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Arylamide Dendrimers with Flexible Linkers via Haloacyl Halide Method

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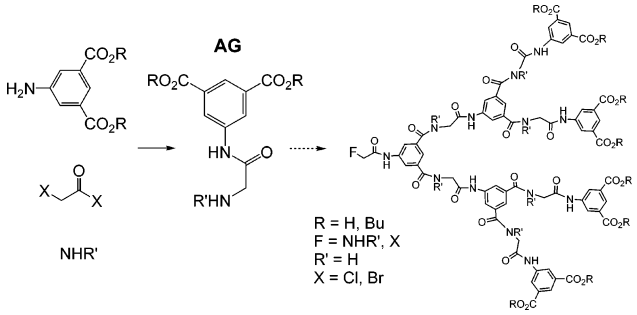
ABSTRACT



Soluble arylamide dendrons with flexible linkers, peripheral ester or carboxyl groups (R), and focal amino or halogen functionalities (F) were synthesized from aryl glycineamide (AG) building blocks. The AG blocks were prepared in high yields from trivial starting materials by Fischer's haloacyl halide method, which also could be extended to the dendrimer synthesis itself. The G2 AG dendrons were coupled to a Pd porphyrin core, demonstrating outstanding encapsulation efficiency in aqueous solutions.

Among all dendrimers[1] with aromatic backbones, dendritic arylamides[2] are attractive because of their high chemical stability, the low cost of their building blocks, and effective protocols available for their assembly.[3] Arylamide dendrimers based on 5-aminoisophthalic acid (5-AIPA) were, in fact, among the first reported dendritic macromolecules;[4] however, because of the difficulties in their handling and characterization,[4b] the practical potential of these materials has barely been uncovered even today. Such dendrimers, on the other hand, could present interest for material science and also be useful in applications where encapsulation in polyaromatic scaffolds with multiple peripheral ester or carboxyl groups is required, e.g., in the design of biomedical image tracers.[5]

The problems associated with the 5-AIPA building block come mainly from (1) the low nucleophilicity of its amino group and (2) impeded internal rotations of the 5-AIPA based skeleton, which cause poor solubility and difficulties in characterization of the resulting dendrimers. A way to make the focal functionality more reactive and to simultaneously increase the flexibility of the dendritic backbone is to extend the amino end in the 5-AIPA molecule by a flexible fragment, terminated with an appropriate group, e.g., aliphatic amine. Voit et al.[6] and others[7−9] constructed a number of

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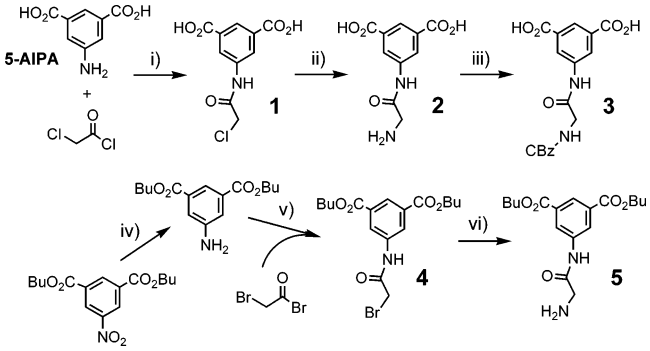
alkyl−aryl amide dendrimers applying similar strategies to 5-hydroxyisophthalic and other aromatic acids; however, none of the reported chemistries became widely used in the dendrimer practice. Here, we introduce an efficient synthesis of alkyl−aryl amide dendrons with flexible linkers that makes use of the classic Fischer haloacyl halide method.[10] The developed approach is inexpensive, has a broad scope, and allows for modification of the dendrimer periphery, interior, focal functionality, and/or internal topology, without changing its basic chemistry. The synthesis of aryl glycineamide or simply *aryl-glycine* (AG) dendrimers is presented to exemplify the developed methodology.

The building blocks **3** and **5** for assembly of AG dendrimers were synthesized as shown in Scheme 1. The

Scheme 1. Synthesis of Aryl-glycine (AG) Building Blocks[a]



[a] Conditions: (i) 4 M NaOH aq, 0 °C, 94%; (ii) NH_3 aq, 1−2 h, 98%; (iii) CBzCl/$NaHCO_3$ aq, 2 h, 82%; (iv) NH_4CO_2H, Pd/C, MeOH/THF, 93%; (v) Na_2CO_3, CH_3CN, 98%; (vi) NH_3/MeOH, 78%.

synthesis of diacid **3** starts with acylation of 5-AIPA with chloroacetyl chloride under the classic Schotten−Baumann conditions, giving chloride **1** in a nearly quantitative yield. **1** is further treated with aqueous ammonia, and amino acid **2** is isolated upon removal of the excess of ammonia and addition of EtOH to the aqueous solution. The benzyloxycarbonyl (CBz) protection is installed on the amino end of **2** by reacting it with an excess of CBz-Cl in aqueous solution over an excess of $NaHCO_3$. The CBz-protected building block **1** is isolated from the mixture upon filtration and acidification by HCl.

