of a significant dipole and the emergence of a signature UV-active electronic transition. These manifestations of the TBI have particular significance for supramolecular studies and render cyclic β-aminoketones promising candidates for supramolecular scaffolds. Chapter 1 describes the basis of the TBI for the β-aminoketones, Chapter 2 describes efforts and successes towards the synthesis of AATs capable of forming molecular assemblies, and Chapter 3 describes the preliminary results for using N-substituted-4-piperidones in sensing applications.
Acknowledgements

My sincerest thanks and appreciation is extended to Professor Ronald K. Castellano, whose time, mentorship, and insight have afforded me such a rich and rewarding research experience.

Additional thanks is extended to the entire Castellano group, both past and present, for their support. In particular, I want to thank Pamela Cohn for her advice and numerous fruitful discussions and Matthew Baker, who has been a spectacular mentor with an unrivaled patience for my endless questions, a trait I greatly admired and hope to one day emulate. This work was made possible by the substantial time and effort these individuals have invested in helping me navigate the tortuous path to becoming a scientist, and I thank them.
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3 – 8 Potential synthetic manipulations of para-nitro $\alpha$-methylbenzylamine (±)-3-9
Chapter 1: Introduction to cyclic β-aminoketones

Supramolecular chemistry is the study of non-covalent interactions and their use in directing molecules into structurally and chemically complex systems. The implementation of such interactions to form non-covalent assemblies with properties unique from the component molecules is inspired by biology; examples include cellular membranes, proteins, and DNA. The non-covalent forces inherent to these biological structures, including hydrogen bonding, dipole-dipole, π-π, ionic, and van der Waals interactions, have been employed in the pursuit of synthetic supramolecular architectures. A distinct interaction, not often used in nature nor in synthetic systems to develop non-covalent assemblies, is the through-bond interaction (TBI) of a donor-σ-acceptor framework.

The donor-σ-acceptor framework is defined by an electron donor that communicates with an electron acceptor via a saturated spacer. The two groups are able to interact with one another the strongest when in an antiperiplanar alignment since the orbitals in this arrangement have the proper symmetry to interact through the σ* orbitals of the intervening saturated spacers (e.g., Figure 1-1). The TBI is observed most readily in systems where the donor is a high-lying HOMO, often non-bonding, and the acceptor is a low-lying LUMO, often anti-bonding. For these matched cases, the TBI stabilizes the system and causes a variety of electronic effects on the molecule including attenuation of nucleophilicity and distortion of bond lengths. Two additional manifestations of the TBI include the development a significant dipole and the emergence of a signature charge-transfer UV-active transition; these directing and reporting capabilities of the donor-σ-acceptor framework make it an attractive core for the development of novel supramolecular scaffolds.
β-Aminoketones are a common class of donor-σ-acceptor molecules,\textsuperscript{12-16} where the nitrogen’s lone pair of electrons is the donor and the $\pi^*$ orbital of the carbonyl is the acceptor (Figure 1-1). The multiple electronic effects from the TBI of the donor-σ-acceptor motif present numerous opportunities for using β-aminoketones in supramolecular studies. To enhance the effects from the TBI, the β-aminoketone can be incorporated into a cyclic structure, limiting the conformational flexibility of the system. Since the TBI is sensitive to the geometry of the interacting groups, the rigidity of the resulting cyclic β-aminoketones is expected to lead to an enhanced TBI, resulting in a corresponding enhancement of the electronic effects including the dipole. The directionality and strength of this dipole could be used to direct self-assembly for these types of cyclic compounds.\textsuperscript{12} Furthermore, the charge-transfer UV-active transition associated with the TBI is believed to arise from an electron transfer between the nitrogen and the carbonyl motifs; the strength of this transition follows the same geometric dependency as the TBI and thus the geometry of the β-aminoketone can be probed via spectroscopic techniques.\textsuperscript{12-16} The ability to differentiate between TBI-active and TBI-inactive conformations/configurations of the cyclic β-aminoketones makes these molecules potentially useful for sensing applications.
Chapter 2: Synthesis and supramolecular characterization of tri-α-amido 1-aza-adamantanetriones

Introduction

1-Aza-adamantanetriones (AATs)\textsuperscript{17-19} are model cyclic β-aminoketones for studying the donor-σ-acceptor framework;\textsuperscript{9,20} the constrained bridgehead nitrogen’s lone pair of electrons is properly aligned to interact with the \( \pi^* \) orbitals of the carbonyls via the two-carbon spacers (Figure 2-1a). This hyperconjugative effect decreases the nucleophilicity and basicity of the nitrogen’s lone pair of electrons,\textsuperscript{21} alters bond lengths, and gives rise to a signature UV signal.\textsuperscript{22} The shape persistence of the core and the dipole from the through-bond interaction (TBI), two common elements found in self-assembling molecules, make the AATs prime candidates for incorporating the donor-σ-acceptor framework into a self-assembling molecule. Furthermore, the ability to append peripheral functionality allows for the introduction of additional directing groups to facilitate this self-assembly.

![Figure 2-1](https://example.com/figure21.png)

Figure 2-1. The (a) AAT core,\textsuperscript{17-19} (b) 1\textsuperscript{st} generation AATs,\textsuperscript{23} and (c) tri-α-amido AATs.\textsuperscript{22-26}

Achieving an AAT supramolecular architecture is desirable because of the implication that the assembly could have organoelectronic applications. If a one-dimensional array of AATs was realized via judicious choice of peripheral functionality (e.g., Figure 2-2), computational studies\textsuperscript{27} suggest that the HOMO-LUMO gap of the entire assembly could be lowered into the semi-conducting regime. This property emerges, along with a delocalization of individual AAT
molecular orbitals over the entire assembly, as the AATs self-assemble into a periodic one-dimensional array. The individual AAT molecules do not exhibit this electronic property; only when the molecules assemble into an infinite one-dimensional array does this property emerge. Such a low band-gap supramolecular structure from a donor-σ-acceptor framework would be fundamentally different from, and complementary to, the current forerunners of the field, π-conjugated materials. The potential emergent electronic properties of an AAT supramolecular structure continue to inform and encourage exploration of the AAT chemistry.

![Figure 2-2. Schematic of possible one-dimensional self-assembly of tri-α-amido AATs.
Atom designations are dark blue = nitrogen, light blue = carbon, white = hydrogen, red = oxygen.](image)

Our efforts\textsuperscript{24} at developing a self-assembling AAT have not yet achieved the coveted goal of the one-dimensional array, but they have led to: (1) the development of a library of AAT molecules with functionality not present in previous derivatives, (2) the discovery of AAT organogelators with the highest gel stability for these molecules to date, (3) the exploration of macro- and nano-scale gel morphology via transmission and scanning electron microscopy along with polarized optical microscopy, and (4) the development of a new post-cyclization functionalization approach for accessing more diverse AAT derivatives.

**Previous Work**

Previous work in the Castellano lab\textsuperscript{22,23,25,26} has demonstrated the feasibility of using substituted AATs as novel scaffolds for supramolecular applications. A variety of simple aryl-
substituted AATs were obtained\textsuperscript{22,23} from phloroglucinol precursors via a triple Mannich-type cyclization with hexamethylenetetramine (HMTA) first described by Risch et al.\textsuperscript{17-19} (where R = H in Figure 2-3). The AAT with unsubstituted peripheral phenyl groups acted as an organogelator (0.50 \( \% \)wt) in both DMSO and CHCl\(_3\), indicative of a molecular assembly (Figure 2-1b).\textsuperscript{23} This supramolecular behavior encouraged further studies into obtaining AATs with more complex functionality to both enhance and direct the self-assembly of these molecules.

![Figure 2-3. The triple Mannich-type cyclization of phloroglucinol derivatives yielding the AATs.](image)

Efforts towards the synthesis of more elaborate AATs quickly led to the incorporation of \( \alpha \)-amido linkages (Figure 2-1c).\textsuperscript{26} The resulting tri-\( \alpha \)-amido AATs are insoluble in most common solvents, with limited improvement upon incorporation of lengthy alkyl chains, but they display enhanced aggregation in chlorinated solvents compared to previous derivatives. The enhanced aggregation and general insolubility of these molecules is attributed to the presence of an intramolecular hydrogen bonding framework composed of a 7-membered ring between the amide hydrogens and the carbonyls of the AAT core. Intermolecular hydrogen bonding is also possible in these systems, which would further enhance assembly. Additionally, the opposing dipoles of the amide and AAT core lead to favorable electrostatic interactions. The aforementioned effects of the tri-\( \alpha \)-amido AATs are believed to cause the macroscopic event of organogelation by stabilizing both the self-assembling AAT conformer and the TBI of the core.\textsuperscript{26}

The initial synthetic route to the tri-\( \alpha \)-amido AATs began with commercially available 1,3,5-trimethoxybenzene (Figure 2-4).\textsuperscript{22,23,25,26} After tribromomethylation of 1,3,5-
trimethoxybenzene, the bromides were displaced with cyanide, yielding compound 2-2. A subsequent hydrolysis led to tricarboxylic acid 2-3. Upon formation of the acid chloride from 2-3, the reactive intermediate was captured with aniline derivatives, generating 2-4. After deprotection to the phloroglucinol using BBr₃, a subsequent Mannich-type cyclization with HMTA yielded substituted AAT derivatives 2-5.

![Figure 2-4. The initial synthetic route to the tri-α-amido AATs.](image)

This route to the tri-α-amido compounds prevented many functional groups from being appended to the AAT periphery due to the need for harsh deprotection conditions after introduction of the side arms. To overcome the general limitations imposed by BBr₃ deprotection, a common intermediate for accessing the α-amido phloroglucinol and corresponding AATs was developed: benzotrifuranone (BTF, 2-7 in Figure 2-5). BTF has opened up AAT chemical space since its synthesis does not require deprotection conditions after addition of the peripheral functionality.
The synthesis of BTF follows a similar course to that of the previous route to the tri-α-amido AATs (Figure 2-5). Starting from compound 2-2, concomitant deprotection of the methoxy groups and hydrolysis of the nitriles is accomplished in a single operation with refluxing HBr. Subsequent dehydration of 2-6 with poly-phosphoric acid yields cyclized BTF 2-7. The side arms are then simply appended upon addition of the free amine; favorable production of the amide bond and stable conjugate base (a substituted phenol) precludes the need for additional coupling reagents. Furthermore, since the peripheral functionality is introduced after the harsh deprotection conditions, delicate side arms can now be appended.

![Figure 2-5. The synthesis of benzotrifuranone (BTF) starting from compound 2-2.](image)

**Design**

The successful design of a self-assembling AAT hinges on the choice of peripheral functionality because the TBI alone has not been shown to be an adequate driving force for one-dimensional self-assembly. Although the introduction of the α-amido linkages has enhanced the assembly of these molecules, the ordering is still not fully understood nor characterized. With the recent development of the BTF intermediate, a cornucopia of functionality has become available for further study of AAT assembly.

