

DENDRIMERS WITH ANTHYRIDINE-BASED HYDROGEN-BONDING UNITS AT THEIR CORES: SYNTHESIS, COMPLEXATION AND SELF-ASSEMBLY STUDIES

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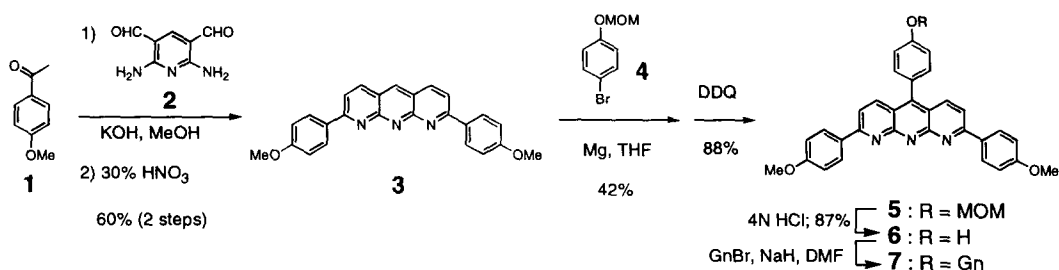
Abstract: Generation 1-4 Fréchet-type dendritic bromides were covalently linked to anthryridine (**6**) to give "sticky" dendrons **7a-7d**. The binding constants of 1:1 complexes between **7** and benzamidinium salt **8** were measured to assess their ability to act as building blocks for self-assembly. A 2:1 complex of **7** and pentamidine **9** formed in 1% CD₃CN/CDCl₃, indicating the utility of these compounds for constructing larger dendritic assemblies.

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Over the past decade there has been considerable interest in structures with nanometer dimensions.¹ Organic compounds are classically constructed with covalent bonds, often in multi-step syntheses; but with the exception of polymers, this approach rarely results in materials with nanoscale dimensions. An alternative biomimetic strategy has emerged recently which relies on the programmed self-assembly of smaller subunits through non-covalent interactions.² For example, Whitesides extensively studied hydrogen-bonded, rosette-like structures built of melamine and barbituric acid units.³ Lehn employed the coordination chemistry of oligo-pyridines to form various helicates, ladder polymers, and molecular grids.⁴ Stoddart explored the use of catenanes in self-assembly.⁵ Rebek's self-assembling capsules⁶ and Ghadiri's peptidic nanotubes⁷ are elegant examples of functional assemblies. Numerous other examples are present in the literature.⁸

Many self-assembly processes in nature involve biopolymers, particularly proteins. The abiotic examples cited above involve relatively low molecular weight compounds which raises the question of whether one could create discrete aggregates of synthetic macromolecules with molecular weights and sizes approaching those of proteins. For this purpose dendrimers are ideal building blocks because they are monodisperse, and easily prepared and functionalized.⁹ Newkome¹⁰ and Aida¹¹ assembled dendritic complexes by using metal centers. We recently reported the hydrogen-bond-mediated formation of a discrete aggregate of six identical dendrimers.¹² Herein, we report the formation of heteromeric supramolecular structures assembled from small guest molecules and dendritic building blocks containing complementary hydrogen-bonding motifs. A distinct advantage of the two-component self-assembly strategy (vs. single component approach) is the ability to vary stoichiometry to more readily study the assembly and to potentially affect its structure.

Scheme 1



The dendritic building blocks were constructed by attaching polyether dendrimers to a 1,9,10-anthryridine core, which presents the hydrogen-bond acceptor-acceptor-acceptor (AAA) motif (Scheme 1). Double Friedländer condensation between **1** and **2** followed by oxidation with 30% nitric acid afforded anthryridine **3**.¹³ The Grignard reagent derived from **4** was added to **3** and subsequent oxidation with DDQ gave **5** in high yield. Acidic deprotection gave phenol **6** in 87% yield and alkylation with generation 1 to 4 Fréchet-type dendritic bromides gave **7a-d**. Dendritic anthryridines **7a-d** (Chart 1) were shown to be pure and to have the assigned structures by ¹H and ¹³C NMR, size exclusion chromatography (SEC), matrix assisted laser desorption ionization mass spectrometry (MALDI), and elemental analysis (Table 1).

Chart 1

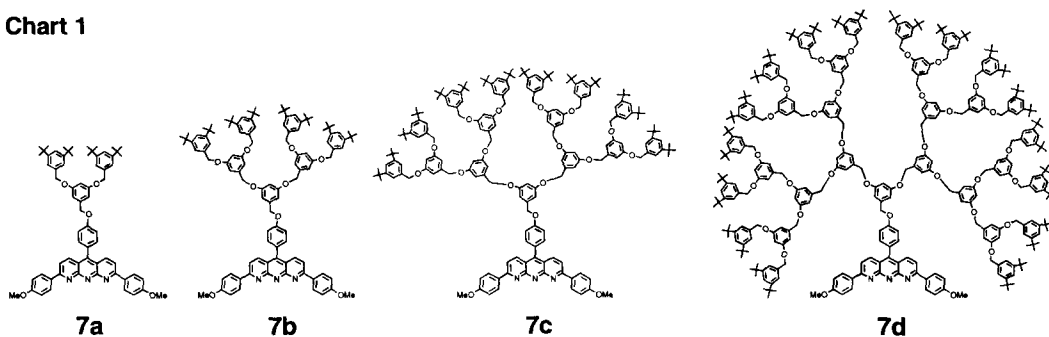


Table 1. Characterization of **7a-d**. The SEC values (polystyrene) were obtained on a Waters Ultrastaygel HR3 column (MW range 500 to 30,000) in CH2Cl2 or THF.