Initial work has focused on the implementation of aromatic side arms; aryl groups are known for the easy systematic perturbation of their π-system electronics and facile manipulation of their chemical structure. In conjunction with the directing effect of the π-systems, lengthy
alkyl chains were included in the design of the first derivatives in aims of enhancing solubility and encouraging microsegregation between the domains of the AATs: core, amides, \( \pi \)-systems, and alkyl chains. The goal is to optimize this microsegregation to such an extent that a liquid-crystalline state emerges. If such a one-dimensional liquid crystalline phase was realized, the consequences could include not only the attainment of the elusive low-band gap supramolecular architecture for the AATs and rigorous characterization of the assembly, but also self-healing properties characteristic of liquid crystalline phases. The use of such ordered phases for organic optoelectronic applications is well documented and provides inspiration for future directing groups of AAT self-assembly.\(^6\,7\)

**Synthesis**

Efforts towards formation of AAT derivatives with \( \pi \)-systems and lengthy alkyl chains commenced with the synthesis of di-dodeoxy and di-hexoxy aniline derivatives following literature precedent (Figure 2-6).\(^{30\,31}\) From commercially available catechol, the respective alkyl chain was appended via etherification of the corresponding alkyl bromide (2-8a,b). Nitration was performed on 2-9a,b under standard conditions, followed by hydrogenation of nitrated 2-10a,b with Pd/C and \( \mathrm{H}_2 \), yielding aniline derivatives 2-11a,b. The low yields from this reduction could arise from ligation of the resulting nitrogens to the palladium catalyst, thus preventing further turnovers of the substrate. When 2-11a,b were reacted with BTF, phloroglucinols 2-12a,b were obtained in acceptable yields; however, when the cyclization was attempted, no AAT formation was detected for either of the compounds. Despite the previous reaction of the para-dodecyl phloroglucinol derivatives\(^{26}\) under similar conditions, the steric bulk of the three di-alkyl side chains is believed to have shielded the phloroglucinol core from reacting with HMTA.
Additionally, rigorous purification of the phloroglucinols was challenging due to their waxy nature, potentially leaving impurities that led to degradation.

\[
\begin{array}{c}
\text{OH} & \text{OH} \\
\text{2-6} & \text{2-7} \\
\text{a} & \text{a} \\
\text{b} & \text{b} \\
\text{R = C}_2\text{H}_{25} & \text{R = C}_9\text{H}_{13} \\
\text{K}_2\text{CO}_3 & \text{HNO}_3 \\
\text{DMF} & \text{NaNO}_2 \\
\text{85 \%} & \text{65 \%} \\
\text{2-9} & \text{2-10} \\
\text{2-11} & \text{2-12} \\
\text{a} & \text{a} \\
\text{b} & \text{b} \\
\text{40 \%} & \text{24 \%} \\
\text{10\% Pd/C} & \text{BTF (2-7)} \\
\text{258^\circ C} & \text{MeOH} \\
\end{array}
\]

Figure 2-6. Attempted synthesis of AATs with lengthy peripheral alkyl chains.

Having encountered difficulties in accessing the lengthy alkoxy substituted tri-\(\alpha\)-amido AATs, the study proceeded on to a more fundamental investigation into the structure-activity relationship of the peripheral aryl groups. Specifically, an exploration into the effects of the peripheral \(\pi\) systems both on the assembly of individual AATs and the assembly of mixtures of AATs with complementary electronics was initiated.

Starting from BTF, a series of electron-rich and electron-deficient phloroglucinols were synthesized, as shown in Figure 2-7. BTF was first dissolved in an aprotic solvent (e.g., THF or toluene) and then treated with an excess of nucleophile, mainly aniline derivatives. The vessel was heated to the range of 60 to 110 \(^\circ\)C depending on the nucleophilicity of the aniline (the electron-deficient compounds were drastically less nucleophilic than the parent aniline compound). Unreacted nucleophile could be retrieved through simple extraction and purification.
procedures, and some of the phloroglucinol derivatives, 2-13a,e,g,h, precipitated from solution, allowing facile collection and subsequent purification; phloroglucinols 2-13b,c,d,f,i,j,k,l were purified with chromatography.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Yield (2-13)</th>
<th>Yield (2-14)</th>
<th>Entry</th>
<th>Nucleophile</th>
<th>Yield (2-13)</th>
<th>Yield (2-14)</th>
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<tr>
<td>i</td>
<td>H₂N</td>
<td>78% (2-13a)</td>
<td>75% (2-14a)</td>
<td>viii</td>
<td>H₂N</td>
<td>76% (2-13g)</td>
<td>35% (2-14g)</td>
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<tr>
<td>ii</td>
<td>H₂N</td>
<td>56% (2-13b)</td>
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<td>viii</td>
<td>H₂N</td>
<td>68% (2-13h)</td>
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<tr>
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<td>H₂N</td>
<td>78% (2-13c)</td>
<td>53% (2-14c)</td>
<td>ix</td>
<td>H₂N</td>
<td>55% (2-13i)</td>
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<td>H₂N</td>
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<td>11% (2-14d)</td>
<td>x</td>
<td>H₂N</td>
<td>25% (2-13j)</td>
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<tr>
<td>v</td>
<td>H₂N</td>
<td>33% (2-13e)</td>
<td>53% (2-14e)</td>
<td>xi</td>
<td>H₂N</td>
<td>36% (2-13k)</td>
<td>– (2-14k)</td>
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<tr>
<td>vi</td>
<td>H₂N</td>
<td>91% (2-13f)</td>
<td>40% (2-14f)</td>
<td>xii</td>
<td>H₂N</td>
<td>40% (2-13l)</td>
<td>– (2-14l)</td>
</tr>
</tbody>
</table>

a.) Entries i,v, vii, and viii had 9 equiv of nucleophile added to 1 equiv of BTF in toluene at reflux 16 – 48 hours
b.) AATs were formed with 1.5 – 3 equiv HMTA in i-PrOH at reflux 16 – 120 hours
c.) Entries ii, iii, and iv had 9 equiv of nucleophile added to 1 equiv BTF in THF at reflux 16 – 72 hours
d.) Entry ix had 6 equiv of nucleophile added to 1 equiv BTF in DMF at 120 °C for 24 hours
e.) Entries xi and xii AAT formation displayed no reaction for 5 days

Figure 2-7. Synthesis of a library of electron-rich and electron-poor phloroglucinol and AAT derivatives.
Some of the phloroglucinol-forming reactions produced precipitates that were actually intermediates—substituted once or twice ring opened BTF. For example, despite the predicted nucleophilicity of 3,5-dimethoxyaniline, the twice-opened BTF was isolated as a major product owing to its insolubility; several nights in THF at reflux were required to form an appreciable amount of the desired phloroglucinol. Other derivatives with electron-deficient peripheral π-systems, such as 2-13k and 2-13l, also required the more polar solvent THF to keep the intermediates soluble. The insolubility of these phloroglucinol derivatives is attributed to the increased strength of the hydrogen bonding network and the stronger π-stacking between the molecules. Attempts at using more polar solvents, such as DMF, for the ring-opening reaction often led to poor yields and incomplete conversion, a subject of continuing investigations. These effects demonstrate the delicate balance between introducing intermolecular forces to enhance AAT assembly and overcoming the resulting undesirable effects on solubility and reactivity.

The obtained phloroglucinol derivatives were continued on to their respective AATs via the aforementioned cyclization conditions. As a general procedure, the phloroglucinol was stirred in 2-propanol with 1.5 – 3 equivalents of HMTA at reflux for 1 to 5 days. The insolubility of the phloroglucinol derivatives required these lengthy reaction times, but the AAT was then easily collected via vacuum filtration after washing. The inability of some of the electron-deficient species (2-13k and 2-13l) to cyclize to the AAT can be ascribed to issues of insolubility (vide supra), since only starting material was recovered.

Supramolecular Characterization

Organogelation studies were initiated to investigate the effect of the peripheral electronics on the assembly behavior of the AATs. The AAT derivatives were insoluble in most
processable solvents, excluding DMF, DMSO, and pyridine; however, compounds 2-14e,g,j formed stable organogels (as defined by the inverted vial technique\textsuperscript{33-35}) in a limited range of solvents upon heating to an isotropic phase and then undisturbed cooling to room temperature. AAT 2-14e formed an opaque gel in CHCl\textsubscript{3} with only 0.25 – 2.0 wt\% in solution, AAT 2-14g formed a gel in 1,1,2,2-tetrachloroethane (TCE) from 0.20 – 3.0 wt\%, and AAT 2-14j formed a gelatinous phase in toluene and benzene with ranges from 0.20 – 3.0 wt\% (Figure 2-8). Importantly, these gels do not demonstrate degradation over several weeks under ambient conditions.

![Figure 2-8](image)

**Figure 2-8.** Inverted vials of organogels. (A) 0.30 wt\% gel of 2-14e in CHCl\textsubscript{3}, (B) 0.30 wt\% gel of 2-14g in TCE, (C) 0.20 wt\% gel of 2-14j in toluene, (D) 0.30 wt\% gel of 1:1 molar ratio of 2-14e and 2-14g in TCE, (E) 0.25 wt\% gel of 1:1 molar ratio of 2-14e and 2-14g in a mixture of 2:1 CHCl\textsubscript{3}: TCE.

The stability of the organogels was probed via the “dropping-ball” method,\textsuperscript{36} where the temperature ($T_{gel}$) at which the gel phase is transformed to the isotropic solution phase is found
by observing the movement of a steel ball through the gel. A 0.30 wt% solution of **2-14g** in TCE showed a $T_{gel}$ of 110 °C, making it the most thermally stable AAT organogel formed to date. This stability could be due to the forces described previously for electron-deficient peripheral π-systems and/or the morphological findings from the POM data (*vide infra*). The 0.30 wt% solution of **2-14e** in CHCl$_3$ had a $T_{gel}$ measurement of 45 °C, similar to previous AAT derivatives. An important note is that the transition probed by this method did not allow the gel to be reacquired from simple cooling; the solution had to be heated to an isotropic solution and then allowed to cool to reform the stable organogel. Despite the robust thermal stability of these gels, moderate mechanical shock resulted in destruction of the gel, forming instead a loose suspension. Compound **2-14j** demonstrated a different gelation profile, for even though a 0.30 wt% solution in toluene gelled and had a $T_{gel}$ of 72 °C, cooling the gel after the $T_{gel}$ measurement left a gelatinous phase unable to hold up its own weight when inverted.

Now that AATs with electron-rich and electron-deficient π-systems were found to be organogelators, the effect of mixing complementary AATs on gel morphology/formation could be investigated for the first time. An equimolar mixture of **2-14e** and **2-14g** was added to TCE, forming a gel with a critical gelation concentration of 0.30 wt% and a $T_{gel}$ of 55 °C. In a solution of 1:2 (w/w) TCE:CHCl$_3$, a mixed gel was generated with a critical gelation concentration of 0.20 wt%. Of special note is that **2-14g** only gelates TCE at 0.25 wt%, while **2-14e** is soluble in TCE up to 2.0 wt%. Since a gel is still formed below the individual AATs’ critical gelation concentrations, this suggests that the complementary interactions between **2-14e** and **2-14g** enhance the gelation behavior of the mixture. Thus, the possibility of tuning molecular assembly via mixing of complementary AAT molecules has emerged as a potential route to AAT supramolecular architectures.
While exploration of the organogel’s macroscopic properties has provided insight into the assembly of the AAT molecules, information has also been gained from investigation into the nano-level structure of these gels. The gels of 2-14e and 2-14g were freeze-dried and subsequently visualized using transmission-electron microscopy (TEM) to explore the morphological basis for the gelation behavior (Figure 2-9). Each sample demonstrates high-aspect ratio fibers on the order of millimeters, a common occurrence for organogelators and an indicator of a favored axis for molecular assembly. These fibers are in bundles that comprise sheets about 200 nm in width, and display multiple fractures and splinters at the extremes of the sheets. In particular, the mixed gel (Figure 2-9d) shows numerous fractures perhaps due to greater interactions between the AATs with similar electronics than between the AATs with different electronics.

Figure 2-9. Micrographs of freeze-dried gels. TEM images of (A) high-aspect ratio fibers from 2-14e, nanoscale structures of both 2-14e fibers (B) and of 2-14g fibers (C), and aggregates from mixed gel of 1:1 2-14e and 2-14g
Due to the difference in the overall gelation behavior of 2-14j to 2-14e and 2-14g, the nano-level structures were expected to have appreciable differences. The scanning electron micrograph (SEM) of the critical point dried gel sample of 2-14j showed such a difference (Figure 2-10). As can be seen in the figure, the sheets are mostly composed of 5 µm thick lamellar structures with 3 µm fibers entangled in the sheets. The presence of both the sheets and the entangled fibers in a single sample has not been previously reported for AAT organogels and could be the basis for the macroscopic differences for 2-14j organogels.

![Figure 2-10. SEM images of fiber networks for the critical-point dried gels of 2-14j.](image)

The information provided from the TEM and SEM techniques is insightful, but it may not directly reflect the native gel morphology due to the required preparation for imaging. A technique for investigating native gel morphology, albeit with less resolution, is polarized optical microscopy (POM). This technique has shown details of the gel’s structure that were not evident from either the TEM or SEM techniques. The gel of 2-14e shows a uniform distribution of crystalline fibers, while the gel of 2-14g shows a dual morphology, spherulitic crystal growth interspersed with exceedingly long high-aspect ratio fibers (Figure 2-11). The dual morphology could be the reason for the high thermal stability of the 2-14g organogel, perhaps itself a
macroscopic effect of the enhanced $\pi$-interactions of the electron deficient AAT derivatives (vide supra).

The insolubility of the other AAT derivatives in most of the solvents tested for organogelation (e.g., CH$_3$CN, hexane, EtOAc, CH$_3$Cl, CH$_2$Cl$_2$, CHCl$_3$, CCl$_4$, Toluene, TCE) prevented extensive investigation into the effect of the peripheral $\pi$-system electronics on AAT assembly. While promising and insightful results have emerged from this approach to the AATs, the challenges and difficulties of the synthesis and characterization limit the approach’s utility.

Figure 2-11. POM images of the native gel morphologies of 2-14e (top row) and 2-14g (bottom row). The right column of images was taken with the polarizers crossed.

The insolubility of the other AAT derivatives in most of the solvents tested for organogelation (e.g., CH$_3$CN, hexane, EtOAc, CH$_3$Cl, CH$_2$Cl$_2$, CHCl$_3$, CCl$_4$, Toluene, TCE) prevented extensive investigation into the effect of the peripheral $\pi$-system electronics on AAT assembly. While promising and insightful results have emerged from this approach to the AATs, the challenges and difficulties of the synthesis and characterization limit the approach’s utility.
Future Directions

The limitations of the possible functionality on the AAT periphery were originally due to harsh deprotection conditions required to form the phloroglucinol, but now limitations have arisen for the general synthetic strategy to the AATs: adding peripheral functionality and then attempting to cyclize to the AAT. The success or failure of the cyclization has been shown to be dependent on the steric, electronic, and solubility of the phloroglucinol precursors (vide supra). An alternative strategy to overcome these problems is one where a common AAT intermediate with peripheral synthetic handles is first formed and then diverse functionality is added via well-established coupling reactions.

To investigate such a hypothesis, initial work focused on accessing tri-α-amido AATs with synthetic handles (Figure 2-12). The ring-opening of the benzotrifuranone with both allyl and propargyl amines gave acceptable yields of the respective phloroglucinols, 2-15 and 2-17; however, when the phloroglucinol compounds were exposed to the cyclization conditions, the yields of the AATs were quite low. After multiple attempts at optimizing the cyclization conditions, the yields of the AATs were only modestly improved. It became apparent once again that the Mannich-type cyclization can be adversely affected by peripheral functionality.
Due to the aforementioned challenges of accessing the tri-α-amido AATs, a less functionalized AAT intermediate was targeted as a potential precursor for the post-cyclization functionalization approach. Previously reported AAT 2-22 with alkenyl functionality was chosen as a prime candidate; the simple synthetic route from commercially available starting materials and the ample reactions available for alkenes made this an attractive route for post-cyclization functionalization (Figure 2-13).

The synthesis of tri-allyl AAT 2-22 began with the O-allylation of phloroglucinol, 2-19. This reaction produced numerous by-products because there are six available sites for initial
alkylation (both at the enolic carbons and at the oxygens), and then multiple sites for further alkylations. It was found that the best yields of the O-alkylated product were achieved when allyl bromide was added dropwise at room temperature to the previously deprotonated phloroglucinol. After isolating tri-O-allylated product 2-20, a thermal Claisen rearrangement was performed. This reaction led to numerous products which could not be effectively purified. Thus, after removal of the N,N-diethylaniline solvent, the material was continued forward to the cyclization conditions with HMTA in methanol. Fortuitously, the resulting tri-allyl-AAT 2-22 preferentially crystallized out of the reaction mixture upon cooling. The isolation of the desired tri-allyl AAT from the myriad other compounds is likely due to the inability of the “incorrect” compounds to form their respective AAT(s). This inability to cyclize could arise from either an incomplete Claisen rearrangement, leaving alkylated oxygens, or inhibitory dialkylation at the carbons. Either of these cases would prevent the Mannich-type cyclization from occurring to form the insoluble AAT. Despite the low yields (10% from starting materials) and difficulties in purification following this route to tri-allyl AAT 2-22, the rapid access to an AAT with synthetic handles from cheap commercially available starting materials makes this approach a powerful method for the initial foray into the exploration of post-cyclization functionalization.

To begin to investigate the reactivity of the pendant alkene groups, thiol-ene coupling conditions were examined. Thiol-ene chemistry, a so-called “click” reaction, has been shown to be a powerful synthetic transformation, especially for cleanly appending peripheral functionality on supramolecular platforms, and was thus pursued for the tri-allyl AAT compounds.

Before thiol-ene coupling was attempted on 2-22, a model compound was studied (Figure 2-14). Allyl-phenol 2-23 was first tested with 2-mercaptoethanol in TCE at 80 °C with AIBN as
the radical initiator. The reaction was found to give high yields of 2-24, with minimal by-products. When these conditions were tested with the tri-allyl AAT 2-22, the reaction produced numerous products by TLC and NMR analysis. Through the use of preparatory thin-layer chromatography, AAT 2-25 was isolated as one of the many products (10% yield). Although the unoptimized yield is low, most likely due to the instability of the AAT core to the radical conditions, the presence of the desired product is encouraging for future work on using the post-cyclization strategy for obtaining novel AAT derivatives.

![Chemical structures](image)

Figure 2-14. Post-cyclization functionalization with thiol-ene chemistry.

**Conclusion**

The development of the BTF intermediate \(^{29}\) has granted access to a diverse array of 1-aza-adamantanetrones. AATs with electron-rich and electron-deficient peripheral \(\pi\)-systems, not obtainable using previous methodology, have been accessed and their supramolecular consequences explored via organogelation studies. Important information has been gleaned from the use of TEM, SEM, and POM techniques for analyzing the gel morphology at differing levels of resolution, giving nano-level structural information that mirrors differences in the macroscopic properties. The scope of the supramolecular characterization was limited because
some of the electron-deficient phloroglucinol derivatives were unable to be synthesized or cyclized, and many of the AAT derivatives were insoluble in common solvents. Due to the difficulty in cyclizing some of the functionalized phloroglucinols, a new approach was envisioned for accessing even more synthetically diverse AAT compounds: post-cyclization functionalization. This approach, while still nascent, offers a general solution for the obtainment of AAT derivatives that can potentially self-assemble into the desired one-dimensional array for organoelectronic studies.

**Experimental Section**

**General.** Reagents and solvents were purchased from Acros, Aldrich, or Fluka and used without further purification unless otherwise specified; 2-naphthylamine was purchased from Toronto Research Chemicals, Inc. THF and DMF were degassed in 20 L drums and passed through two sequential purification columns (molecular sieves) under a positive argon atmosphere using a custom Glass Contour solvent system (Glass Contour, Inc.). Thin layer chromatography (TLC) was performed on Dynamic Adsorbents, Inc. aluminum backed TLC plates with visualization via UV light or staining. \(^1\)H NMR and \(^{13}\)C NMR were recorded on a Varian Mercury 300, Gemini 300, or an Inova 500 spectrometer. Chemical shifts (\(\delta\)) are given in parts per million (ppm) relative to residual protonated solvent (CHCl\(_3\): \(\delta_H\) 7.27 ppm, \(\delta_C\) 77.00 ppm; DMSO: \(\delta_H\) 2.50 ppm, \(\delta_C\) 39.50 ppm; pyridine: \(\delta_H\) 7.22, 7.58, 8.74 ppm, \(\delta_C\) 123.9, 135.9, 150.4 ppm). Abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). MS spectra (HRMS) were acquired on a Bruker APEX II 4.7 T Fourier Transform Ion Cyclone Resonance mass spectrometer (Bruker Daltonics, Billerica, MA). DSC and TGA thermograms were taken on a Thermal Analysis DSC Q1000 and TGA Q5000, respectively. POM images were recorded by a Leica DFC295 camera using a Leica DMLP microscope.
**Representative gel formation.** 1-Aza-adamanetranitrene 2-14g (5.1 mg, 0.30% by weight) and 1,1,2,2-tetrachloroethane (TCE, 1.71 g) were combined in a sealed vial. The vial was then heated with a heat gun until a homogenous solution was formed. The vial was then allowed to gradually cool to room temperature on the bench top, during which time the gel rapidly formed (ca. 10 min).

**Representative T\textsubscript{gel} determination.** An organogel of 2-14g in TCE with a volume of ca. 2.0 mL was prepared in a vial with a diameter of 10 mm. After the gel had aged for 12 hours at 25 °C, a steel ball with a diameter of 2 mm was placed on top of the gel, the vial was resealed, and placed in an oil bath. The temperature was slowly increased (ca. 0.5 °C/min), and monitored using a thermometer submerged in a vial containing an equal weight of neat TCE also in the oil bath, while observing the position of the steel ball. The temperature at which the ball touched the bottom of the vial was taken as the T\textsubscript{gel} temperature. This experiment was carried out three times, and the T\textsubscript{gel} temperatures obtained were reproducible to within ± 2 °C.

**Representative gel freeze drying procedure.** A vial containing the organogel of 2-14g in TCE was frozen in liquid nitrogen and transferred to a freeze dry system (Labconco FreeZone 4.5 L) overnight.

**Critical point drying (CPD) of 2-14f gels.** Supercritical fluid drying of 2-14f gels was performed in a 3000 psi rated vessel (Parr Instruments). Samples were placed into regenerated cellulose dialysis bags with a pore diameter of 12000 to 14000 MWCO (Fisher Scientific, USA). Samples were placed inside the drying chamber and liquid CO\textsubscript{2} was introduced. Toluene was exchanged with liquid CO\textsubscript{2} over 5~6 solvent exchange steps. After complete solvent removal, the vessel containing the liquid CO\textsubscript{2} was heated via a water jacket and water bath to 50 °C and 1500
psi. At equilibrium, the supercritical CO₂ was released from the vessel at a rate no greater than 4 L/min.

**Dried gel analysis by TEM.** Some of the dried gel was flaked onto a Formvar/Carbon 200 mesh copper grid (Ted Pella, Inc.). The sample was then imaged on a JEOL TEM 200CX.

**Dried gel analysis by SEM.** For all scanning electron microscopy (SEM) experiments, a JEOL JSM 6400 scanning electron microscope was used. Samples were adhered to SEM stubs using conductive copper tape, then sputtered with Au/Pd to improve the resolution of the images. The sputtering current was 45 mA, the Ar pressure was 75 mTorr, and the sputtering time was 60 s. This yielded an Au/Pd film that was ~16 nm thick. The SEM measurements were operated at 15 kV.

**Synthesis of Benzotrifuranone (BTF).** The details of the synthesis of benzotrifuranone (2-7) and 2-1, 2-2, and 2-6 from trimethoxybenzene can be found in reference 29.
To a flame dried round-bottom flask was added pyrocatechol (5.03 g, 45.7 mmol), anhydrous K$_2$CO$_3$ (27.7 g, 200 mmol), and dry DMF (40 mL). The resulting suspension was heated to 80 °C for 45 minutes. 1-Bromododecane (25.4 g, 100 mmol) was then added dropwise over a 5 minute period. Reaction was stirred for 16 hours under argon. The reaction was quenched upon addition of 400 mL ice-water. The resulting aqueous solution was extracted with CH$_2$Cl$_2$ (4 × 100 mL). The organics were collected, dried with MgSO$_4$, and had dry vacuum chromatography performed with CH$_2$Cl$_2$. Solvent was subsequently removed in vacuo yielding a white solid (19.7 g, 97%). Material was continued to the next step without characterization.