Compound	Yield of 7	Molec. Form.	Theor. MW	SEC MW	MALDI MW
7a	68%	$C_{68}H_{73}N_3O_5$	1012.3	1222	
7b	70%	$C_{112}H_{129}N_3O_9$	1661.3	1885	
7c	63%	$C_{200}H_{241}N_3O_{17}$	2959.1	2976	2959.8
7d	52%	$C_{376}H_{465}N_3O_{33}$	5554.8	4654	5552.8

Although the 2,6-diamino-1,4-dihydropyridine unit provides a donor-donor-donor (DDD) hydrogen-bonding motif fully complementary to the AAA site of **7**, it is unstable to oxidation.¹⁴ For this reason the benzamidinium group, containing a hydrogen-bond DD motif was chosen as the guest. Compound **8**, available from another study,¹⁵ bound **7** in chloroform-*d* (CDCl_3) by hydrogen-bonding as evidenced by substantial downfield shifts (^1H NMR) in one set of benzamidinium NH protons. Preliminary ^1H NMR titration experiments in CDCl_3 indicated that the association constants (K_{assoc}) were too high to be determined accurately, so the studies were performed in 10% $\text{CD}_3\text{CN}/\text{CDCl}_3$, a more competitive solvent. The stoichiometry of **7-8** complexes was found to be 1:1 by Job's analysis.¹⁶ The K_{assoc} values, determined using a ^1H NMR dilution method showed tight and generation independent binding between **7** and **8** (Table). The lack of an effect of the dendrimer generation on the K_{assoc} was expected because the dendrimers were attached to the anthridine in a geometry that would tend to orient them away from the hydrogen-bonding site.

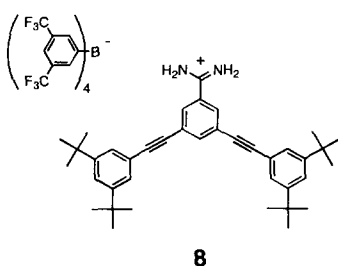


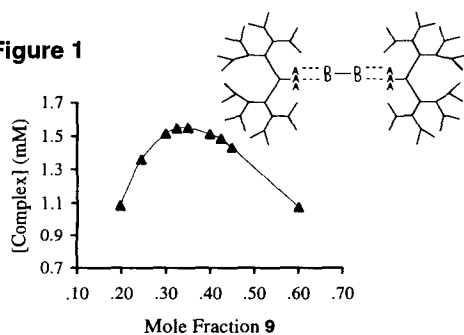
Table. Summary of Binding Studies Between **7 and **8**.^a**

Compd	NH $\Delta\delta_{\text{max}}$	K_{assoc} (M^{-1})	ΔG° (Kcal/mol)
7a	4.19 ppm	31590	-6.0
7b	4.20 ppm	23400	-5.9
7c	4.23 ppm	29640	-6.0
7d	4.18 ppm	21100	-5.8

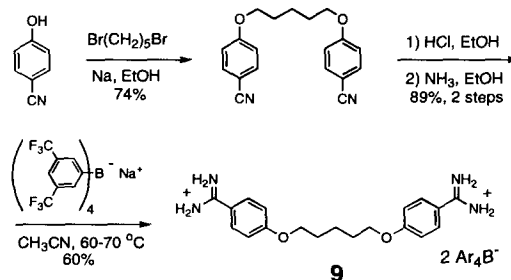
^aAt 293 K in 10% $\text{CD}_3\text{CN}/\text{CDCl}_3$. Saturation ranges are between 10-80%. K_{assoc} are averages of duplicate runs that were within $\pm 15\%$.

With the knowledge of the strong binding between **7** and **8**, pentamidine salt **9** was synthesized as a core unit to assemble two dendrons. Pentamidine is active against the *Pneumocystis carinii* pathogen and is used clinically in the treatment of *P. carinii* pneumonia, the common opportunistic infection in AIDS patients.¹⁷ The synthesis of **9** is outlined in Scheme 2. Both **8** and **9** were used as their tetrakis[3,5-bis(trifluoromethyl)phenyl]borate salts to enhance their solubility in organic solvents.¹⁸ Using Job's method, the stoichiometry of the **7c-9** complex in 1% acetonitrile-*d*₃/ CDCl_3 was determined to be 2:1 (Figure 1). Thus by this modular self-assembly approach, a didendron with molecular weight >10,000 amu was formed from smaller, accessible subunits.

Figure 1



Scheme 2



The results described herein indicate that a simple dendron can be formed by hydrogen-bonding interactions between monodendrons and a complementary ditopic core molecule. The advantage of the self-assembly approach is the comparative ease with which smaller subunits can be synthesized and an economy in molecular construction when a set of modular building blocks are available. There are also cases where reversible assembly is desirable, whether it is for more rapid clearance from the body in a medicinal application or for easier materials processing as increased temperatures favor smaller molecular weight distributions. Much more complicated assemblies might be produced using the strategy outlined here, including hyperbranched polymeric assemblies.

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