To a flame dried round-bottom flask was added 1,2-bis(dodecyloxy)benzene (5.01 g, 11.2 mmol), NaNO$_2$ (0.108 g, 1.56 mmol), and dry CH$_2$Cl$_2$ (100 mL). The reaction mixture was allowed to cool in an ice-water bath for 20 minutes. 15.8M HNO$_3$ (2.15 mL) was subsequently added dropwise to the stirred solution. After one hour, the round-bottom was removed from the ice-water bath and allowed to stir for 45 minutes at room temperature under argon. The solution was washed with water (2 × 100 mL) and saturated NaCl solution (1 × 100 mL). The organic layers were collected, dried with Na$_2$SO$_4$, and had solvent removed in vacuo. The material was dissolved in CH$_2$Cl$_2$ and passed through a plug of silica in dry vacuum chromatography in CH$_2$Cl$_2$. Solvent was removed in vacuo yielding 5.52 g (78%) of

1,2-bis(dodecyloxy)-4-nitrobenzene (2-9a).
product. $^1$H NMR (CDCl$_3$) $\delta$ 0.88 (t, $J = 6.9$ Hz, 6H), 1.26 (s, 28H), 1.55 (s, 8H), 1.85 (m, 4H), 4.07 (t, $J = 6.9$ Hz, 4H), 6.87 (d, $J = 9$ Hz, 1H), 7.72 (d, $J = 2.4$ Hz, 1H), 7.85 (m, 1H).

1,2-bis(hexyloxy)-4-nitrobenzene (2-10b). To a flame dried round-bottom flask was added 1,2-bis(hexyloxy)benzene (2.55 g, 9.20 mmol), NaNO$_2$ (0.0970 g, 1.38 mmol), and dry CH$_2$Cl$_2$ (50 mL). The reaction mixture was allowed to cool in an ice-water bath for 20 minutes. 15.8 M HNO$_3$ (1.75 mL) was subsequently added dropwise to the stirred solution. After 30 minutes, the round-bottom was removed from the ice-water bath and allowed to stir for 35 minutes at room temperature under argon. The solution was quenched with saturated NaHCO$_3$ solution (100 mL), then washed with water (2 × 100 mL) and saturated NaCl solution (1 × 100 mL). The organic layers were collected, dried with MgSO$_4$, and had solvent removed in vacuo, yielding 1.94 g (65%) of product. $^1$H NMR (CDCl$_3$) $\delta$ 0.88 (t, $J = 6.1$ Hz, 6H), 1.30 (m, 8H), 1.45 (m, 4H), 1.81 (m, 4H), 4.03 (q, $J = 6.6$ Hz, 4H), 6.84 (d, $J = 9$ Hz, 1H), 7.69 (d, $J = 2.4$ Hz, 1H), 7.85 (m, 1H).

3,4-bis(dodecyloxy)aniline (2-11a). To a flame dried round-bottom flask was added 1,2-bis(dodecyloxy)-4-nitrobenzene (3.00 g, 6.10 mmol), 10% Pd/C (0.30 g, 10 wt%), and dry THF (100 mL). Three balloon volumes of H$_2$ were used to purge the solution, and the reaction was left stirring for 16 hours under positive H$_2$ pressure. The solids were removed by running through celite, and solvent was removed in vacuo yielding a red/brown oil (3.19 g, 476 mmol). The title compound was loaded onto silica with 1:1 CH$_2$Cl$_2$:hexane, and flash chromatography was performed in 3:1 CH$_2$Cl$_2$:hexane (300 mL). The solvent was removed in vacuo, yielding 1.14 g
(40 %) of product. $^1$H NMR (CDCl$_3$) $\delta$ 0.88 (t, $J = 6.8$ Hz, 6H), 1.26 (s, 28H), 1.56 (s, 8H), 1.77 (m, 4H), 3.91 (m, 4H), 6.20 (m, 1H), 6.29 (m, 1H), 6.73 (d, $J = 8.1$ Hz, 1H).

3,4-bis(hexyloxy)aniline (2-11b). To a flame dried round-bottom flask was added 1,2-bis(hexyloxy)-4-nitrobenzene (1.78 g, 5.50 mmol), 10% Pd/C (0.267 g, 15 wt%), and dry THF (50 mL). Three balloon volumes of H$_2$ were used to purge solution, and the reaction was left stirring for 16 hours under positive H$_2$ pressure. The solids were removed by running through celite, and the solvent was removed in vacuo yielding a brown oil. The crude material was purified using flash chromatography on silica with a solvent system of 1:2 ethyl acetate:hexane with 0.1% triethylamine. The solvent was removed in vacuo, yielding the desired product (0.385 g, 24 %). $^1$H NMR (CDCl$_3$) $\delta$ 0.88 (m, 6H), 1.33 (m, 8H), 1.44 (m, 4H), 1.72 (m, 4H), 3.89 (m, 4H), 6.19 (dd, $J = 2.7$ Hz, 8.4 Hz, 1H), 6.29 (d, $J = 2.7$ Hz, 1H), 6.71 (d, $J = 8.4$ Hz, 1H).

2,4,6-(α-amido(dodec oxyphenyl))-phloroglucinol (2-12a). To benzotrifuranone (0.0687g, 0.280 mmol) in dry THF (10 mL), was added 3,4-bis(dodecyloxy)aniline (0.601 g, 1.30 mmol). The solution was heated to 50 °C, and left stirring under argon for 16 hours. The solvent was then removed in vacuo, yielding an oily substance. Flash chromatography with silica was performed with 1:5 ethyl acetate:hexane after the material was dissolved in CH$_2$Cl$_2$. Flash chromatography
was performed with CH$_2$Cl$_2$ on the fractions collected from the first column. Solvent was removed *in vacuo*, yielding the title compound as a brown oil (0.0511 g, 11%). $^1$H NMR (CDCl$_3$) $\delta$ 0.88 (m, 18H), 1.26 (s, 84H), 1.44 (m, 12H), 1.66 (s, 9H), 1.77 (m, 15H), 3.65 (t, $J$ = 6 Hz, 6H), 3.76 (s, 6H), 3.93 (t, $J$ = 6 Hz, 12H), 6.78 (d, $J$ = 6.6 Hz, 3H), 6.88 (dd, $J$ = 2.4 Hz, 7 Hz, 3H), 7.12 (d, $J$ = 2.4 Hz, 3H), 7.96 (br s, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$ 5.89, 14.35, 22.93, 26.28, 29.60, 29.70, 29.89, 32.17, 69.47, 69.96, 103.34, 107.83, 113.38, 114.44, 130.70, 149.6, 154.13, 172.90, 214.85.

![Structure of 2,4,6-(α-amido(hexoxyphenyl))-phloroglucinol (2-12b).](image)

**2,4,6-(α-amido(hexoxyphenyl))-phloroglucinol (2-12b).** To benzotrifuranone (0.0655 g, 0.270 mmol) in dry THF (10 mL), was added 3,4-bis(hexyloxy)aniline (0.698 g, 2.40 mmol). The solution was heated to 50 $^\circ$C and was left stirring under argon for 2 days. Solvent was removed *in vacuo* yielding an oily substance. Flash chromatography with silica was performed with CH$_2$Cl$_2$ on the crude mixture. The solvent was then removed *in vacuo*, yielding a brown oil (0.194 g, 64%). More stringent purification was desired, so the material was dissolved in minimal acetone, heated, and methanol was added until the solution stopped becoming cloudy. The vessel was allowed to cool in the refrigerator, developing a waxy grey precipitate. This procedure was repeated twice more on the precipitated product after which the solvent was removed *in vacuo*, yielding the purified title compound as a light brown waxy solid (0.0589 g, 20
%). $^1$H NMR (CDCl$_3$) δ 1.01 (m, 18H), 1.40 – 1.70 (m, 48H), 1.89 (m, 12H), 3.90 (s, 6H), 4.04 (m, 12H), 6.89 (dd, $J = 3.6$ Hz, 8.6 Hz, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 7.39 (d, $J = 3.9$ Hz, 1H).

For respective structures of 2-13 and 2-14 series, see above table (Figure 2-7). Synthesis and characterization of compound series 2-13 and 2-14 were also reported in reference 24.
Representative Synthesis of Phloroglucinols from BTF: Synthesis of 2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(3,4-dimethoxyphenyl)acetamide) (2-13e). To a 25 mL round bottom flask equipped with stirbar and reflux condenser was added BTF 2-5 (250 mg, 1.02 mmol) and 4-aminoveratrole (1.40 g, 9.14 mmol) followed by degassed toluene (10 mL). The reaction vessel was placed in an oil bath and heated to reflux overnight under an argon atmosphere. The solution was then cooled to room temperature and the precipitates were removed by filtration and subsequently washed with toluene, ethyl acetate, and hexanes. Compound 2-13e (240 mg, 33%) was obtained as a light brown solid and used without further purification. $^1$H NMR ($d_6$-DMSO) δ 3.70 (m, 24H), 6.88 (d, $J = 8.8$ Hz, 3H), 7.09 (dd, $J = 8.7$, 2.2 Hz, 3H), 7.32 (d, $J = 2.2$ Hz, 3H), 9.53 (s, 3H), 10.12 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) δ 32.25, 55.31, 55.66, 103.38, 104.60, 111.39, 111.94, 132.33, 144.99, 148.46, 153.64, 171.35. HRMS (ESI) calculated for C$_{36}$H$_{40}$N$_3$O$_{12}$ [M+H]$^+$ 706.2607, found 706.2608.

2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-phenylacetamide) (2-13a). The compound was synthesized starting from BTF (150 mg, 0.610 mmol), aniline (283 mg, 3.00 mmol), and DMF (7 mL). The reaction vessel was heated to 120 °C for 15 hours. Upon cooling to room temperature, the reaction mixture was poured into brine (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with 1 M HCl and water, and then dried over Na$_2$SO$_4$. The solvent was removed and the residue was purified by flash column chromatography (1:3 to 1:1 ethyl acetate:hexanes) to yield 2-13a (240 mg, 97%). The spectroscopic data matches the literature. $^{26}$ $^1$H NMR ($d_6$-DMSO) δ 3.71 (s, 6H), 7.05 (t, $J = 7.5$ Hz, 3H), 7.30 (t, $J = 7.8$ Hz, 6H), 7.61 (d, $J = 7.8$ Hz, 6H), 9.32 (s, 3H), 10.21 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) δ 32.4, 103.4, 119.3, 123.4, 128.7, 138.9, 153.6, 171.6.
2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(4-dodecylphenyl)acetamide) (2-13b). BTF (52 mg, 0.21 mmol) was added to a stirred solution of 4-dodecylaniline (405 mg, 1.55 mmol) in THF (5 mL). The reaction vessel was heated to reflux for 16 hours. Precipitates were removed by filtration and washed with hexanes to yield 2-13b (122 mg, 56%) as a white solid. The spectroscopic data matches the literature.\(^{26}\) \(^1\)H NMR (\(d_6\)-DMSO / CDCl\(_3\)) \(\delta\) 0.83 (t, \(J = 6.5\) Hz, 9H), 1.21 (m, 66H), 3.70 (s, 3H), 7.04 (d, \(J = 8.5\) Hz, 6H), 7.46 (d, \(J = 8.5\) Hz, 6H), 9.71 (s, 3H), 10.11 (s, 3H).

2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(4-methoxyphenyl)acetamide) (2-13c). BTF (78 mg, 0.32 mmol) and \(p\)-anisidine (40 mg, 3.2 mmol) were heated to reflux overnight in toluene (5 mL). Isolation of solids from the reaction mixture by filtration and subsequent washing yielded 2-13c (152 mg, 78% yield) as a white powder. \(^1\)H NMR (\(d_6\)-DMSO) \(\delta\) 3.70 (m, 15H), 6.87 (d, \(J = 8.9\) Hz, 6H), 7.50 (d, \(J = 8.9\) Hz, 6H), 9.64 (s, 3H), 10.14 (s, 3H). \(^13\)C NMR (\(d_6\)-DMSO) 32.20, 55.13, 103.41, 113.82, 121.09, 131.83, 153.69, 155.42, 171.42. HRMS (ESI) calculated for C\(_{33}\)H\(_{34}\)N\(_3\)O\(_9\) [M+H]\(^+\) 616.2290, found 616.2283.

2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(3,5-dimethoxyphenyl)acetamide) (2-13d). BTF (150 mg, 0.62 mmol) and 3,5-dimethoxyaniline (1.16 g, 7.57 mmol) were heated to reflux overnight in THF (4 mL). After cooling to room temperature, precipitates were removed by filtration and subsequently washed with ethyl acetate and hexanes. Further isolation of product from the filtrate was possible by column chromatography with a 5% MeOH:CH\(_2\)Cl\(_2\) eluent. The products from both purification methods were combined to yield 2-13d (177 mg, 42% yield) as a light brown solid. \(^1\)H NMR (\(d_6\)-DMSO) \(\delta\) 3.69 (m, 24H), 6.20 (s, 3H), 6.86 (d, \(J = 1.9\) Hz, 6H), 9.13 (s, 3H), 10.10 (s, 3H). \(^13\)C NMR (\(d_6\)-DMSO) \(\delta\) 32.41, 55.03, 95.44, 97.51, 103.31,
140.64, 153.55, 160.42, 171.47. HRMS (ESI) calculated for C$_{36}$H$_{40}$N$_3$O$_{12}$ [M+H]$^+$ 669.2555, found 669.2594.

2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acetamide) (2-13f). BTF (100 mg, 0.41 mmol) and 2,3-dihydrobenzo[b][1,4]dioxin-6-amine (490 mg, 3.2 mmol) were combined in THF (10 mL) and the reaction vessel was heated to reflux overnight. After cooling to room temperature, the solvent was removed in vacuo, and the residue was redissolved in ethyl acetate and washed with 0.1 N HCl, deionized H$_2$O, and then dried over Na$_2$SO$_4$. Remaining solvent was removed in vacuo to yield 2-13f (260 mg, 91%) as a brown solid. $^1$H NMR (d$_6$-DMSO) δ 3.66 (s, 6H), 4.20 (s, 12H), 6.77 (d, $J = 8.6$ Hz, 3H), 6.98 (dd, $J = 8.8$ Hz, 2.2 Hz, 3H), 7.22 (d, $J = 2.2$ Hz, 3H), 9.49 (s, 3H), 10.07 (s, 3H). $^{13}$C NMR (d$_6$-DMSO) δ 32.23, 63.89, 64.14, 103.38, 108.59, 112.69, 116.73, 132.44, 139.48, 142.86, 153.62, 171.32. HRMS (ESI) calculated for C$_{36}$H$_{33}$N$_3$O$_{12}$Na [M+Na]$^+$ 722.1956, found 722.1947.

2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(4-fluorophenyl)acetamide) (2-13g). BTF (100 mg, 0.41 mmol) and p-fluoroaniline (400 mg, 3.66 mmol) were heated to reflux in toluene (10 mL) overnight. The solids were removed by filtration and washed with toluene, ethyl acetate, and hexanes to yield compound 2-13g (180 mg, 76%) as an off-white powder. $^1$H NMR (d$_6$-DMSO) δ 3.69 (s, 6H), 7.14 (t, $J = 8.8$ Hz, 6H), 7.62 (dd, $J = 8.9$, 5.0 Hz, 6H), 9.25 (s, 3H), 10.24 (s, 3H). $^{13}$C NMR (d$_6$-DMSO) δ 32.23, 63.89, 64.14, 103.38, 108.59, 112.69, 116.73, 132.44, 139.48, 142.86, 153.62, 171.32. HRMS (ESI) calculated for C$_{30}$H$_{28}$F$_3$N$_4$O$_6$ [M+NH$_4]^+$ 602.1509, found 602.1528.

2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(4-methylesterphenyl)acetamide) (2-13h). BTF (200 mg, 0.81 mmol) and methyl-4-aminobenzoate (1.80 g, 12.2 mmol) were heated to reflux in THF (10 mL) over two days. The solvent was then removed in vacuo, and the solids
were suspended and sonicated in ethyl acetate, and isolated by filtration to yield compound 2-13h (380 mg, 68%) as a white powder. $^1$H NMR ($d_6$-DMSO) $\delta$ 3.72 (s, 6H), 3.81 (s, 9H), 7.74 (d, $J = 8.8$ Hz, 6H), 7.91 (d, $J = 8.8$ Hz, 6H), 8.85 (s, 3H), 10.42 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) $\delta$ 32.48, 51.86, 103.29, 118.47, 123.79, 130.26, 143.60, 153.57, 165.80, 171.58. HRMS (ESI) calculated for C$_{36}$H$_{34}$N$_3$O$_{12}$ [M+H]$^+$ 700.2137, found 700.2147.

$^{2,2',2''-}$-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(naphthalen-2-yl)acetamide) (2-13i). BTF (86 mg, 0.35 mmol) was dissolved in DMF (5 mL) and heated to 60 °C while sparging the solution with argon. 2-Naphthylamine (450 mg, 3.2 mmol) was added in one aliquot and the reaction was allowed to stir under argon at 120 °C over two nights. The reaction mixture was cooled, poured into ethyl acetate, and washed with 0.1 N HCl, H$_2$O, and brine. The organic layers were dried over Na$_2$SO$_4$ and the solvent was removed in vacuo. The residue was triturated with CH$_2$Cl$_2$ and the insoluble material was removed by filtration and washed to yield 2-13i (130 mg, 55%) as a light tan solid. $^1$H NMR ($d_6$-DMSO) $\delta$ 3.81 (s, 6H), 7.40 (m, 3H), 7.45 (m, 3H), 7.64 (d, $J = 8.6$ Hz, 3H), 7.79 (d, $J = 8.1$ Hz, 3H), 7.83 (d, $J = 8.1$Hz, 3H), 7.86 (d, $J = 8.8$ Hz, 3H), 8.30 (s, 3H), 9.31 (s, 3H), 10.37 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) $\delta$ 32.45, 103.51, 115.52, 120.05, 124.63, 126.38, 127.30, 127.47, 128.33, 129.78, 133.36, 136.51, 153.68, 171.75. HRMS (ESI) calculated for C$_{42}$H$_{33}$N$_3$O$_6$Na [M+Na]$^+$ 698.2262, found 698.2253.

$^{2,2',2''-}$-(2,4,6-trihydroxybenzene-1,3,5-triyl)tris(N-(7-dodecyl-naphthalen-2-yl)acetamide) (2-13j). BTF (26 mg, 0.11 mmol) and 7-dodecyl-2-aminonaphthalene (290 mg, 0.94 mmol) were combined in THF (5 mL) and allowed to stir at reflux overnight. Upon cooling, precipitates formed in the reaction mixture that were removed by filtration and washed to yield 2-13j (30 mg, 25%) as a white powder. $^1$H NMR ($d_5$-pyridine) $\delta$ 0.88 (t, $J = 6.6$ Hz, 9H), 1.32 (m, 54H), 1.68 (m, 6H), 2.73 (t, $J = 7.2$ Hz, 6H), 4.38 (s, 6H), 7.39 (d, $J = 8.7$ Hz, 3H), 7.89 (m, 15 H), 8.63 (s,
3H), 11.74 (s, 3H). $^{13}$C NMR ($d_5$-pyridine) $\delta$ 14.61, 23.26, 29.93, 30.14, 30.22, 30.27, 32.00, 32.44, 36.52, 105.30, 118.31, 121.61, 123.12, 126.89, 128.33, 128.72, 128.77, 131.77, 133.15, 136.82, 140.25, 155.92, 174.34. HRMS (ESI) calculated for C$_{78}$H$_{105}$N$_5$O$_6$Na [M+Na]$^+$ 1202.7901, found 1202.7805.

2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triy]tris(N-(3-cyanophenyl)acetamide) (2-13k). BTF (200 mg, 0.81 mmol) and 3-aminobenonitrile (2.10 g, 17.6 mmol) were heated to reflux in dry, degassed THF over three nights. The reaction precipitates were removed by filtration and washed with hot ethyl acetate and hot i-PrOH to yield 2-13k (175 mg, 36%) as an off-white powder. $^1$H NMR ($d_6$-DMSO) $\delta$ 3.71 (s, 6H), 7.52 (m, 6H), 7.84 (dt, $J$ = 7.0, 2.1 Hz, 3H), 8.08 (s, 3H), 8.83 (s, 3H), 10.40 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) $\delta$ 32.34, 103.29, 111.53, 118.70, 121.72, 123.64, 126.66, 130.22, 139.97, 153.58, 171.57. HRMS (ESI) calculated for C$_{33}$H$_{25}$N$_6$O$_6$ [M+H]$^+$ 601.1830, found 601.1825.

2,2',2''-(2,4,6-trihydroxybenzene-1,3,5-triy]tris(N-(3-nitrophenyl)acetamide) (2-13l). BTF (75 mg, 300 µmol) and 3-nitroaniline (630 mg, 4.6 mmol) were heated to reflux in dry, degassed THF overnight. Precipitates from the reaction were removed by filtration and washed to yield compound 2-13l (80 mg, 40%) as a white powder. $^1$H NMR ($d_6$-DMSO) $\delta$ 3.74 (s, 6H), 7.60 (m, 3H), 7.92 (m, 6H), 8.65 (s, 3H), 8.80 (s, 3H), 10.54 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) $\delta$ 32.38, 103.30, 113.17, 117.58, 125.03, 130.13, 140.35, 147.93, 153.60, 171.60. HRMS (ESI) calculated for C$_{30}$H$_{24}$N$_6$O$_{12}$Na [M+Na]$^+$ 683.1344, found 683.1344.

**Representative Procedure for the Synthesis of AATs from Phloroglucinols: Synthesis of N-(3,4-dimethoxyphenyl)-2-(4,6,10-triioxo-5,7-di-3,4-dimethoxyphenylcarbamoylmethyl-1-aza-tricyclo[3.3.1.13,7]dec-3-yl)-acetamide (2-14e).** To a 10 mL round bottom flask with stirbar and
reflux condenser was added compound 2-13e (125 mg, 0.180 mmol) followed by HMTA (75 mg, 0.53 mmol) and degassed i-PrOH (4 mL). The reaction vessel was then put in an oil bath and allowed to reflux with stirring overnight under an argon atmosphere. The next day the reaction vessel was allowed to cool to room temperature and the precipitates were removed by filtration and washed with i-PrOH (1 mL). The solids were then resuspended in ethyl acetate (10 mL), sonicated, and filtered to yield compound 2-14e (75 mg, 53%) as a slightly tan solid. $^1$H NMR ($d_6$-DMSO) $\delta$ 2.73 (br s, 6H), 3.69 (br s, 18H), 3.93 (br s, 6H), 6.84 (d, $J = 8.8$ Hz, 3H), 7.01 (dd, $J = 8.6$, 1.6 Hz, 3H), 7.27 (d, $J = 1.6$ Hz, 3H), 9.87 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) 33.66, 55.35, 55.73, 70.21, 70.37, 104.08, 110.74, 112.06, 133.07, 144.54, 148.49, 167.15, 198.27. HRMS (ESI) calculated for C$_{39}$H$_{43}$N$_4$O$_{12}$ [M+H]$^+$ 759.2872, found 759.2902.

2,2',2''-((3s,5s,7s)-4,6,10-trioxo-1-azaadamantane-3,5,7-triyl)tris(N-(4-methoxyphenyl)acetamide) (2-14c). To a solution of 2-13c (99 mg, 0.16 mmol) in i-PrOH (5 mL) was added HMTA (60 mg, 0.43 mmol) and the solution was brought to reflux over three nights under argon. Precipitates formed during the reaction were removed by filtration and washed, yielding 2-14c (37 mg, 34%) as a white solid. $^1$H NMR ($d_6$-DMSO) $\delta$ 2.68 (s, 6H), 3.65 (s, 9H), 3.86 (s, 6H), 6.78 (d, $J = 8.7$ Hz, 6H), 7.39 (d, $J = 8.7$ Hz, 6H), 9.81 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) $\delta$ 33.55, 55.10, 70.18, 70.31, 113.69, 120.36, 132.54, 154.88, 167.04, 198.32. HRMS (ESI) calculated for C$_{36}$H$_{37}$N$_4$O$_9$ [M+H]$^+$ 669.2555, found 669.2594.

2,2',2''-((3s,5s,7s)-4,6,10-trioxo-1-azaadamantane-3,5,7-triyl)tris(N-(3,5-dimethoxyphenyl)acetamide) (2-14d). To i-PrOH (5 mL) was added 2-13d (99 mg, 0.14 mmol) followed by HMTA (56 mg, 0.40 mmol) and the reaction mixture was allowed to reflux for two days. After cooling to room temperature, isolation and washing of the precipitates from the reaction yielded 2-14d (11 mg, 11%) as a light orange solid. $^1$H NMR ($d_6$-DMSO) $\delta$ 2.74 (s,
6H), 3.68 (s, 18H), 6.16 (s, 3H), 6.79 (d, J = 1 Hz, 6H), 9.98 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) $\delta$ 25.48, 33.79, 55.03, 70.16, 95.09, 97.10, 140.96, 160.41, 167.63, 198.13. HRMS (ESI) calculated for C$_{36}$H$_{40}$N$_3$O$_{12}$ [M+H]$^+$ 759.2872, found 759.2877.

2',2''-((3s,5s,7s)-4,6,10-trioxo-1-azaadamantane-3,5,7-triy)tris(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acetamide) (2-14f). To a solution of 2-13f (100 mg, 0.15 mmol) in i-PrOH (5 mL) was added HMTA (64 mg, 0.46 mmol) and the reaction vessel was heated to reflux overnight. Precipitates from the reaction mixture were removed by filtration, resuspended in ethyl acetate, and filtered again with washing to yield 2-14f (44 mg, 40%) as a light brown solid. $^1$H NMR ($d_6$-DMSO) $\delta$ 2.70 (s, 6H), 3.89 (s, 6H), 4.19 (d, $J = 6.5$ Hz, 12H), 6.73 (d, $J = 8.6$ Hz, 3H), 6.92 (dd, $J = 8.1$ Hz, 2.2 Hz, 3H), 7.15 (d, $J = 2.2$ Hz, 3H), 9.82 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) $\delta$ 33.61, 63.88, 64.16, 70.32, 70.15, 107.96, 112.10, 116.60, 133.05, 138.95, 142.84, 167.07, 198.25. HRMS (ESI) calculated for C$_{39}$H$_{37}$N$_4$O$_{12}$ [M+H]$^+$ 753.2403, found 753.2398.

N-(4-fluorophenyl)-2-(4,6,10-trioxo-5,7-di-4-fluorophenylcarbamoylmethyl-1-aza-tricyclo[3.3.1.13,7]dec-3-yl)-acetamide (2-14g). To a solution of 2-13g (95 mg, 160 µmol) in i-PrOH was added HMTA (69 mg, 490 µmol) and the mixture was heated to reflux overnight. Removal of the solids by filtration and subsequent washing yielded 2-14g (33 mg, 35%) as a white powder. $^1$H NMR ($d_6$-DMSO) $\delta$ 2.76 (s, 6H), 3.92 (s, 6H), 7.10 (t, $J = 8.8$ Hz, 6H), 7.54 (dd, $J = 8.7$, 5.0 Hz, 6H), 10.07 (s, 3H). $^{13}$C NMR ($d_6$-DMSO) $\delta$ 25.48, 33.61, 70.17, 115.12 (d, $J = 22.3$ Hz), 120.52 (d, $J = 7.7$ Hz), 135.73, 157.71 (d, $J = 238$ Hz), 167.45, 198.25. HRMS (DART) calculated for C$_{33}$H$_{28}$F$_3$N$_4$O$_6$ [M+H]$^+$ 633.1961, found 633.1979.
N-(4-methylesterphenyl)-2-(4,6,10-trioxo-5,7-di-4-methylesterphenylcarbamoylmethyl-1-aza-tricyclo[3.3.1.13,7]dec-3-yl)-acetamide (2-14h). To a solution of 2-13h (42 mg, 60 µmol) in i-PrOH was added HMTA (25 mg, 180 µmol) and the reaction was heated to reflux over three nights. Solids from the reaction mixture were removed by filtration, washed, and dried to yield compound 2-14h (10 mg, 21%) as a slightly tan powder. \(^1\)H NMR (\(d\_6\)-DMSO) \(\delta\) 2.82 (s, 6H), 3.81 (s, 9H), 3.93 (s, 6H), 7.67 (d, \(J = 7.7\) Hz, 6H), 7.88 (d, \(J = 7.4\) Hz, 6H), 10.40 (s, 3H). \(^{13}\)C NMR (\(d\_6\)-DMSO) \(\delta\) 33.81, 51.73, 70.16, 70.37, 118.17, 123.55, 130.15, 143.57, 165.74, 168.05, 198.27. HRMS (ESI) calculated for C\(_{39}\)H\(_{37}\)N\(_4\)O\(_{12}\) [M+H]\(^+\) 753.2402, found 753.2416.

2,2',2''-((3s,5s,7s)-4,6,10-trioxo-1-azaadamantane-3,5,7-triyl)tris(N-(naphthalen-2-yl)acetamide) (2-14i). To a solution of 2-13i (49 mg, 0.072 mmol) in i-PrOH was added HMTA (30 mg, 0.22 mmol) and the reaction mixture was heated to reflux for 120 hours. After cooling, the insoluble material was isolated, triturated with ethyl acetate, isolated by filtration, and washed to yield 2-14i (35 mg, 66%) as a slightly tan solid. \(^1\)H NMR (\(d\_6\)-DMSO) \(\delta\) 2.88 (s, 6H), 4.00 (s, 6H), 7.37 (m, 3H), 7.44 (t, \(J = 7.5\) Hz, 3H), 7.52 (d, \(J = 8.6\) Hz, 3H), 7.80 (m, 9H), 8.29 (s, 3H), 10.24 (s, 3H). \(^{13}\)C NMR (\(d\_6\)-DMSO) \(\delta\) 33.84, 70.28, 70.46, 114.74, 119.80, 124.35, 126.31, 127.19, 127.38, 128.22, 129.54, 133.44, 136.51, 167.61, 198.31. HRMS (ESI) calculated for C\(_{45}\)H\(_{38}\)N\(_4\)O\(_6\)Na [M+Na]\(^+\) 751.2517, found 751.2517.

2,2',2''-((3s,5s,7s)-4,6,10-trioxo-1-azaadamantane-3,5,7-triyl)tris(N-(7-dodecyl-naphthalen-2-yl)acetamide) (2-14j). To a solution of 2-13j (25 mg, 0.021 mmol) in i-PrOH was added HMTA (8.8 mg, 0.063 mmol) and the reaction mixture was allowed to reflux for 120 hours. After cooling, the insoluble material was isolated, triturated with ethyl acetate, again isolated by filtration, and washed to yield 2-14j (17 mg, 65%) as a white powder. \(^1\)H NMR (\(d\_5\)-pyridine) \(\delta\) 0.87 (t, \(J = 6.9\) Hz, 9H), 1.29 (m, 60H), 1.67 (m, 6H), 2.73 (t, \(J = 7.6\) Hz, 6H), 4.37 (s, 6H), 7.38
(d, J = 8.2 Hz, 3H), 7.68 (s, 3H), 7.8 (d, J = 8.5 Hz, 3H), 7.87 (m, 3H), 8.61 (s, 3H), 11.73 (s, 3H). $^{13}$C NMR ($d_5$-pyridine) $\delta$ 14.98, 23.63, 26.75, 28.34, 30.30, 30.33, 30.53, 30.60, 30.65, 32.40, 32.81, 36.90, 72.11, 75.87, 117.39, 121.57, 127.24, 128.55, 129.02, 131.75, 133.74, 140.11, 169.59, 200.21. HRMS (ESI) calculated for C$_{81}$H$_{108}$N$_4$O$_6$Na [M+Na]$^+$ 1255.8167, found 1255.8136.

1,3,5-tri-allyloxybenzene (2-20). To phloroglucinol dihydrate (5.99 g, 47.5 mmol) and anhydrous K$_2$CO$_3$ (52.4 g, 379 mmol) in a round-bottom flask was added dry DMF (125 mL) and the resulting suspension was heated to 50 ºC for 1 hour with vigorous stirring. The vessel was removed from heat and allowed to cool to room temperature. Allyl bromide (16.5 mL, 190.7 mmol) was then added dropwise via an addition funnel while solution was stirring. The vessel was then heated to 55 ºC and left for 12 hours. After this time, the reaction mixture was quenched and diluted with water (500 mL), and extracted with Et$_2$O (5 × 100 mL). The organic layer was washed with water (5 × 100 mL), dried with Na$_2$SO$_4$, and had solvent removed in vacuo, yielding a red oil. The resulting oil was dissolved in CH$_2$Cl$_2$ and flash chromatography was performed with gradient elution: 2.5% ethyl acetate:hexane (800 mL), 5% ethyl acetate:hexane (600 mL), 10% ethyl acetate:hexane (200 mL). Fractions were collected and solvent was removed in vacuo, yielding 7.95 g (68%) of desired product as a yellow oil. $^1$H NMR (CDCl$_3$) $\delta$ 4.50 (m, 6H), 5.35 (m, 6H), 6.04 (m, 3H), 6.13 (s, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$ 68.8, 94.4, 117.7, 133.1, 160.3.
3,5,7-triallyl-1-aza-tricyclo[3.3.1.13,7]decane-4,6,10-trione (2-22). To 1,3,5-triallyloxybenzene (7.98 g, 32.4 mmol) in a clean round-bottom flask was added \( N,N \)-diethylaniline (55 mL) and the solution was heated to 220 °C for 4 hours. After cooling to room temperature, the reaction mixture was poured into ice-cold 1 M HCl (300 mL) and extracted with ether (6 × 100 mL). These combined ethereal extracts were washed with 1.0 M HCl (2 × 150 mL), water (1 × 200 mL), saturated NaHCO\(_3\) solution (1 × 200 mL), brine (1 × 200 mL), and dried over Na\(_2\)SO\(_4\). After concentration, the red oil (8.05 g) was used without further purification. To 3.94 g of the crude red oil was added HMTA (2.74 g, 19.5 mmol) in a dry flask was added MeOH (20 mL) and the reaction mixture was heated to reflux for 16 hours. After cooling to room temperature, the solid precipitate was collected by suction filtration and washed with small amounts of MeOH until the yellow tint was removed. Upon removal of residual solvent \textit{in vacuo}, the product was afforded as a white crystalline material (0.769 g, 16%). \(^1\)H NMR (CDCl\(_3\)) \( \delta 2.58 (d, \ J = 7.2 \text{ Hz, 6H}), 3.42 (s, 6H), 5.14 (m, 6H), 5.91 (m, 3H). \) \(^13\)C NMR (CDCl\(_3\)) \( \delta 31.6, 69.6, 70.7, 119.1, 132.6, 198.5. \) HRMS (EI) calculated for C\(_{18}\)H\(_{21}\)NO\(_3\) [M] \( 299.1521, \) found 299.1519.

2-(3-(2-hydroxyethylthio)propyl)phenol (2-24). To a stirred solution of tetrachloroethane (5 mL) under argon was added 2-allylphenol (0.606 g, 4.52 mmol), 2-mercaptoethanol (0.96 mL, 13.6 mmol) and AIBN (0.136 g, 0.829 mmol). The reaction was heated to 80 °C and left for one hour. Solvent was removed \textit{in vacuo} and the resulting oil was dissolved in CH\(_2\)Cl\(_2\). Flash
chromatography was performed on the crude material with gradient elution: 0.5% MeOH:CH$_2$Cl$_2$ (100 mL), 1% MeOH:CH$_2$Cl$_2$ (200 mL), 2.5% MeOH:CH$_2$Cl$_2$ (400 mL), 5% MeOH:CH$_2$Cl$_2$ (200 mL). The solvent was removed *in vacuo*, yielding the title compound as a yellow oil (0.788 g, 82%). $^1$H NMR (CDCl$_3$) $\delta$ 1.84 (q, $J$ = 7.2 Hz, 2H), 2.57 (t, $J$ = 7.1 Hz, 6H), 2.75 (t, $J$ = 6.1 Hz, 4H), 3.74 (t, $J$ = 5.6 Hz, 2H), 6.84 (m, 2H), 7.09 (m, 2H).

3,5,7-tri-(3-(2-hydroxyethylthio)propyl)-1-aza-tricyclo[3.3.1.1.3,7]decane-4,6,10-trione (2-25).

To a stirred solution of AIBN (3.4 mg, 0.021 mmol) in tetrachloroethane (3 mL) under argon was added 3,5,7-triallyl-1-aza-tricyclo[3.3.1.1.3,7]decane-4,6,10-trione (23 mg, 0.077 mmol). The vessel was heated to 80 °C and left stirring for 3 days. After this time, the reaction mixture was run through a plug of silica in 10% MeOH:CH$_2$Cl$_2$. Preparatory thin-layer chromatography was then run on the eluent, after solvent had been removed, in 10% MeOH:CH$_2$Cl$_2$. The darkest bands were collected and had silica removed by dissolving the material with 10% MeOH:CH$_2$Cl$_2$ and running through a filter. The eluent had solvent removed *in vacuo*, yielding 4.3 mg of product (10 %). $^1$H NMR (d$_6$-DMSO) $\delta$ 1.63 (br s, 4H), 2.57 (residual solvent peak covers), 2.55 (t, $J$ = 7 Hz, 2H), 3.43 (s, 2H), 3.52 (m, 2H), 4.76 (t, $J$ = 5.6 Hz, 1H). $^{13}$C NMR (d$_6$-DMSO) $\delta$ 23.01, 26.46, 32.34, 33.70, 60.80, 70.47, 70.60, 200.35 HRMS (EI) calculated for C$_{24}$H$_{39}$NO$_6$S$_3$ [M+K]$^+$ 556.1832, found 556.1835.
Chapter 3: Bicyclic $N$-substituted-4-piperidones for sensor applications

Introduction

The cyclic $\beta$-aminoketone core of $N$-substituted-4-piperidones experiences the through-bond interaction (TBI) associated with the donor-$\sigma$-acceptor motif provided the nitrogen substituent can be placed into the axial position (Figure 3-1a). In this configuration, the nitrogen’s lone pair of electrons is in the appropriate geometry to interact with the $\pi^*$ of the carbonyl via the saturated spacer, but in the equatorial position, the alignment is incorrect and the TBI is inactive.$^{20}$ The $N$-substituent can be placed in the axial position, despite the steric destabilization, due to the stabilization imparted by the TBI.$^{16,46}$ While the TBI of the $N$-substituted-4-piperidones allows both the axial and equatorial configurational isomers to be thermodynamically accessible, facile nitrogen inversion allows both to be kinetically accessible.$^{47,48}$ UV/vis spectroscopy can be used to monitor this axial/equatorial equilibrium because the axial isomer displays the TBI UV-active transition, but the equatorial one does not; the ability to monitor this equilibrium spectroscopically makes $N$-substituted-4-piperidones attractive targets for sensing applications.$^{13,14}$

![Figure 3-1](image-url)

Figure 3-1. The axial/equatorial equilibrium made possible by facile nitrogen inversion. Red arrows indicate destabilizing or ineffective intramolecular interactions and green arrows indicate stabilizing interactions for (a) $N$-substituted-4-piperidone, (b) $N$-substituted-4-piperidone systems with 2,6-substituents, (c) $N$-substituted-4-piperidone systems with 3/5-substituents, and (d) bicyclic $N$-substituted piperidone derivatives.
*N*-Substituted-4-piperidones have previously been studied where the steric effects between substituents on the 2,6 positions and the *N*-substituent were observed using spectroscopic techniques (Figure 3-1b); however, investigations into specific intramolecular interactions between the *N*-substituent and functionality at other positions have been less explored (Figure 3-1c). The cyclic structure of such heterocyclic compounds constrains the proximity and spatial orientation between the ring and *N*-substituents, potentially preventing the intramolecular interactions from occurring. By incorporating a bridging cyclic structure across the 3,5 positions of the piperidones, new opportunities arise whereby ring substituents can be placed in more geometrically accessible positions for the *N*-substituent (e.g., Figure 3-1d).

R¹ and R² in Figure 3-1d can be engineered to experience specific interactions that would perturb the axial/equatorial equilibrium by preferentially stabilizing one isomer over the other (e.g., CH—π, π—π, ionic, dipole-dipole). Since only the axial isomer displays the TBI associated UV-active transition, UV/vis spectroscopy can monitor the introduced interaction’s perturbation on the equilibrium. The ability to correlate this equilibrium to the strength of the introduced interaction makes *N*-substituted-4-piperidone derivatives promising for molecular balance applications; these molecular systems would be different compared to many current molecular balances because the introduced through-space interaction would be measured via the through-bond interaction of the donor-σ-acceptor framework.

Our efforts toward developing bicyclic piperidones as unique platforms for molecular balance applications have led to the UV/vis characterization of 3,5-bridged-*N*-substituted-4-piperidone and bisnitrile derivatives and have provided substrates for future investigations.
Design

The cyclic nature of the $N$-substituted-4-piperidones provides a conformationally limited chemical structure that can be further constrained through the incorporation of bridging substituents (*vide supra*). This bicyclic structure not only prevents chair-chair interconversions, which could interfere with the analysis, but also provides a method for placing the interacting substituents in more geometrically accessible positions. It is for these reasons that this study has focused on 3,5-bridged-$N$-substituted-4-piperidones.

The initial design for the bicyclic targets included a 3,5-bridging aryl ring and $N$-substituents with an available $\alpha$-hydrogen (Figure 3-2a); results from molecular modeling suggest that, when the $N$-substituent is in the axial position, the C-H bond can point into the centroid of the aromatic ring with a distance of $\sim 3\text{Å}$ (e.g., Figure 3-3 where $R^1 = \text{phenyl}$ and $R^2 = \text{methyl}$). Although the orientation is not quite perpendicular, the other parameters fall within the bounds of a $\text{CH} - \pi$ interaction.\textsuperscript{52,53} By increasing the acidity of the $\alpha$-hydrogen via careful selection of the $N$-substituents, the strength of the CH—π interaction can be augmented, increasing the equilibrium population of the axial configurational isomers. This shift in the equilibrium should be detectable by UV/vis spectroscopy (*vide supra*), and possibly by NMR studies performed at temperatures where the nitrogen epimerization can be slowed to allow for distinct responses from each species.\textsuperscript{47,48} The correlation between $\alpha$-hydrogen acidity and the spectroscopic signal intensity should allow for a measure of the CH—π interaction strength.
Numerous functionalities at the R$^1$ and R$^2$ positions can modulate the $\alpha$-hydrogen’s acidity including aryl systems, esters, nitriles, or other electron-withdrawing groups, but aryl

Figure 3-2. Axial/equatorial equilibrium for interactions targeted between the 3,5-bridge and N-substituents: (a) CH—π and (b) π—π.

Figure 3-3. (Above) Axial/equatorial equilibrium where R$^1$ = phenyl and R$^2$ = methyl. (Below) MM3 minimized structures using MacroModel version 9.8.107 of the above equilibrium for (a) axial and (b) equatorial configurational isomers where black = carbon, white = hydrogen, red = oxygen, blue = nitrogen.

Numerous functionalities at the R$^1$ and R$^2$ positions can modulate the $\alpha$-hydrogen’s acidity including aryl systems, esters, nitriles, or other electron-withdrawing groups, but aryl
systems were chosen as the first targets; the π-system electronics of the aryl system are easily perturbed and allow for the study of a wide spectrum of α-hydrogen acidity in a single series of related compounds. Furthermore, changes to the π-system do not require substantial changes in molecular size (e.g., para-substituents), which allows for a tighter correlation between the acidity of the α-hydrogen (an electronic effect) and the axial/equatorial equilibrium (sterically unaffected by distal ring substituents). Due to the ease of functionalizing a single aromatic ring (as opposed to two in a single operation), the readily available (±)-α-methylbenzylamine (R\(^1\) = phenyl, R\(^2\) = methyl) was studied as the initial N-substituent (Figure 3-3).

**Synthesis and Characterization**

Synthesis of 3,5-bridged-N-substituted-4-piperidone (±)-3-4 begins with the formation of bisaminol (±)-3-2 via condensation of (±)-α-methylbenzylamine (±)-3-1 with paraformaldehyde and then capture with potassium ethoxide (Figure 3-4).\(^{54-57}\) The unstable nature of the bisaminol to silica and storage, even under argon in a sealed vial, requires immediate purification of the compound with vacuum distillation. After collection of the purified bisaminol, bicyclic piperidone (±)-3-4 is obtained through a double Mannich reaction between the bisaminol and 2-indanone, 3-3, under Lewis acidic conditions (trichloromethylsilane).\(^{55}\) The resulting bicyclic piperidone (±)-3-4 is purified with column chromatography, despite displaying moderate instability to silica. The product is a clear oil, but turns yellow over time under argon in a vial sealed with Teflon and parafilm; although oxidation may be occurring, NMR analysis did not show any appreciable changes to the spectrum. The synthesis, purification, and characterization of piperidone (±)-3-4 and bisnitrile (±)-3-5 (vide infra) are also complicated by diastereotopic protons and non-\(^1\)H NMR spectra.
Racemic bicyclic piperidone 3-4 displays the tentatively assigned TBI UV/vis absorbance around 360 nm (expected around 350 nm\textsuperscript{16}) with an approximate extinction coefficient of 220 M\textsuperscript{-1} cm\textsuperscript{-1}; the signal is not fully resolved from the other UV absorbances, and thus the λ\textsubscript{max} of the shoulder peak is challenging to determine (Figure 3-5). There are multiple reasons that could explain the low intensity of the assigned TBI UV signal. The α-hydrogen may not be acidic enough in the unperturbed system to stabilize the axial isomer, or, less likely, 3-4 may have an intrinsically weak UV absorbance (i.e., ε value).

As seen in other β-aminoketone systems, the transformation of the carbonyl into a better π-acid provides a way of strengthening the TBI\textsuperscript{13,14,49}. Thus, the carbonyl of the piperidone was
transformed into the 1,1-dicyanoethylene chromophore via addition of malononitrile (no additional base was required), providing racemic bisnitrile 3-5. The broad absorbance from the tentatively assigned $\pi\rightarrow\pi^*$ transitions once again obfuscated the TBI transition, but an $\varepsilon$ value of $\sim$308 M$^{-1}$ cm$^{-1}$ was approximated for the shoulder at $\lambda = 358$ nm (Figure 3-6). As predicted, the charge-transfer absorption for the TBI of bisnitrile (±)-3-5 is more intense than for piperidone (±)-3-4, but not tremendously so. Additional UV/vis characterization for these compounds will be performed in solvents with different polarities, as the charge-transfer TBI transition is expected to be affected by this parameter.$^{12-16}$ The presence of a TBI UV-active transition for both the piperidone and bisnitrile derivatives, albeit weak, is promising for future derivatives, which are expected to have stronger signals due to the increase in $\alpha$-hydrogen acidity.

To begin to investigate the effect of increasing $\alpha$-hydrogen acidity on the resulting UV signal, para-nitro (±)-$\alpha$-methylbenzylamine (±)-3-9 was synthesized following literature precedent (Figure 3-7).$^{58}$ Beginning with (±)-$\alpha$-methylbenzylamine (±)-3-1, clean conversion of the free amine to the protected amide (±)-3-6 was accomplished with addition of acetic
anhydride. Subsequent addition of HNO$_3$ effected the nitration; this reaction was sluggish and unreliable, requiring the use of fresh HNO$_3$ for consistent yields. Additionally, an inseparable mixture of both ortho, (±)-3-8, and para, (±)-3-9, nitrated compounds resulted from this reaction. Due to the difficulty in separating the two isomers, the compounds were continued forward to the deprotection step in refluxing 20% HCl. Upon cooling the acidic solution to room temperature, the para-nitro salt selectively precipitated from the reaction mixture. Deprotonation and extraction yielded the desired compound ((±)-3-9) in high purity. The formation of the para-nitro bisaminol was then attempted with the conditions described previously (vide supra), but the product could not be readily isolated via vacuum distillation. The molecular weight or the increased polarity of the para-nitro derivative (±)-3-9 could have caused this difficulty.

Figure 3-7. Synthesis of racemic para-nitro α-methylbenzylamine (±)-3-9.

**Future Work**

Due to the relatively unexplored chemical terrain of the 3,5-bridged-N-substituted-4-piperidones, there are numerous avenues for future research. Efforts so far have focused on obtaining a handle on how to purify, characterize (complex due to the diastereotopic protons of the bicyclic compounds), and functionalize these types of compounds. Future work will focus on obtaining the bisaminol of the para-nitro (±)-α-methylbenzylamine (±)-3-9, and subsequently
forming the piperidone/bisnitrile bicycles to investigate any effects on the UV/vis spectra (Figure 3-8). Low-temperature NMR studies can also potentially be used to investigate the axial/equatorial equilibrium since the axial configurational isomer has an α-hydrogen in the center of an aromatic ring, a highly shielded position compared to the corresponding equatorial position. Additional synthetic work could involve further functionalizing protected para-nitro derivative (±)-3-12 via reduction, formation of diazonium salt (±)-3-14, and subsequent transformation into halides [(±)-3-15, (±)-3-16], or other electron-withdrawing groups [(±)-3-17] (Figure 3-8). Furthermore, using nitriles or esters instead of aryl groups could lead to a larger range of α-hydrogen acidity, but may require the development of new synthetic methodology compatible with the greater acidity of the α-hydrogen.

![Chemical structures](image-url)

Figure 3-8. Future synthetic manipulations of para-nitro compound (±)-3-9.

The future directions for the 3,5-bridging aryl ring system are not limited to investigating the CH—π interaction; π—π interactions could also be explored (Figure 3-2b). To pursue this alternative interaction, synthesis of aniline based bisaminols was attempted, but multiple species formed in the reaction mixture and were not easily separable by distillation. The existence of
multiple species likely arises from the delocalization of the nitrogen’s lone pair of electrons into the phenyl ring, thus inhibiting, or making reversible, the initial condensation with paraformaldehyde. Even when the phenyl group had electron-donating groups added to make the nitrogen more electron-rich, the conversion still did not proceed to completion. Potential solutions for obtaining the desired bisaminols include further heating of the solutions and using more equivalents of paraformaldehyde to shift the equilibrium to preferred formation of the bisaminol.

Conclusions

Initial work towards the development of a molecular balance based on the 3,5-bridged-\(N\)-substituted-4-piperidone bicyclic scaffold has led to the synthesis and characterization of an (\(\pm\))-\(\alpha\)-methylbenzylamine piperidone, (\(\pm\))-3-4, and bisnitrile derivative, (\(\pm\))-3-5. The piperidone displayed the TBI UV-active transition at \(\lambda = 360\) nm with an extinction coefficient of approximately \(220\) M\(^{-1}\) cm\(^{-1}\), but the bisnitrile derivative displayed a slightly stronger TBI transition at \(358\) nm with an approximate \(\epsilon\) value of \(308\) M\(^{-1}\) cm\(^{-1}\). These findings are consistent with either a minor population of the molecules with the \(N\)-substituent in the axial position or a small \(\epsilon\) value for the charge-transfer transition, due to symmetry and overlap considerations. To probe the effect of the acidity of the \(\alpha\)-hydrogen on the TBI UV transition intensity, para-nitro precursor amine (\(\pm\))-3-9 was synthesized, but the bisaminol has not yet been isolated. The difficulty in obtaining the bisaminols, due to the requirement that the compounds be able to be distilled, along with the moderate decomposition of the bicyclic compounds on silica/alumina and the potential overlap of the UV absorbances from the \(\pi\rightarrow\pi^*\) and charge-transfer transitions are all general limitations that will need to be overcome if the \(N\)-substituted-4-piperidone compounds are going to be used for sensing and molecular balance applications.
Experimental Section

**General.** Reagents and solvents were purchased from Acros, Aldrich, or Fluka and used without further purification unless otherwise specified. THF and DMF were degassed in 20 L drums and passed through two sequential purification columns (molecular sieves) under a positive argon atmosphere using a custom Glass Contour solvent system (Glass Contour, Inc.). Thin layer chromatography (TLC) was performed on Dynamic Adsorbents, Inc. aluminum backed TLC plates with visualization via UV light or staining. $^1$H NMR and $^{13}$C NMR were recorded on a Varian Mercury 300, Gemini 300, or an Inova 500 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to residual protonated solvent (CHCl$_3$: δ$_H$ 7.27 ppm, δ$_C$ 77.00 ppm; DMSO: δ$_H$ 2.50 ppm, δ$_C$ 39.50 ppm; pyridine: δ$_H$ 7.22, 7.58, 8.74 ppm, δ$_C$ 123.9, 135.9, 150.4 ppm). Abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). MS spectra (HRMS) were acquired on a Bruker APEX II 4.7 T Fourier Transform Ion Cyclone Resonance mass spectrometer (Bruker Daltonics, Billerica, MA). UV/vis measurements were taken using a Varian CARY 100 Bio UV/visible spectrophotometer and analyzed using Origin 7.5 Software.

**General procedure for obtainment of UV/vis spectra.** Compounds were first diluted with CH$_2$Cl$_2$ to appropriate stock concentration, and then further dilutions were performed to yield the desired final concentrations using 10 mL volumetric flasks. The background UV/vis spectra were taken in only CH$_2$Cl$_2$. The same quartz cuvette was used for each absorbance measurement, and was washed with each respective solution three times before the UV/vis absorbance measurements were taken.
(±)-N,N-bis(ethoxymethyl)-1-phenylethanamine ((±)-3-2). To a flame dried round-bottom flask was added paraformaldehyde (2.38 g, 79.1 mmol), anhydrous K$_2$CO$_3$ (5.34 g, 38.8 mmol), and dry EtOH (9.1 mL) under argon. (±)-α-Methylbenzylamine (5.0 mL, 39 mmol) was subsequently added dropwise to the stirred solution, and the reaction was left stirring at room temperature for 16 hours. The solids were removed via vacuum filtration and washed with dry EtOH. The majority of the ethanol was removed via short-path distillation. Fractional short-path vacuum distillation was performed on the remaining oil; the desired product came off at 55 °C at 10 torr, yielding the title compound as a clear oil (5.77 g, 63%). Note: Material degrades over time when left sealed under argon at room temperature. $^1$H NMR (CDCl$_3$) δ 1.16 (t, $J = 6.8$ Hz, 3H), 1.49 (d, $J = 6.8$ Hz, 1H), 3.38 (m, 2H), 4.30 (m, 2H), 7.35 (m, 5H).

((±)-3-4). To a flame dried round-bottom flask was added 2-indanone (0.1040 g, 0.79 mmol), (±)-N,N-bis(ethoxymethyl)-1-phenylethanamine (0.4482 g, 1.89 mmol), and dry CH$_3$CN (7 mL) under argon. The round-bottom was placed in an ice-water bath and trichloromethylsilane (204 µL, 1.74 mmol) was subsequently added dropwise to the stirred solution. The reaction was left stirring at room temperature for 32 hours, and subsequently quenched with saturated NaHCO$_3$ solution (10 mL), and extracted with ethyl acetate (3 × 50 mL). The organic layers were collected, washed with saturated NaCl solution (1 × 50 mL), and dried with Na$_2$SO$_4$. After the
solvent was removed *in vacuo*, a red oil was obtained. Flash chromatography was performed on the crude product in 1:20 ethyl acetate:hexane to afford the product as a yellow oil (0.0284 g, 13%). $^1$H NMR (CDCl$_3$) $\delta$ 1.21 (d, $J = 6.7$ Hz, 3H), 2.74 (m, 2H), 3.12 (m, 2H), 3.33 (br s, 2H), 3.60 (q, $J = 6.7$ Hz, 1H), 6.84 (m, 2H), 7.16 (m, 3H), 7.24 (m, 2H), 7.34 (m, 2H).

1H NMR (CDCl$_3$) $\delta$ 1.57 (d, $J = 6.7$ Hz, 3H), 3.16 (d, $J = 11.4$ Hz, 1H), 3.45 (d, $J = 11.5$ Hz, 1H), 3.50 – 3.60 (m, 1H), 3.63 (m, 2H), 3.75 – 3.86 (m, 1H), 3.91 (q, $J = 6.7$ Hz, 1H), 7.27 (observed by residual solvent peak), 7.32 (m, 3H), 7.42 (m, 4H), 7.52 (m, 1H).

$\text{\((\pm)-3-5\)}$. To a vial equipped with a stir bar was added (±)-3-4 (0.0524 g, 0.189 mmol) and CH$_2$Cl$_2$ (0.06 mL). To a separate vial was added malononitrile (0.0133 g, 0.201 mmol) and CH$_2$Cl$_2$ (0.06 mL). The malononitrile solution was then added to the first vial, and the reaction was left stirring under argon for 5 days (additional CH$_2$Cl$_2$ was added each day). Flash chromatography was performed on the crude reaction mixture with gradient elution; 1:5 ethyl acetate:hexane to 2:5 ethyl acetate:hexane. Removal of the solvent yielded the title compound as a brown oil (4.9 mg, 7.5%). $^1$H NMR (CDCl$_3$) $\delta$ 1.57 (d, $J = 6.7$ Hz, 3H), 3.16 (d, $J = 11.4$ Hz, 1H), 3.45 (d, $J = 11.5$ Hz, 1H), 3.50 – 3.60 (m, 1H), 3.63 (m, 2H), 3.75 – 3.86 (m, 1H), 3.91 (q, $J = 6.7$ Hz, 1H), 7.27 (observed by residual solvent peak), 7.32 (m, 3H), 7.42 (m, 4H), 7.52 (m, 1H).

$\text{\((\pm)-N-(1-phenylethyl)acetamide (\((\pm)-3-6\))}$. To a flame dried round-bottom flask was added acetic anhydride (11.5 mL, 121 mmol). The round-bottom flask was placed into a water bath and (±)-α-methylbenzylamine (5.2 mL g, 40.3 mmol) was subsequently added dropwise. After 45
minutes, the reaction was quenched with ice-water (30 mL), and allowed to stir for 15 minutes. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were collected and washed with 1N NaOH (4 × 30 mL), saturated NaCl solution (1 × 50 mL), and dried with MgSO₄. Solvent was removed in vacuo yielding a white crystalline product (5.84 g, 90%). ¹H NMR (CDCl₃) δ 1.43 (d, J = 6 Hz, 3H), 1.92 (s, 3H), 5.09 (m, 1H), 5.83 (br s, 1H), 7.18 – 7.32 (m, 5H).

(±)-1-(4-nitrophenyl)ethanamine ((±)-3-9). To a round-bottom flask argon in an ice-water bath was added (±)-N-(1-phenylethyl)acetamide (5.84 g, 35.8 mmol) and fresh 15.8 M HNO₃ under. The reaction was left stirring for 3 days under argon and then quenched with 30% NaOH (200 mL). The mixture was subsequently extracted with CH₂Cl₂ (4 × 200mL). The organic fractions were collected and dried with MgSO₄. The solvent was then removed in vacuo, yielding a yellow solid, which was a mixture of both para and ortho-mono nitration products (6.88 g).

The mixture was placed in a round-bottom flask and 20% HCl (38 mL) was added. The reaction was heated to reflux and left under argon for 16 hours. Upon cooling, crystals formed in the reaction medium. The solids were filtered off with vacuum filtration, and then dissolved in 10% NaOH solution and extracted with CH₂Cl₂ (5 × 60 mL). The solvent was removed in vacuo yielding the desired para isomer as an orange oil (2.48 g, 42% over 2 steps). ¹H NMR (CDCl₃) δ 1.41 (d, J = 6.7 Hz, 3H), 1.52 (br. s, 2H), 4.26 (q, J = 6.6 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H).
References


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