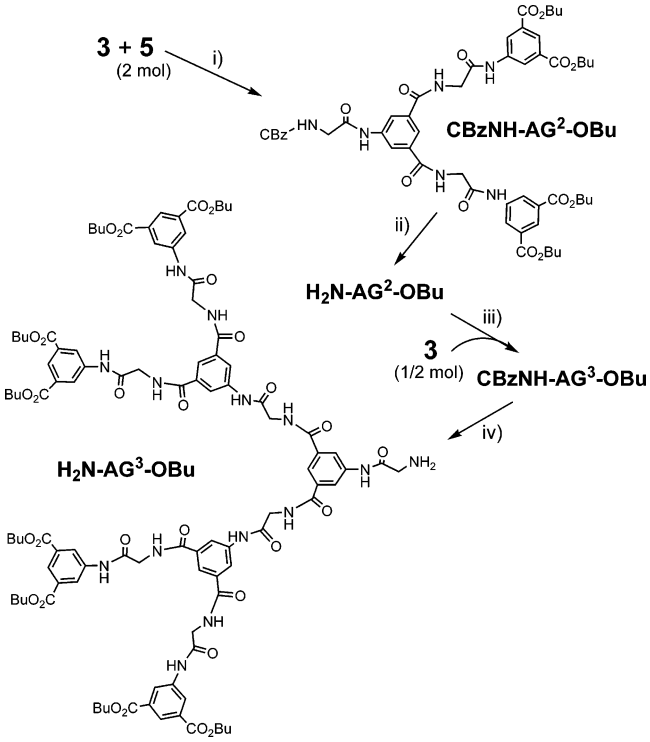
The starting material in the synthesis of **5** is the dibutyl ester of 5-nitroisophthalic acid (5-NIPA). Butyl esters were employed in this work because they gave the desired solubility to the AG dendrons and dendrimers. However, other alcohols can be used for esterification of 5-NIPA as well. For example, higher alcohols, e.g., hexyl, octyl, etc., would facilitate gelation of the AG dendrons in solvents such as ethyl acetate, which can be useful for some applications.

Dibutyl 5-nitroisophthalate can be quantitatively reduced by hydrogen or by ammonium formate in the presence of Pd/C catalyst.[11] The resulting dibutyl 5-aminoisophthalate is acylated by bromoacetyl bromide in acetonitrile in the presence of Na_2CO_3. Using bromoacetyl bromide in this reaction is important because of the subsequent ammonolysis, which occurs much faster in the case of the bromo derivative **4** than that of the chloro analogue. The ammonolysis of the latter can be complicated by the side reactions, e.g., nucleophilic substitutions at the peripheral carbonyl groups, which give rise to mono- and diamides. On the other hand, the ammonolysis of **4** is fast and can be accomplished with no loss of the ester functionalities, giving amine **5** in 78% yield. Another important feature of the acylation (step v) in Scheme 1 is the use of Na_2CO_3 instead of more common organic bases such as Et_3N or pyridine. Apparently, the latter undergo quantitative quarternization by bromide **4**, leaving poorly soluble and unreactive quaternary ammonium salts.

It is important to mention that neither of the intermediate products **1** and **4** in the syntheses of **3** and **5** need to be isolated and purified. They can be introduced into the following transformations directly from the preceding syntheses, following the precipitation upon acidification (**1**) or evaporation of the solvent (**4**). Building blocks **3** and **5**, on the other hand, and amino acid **2** are obtained in high yields by precipitation/crystallization, which makes the overall synthesis shown in Scheme 1 inexpensive and easily scalable to multigram or larger quantities.

An example of the dendrimer assembly from blocks **3** and **5** is depicted in Scheme 2. The resulting dendrons are abbreviated as F-AG^n-T, where F is the focal group (e.g., CBzNH-benzyloxycarbonyl-protected amino group), AG^n is

Scheme 2. Convergent Synthesis of G2 and G3 AG Dendrons Using Coupling−Deprotection Procedure[a]



[a] Conditions: (i) CDMT/NMM, THF/DMF, 4 h, 0 °C, 81%; (ii) H_2, Pd/C, DMF, rt, 12 h, 97%; (iii) as in step i, 73%; (iv) as in step ii, 82%.

the AG framework of generation *n*, and T is the terminal group (e.g., OBu-butyl esters). In this nomenclature, diacid **3** and amine **5** would be termed CBzNH-AG[1]-OH and H_2N-AG[1]-OBu, respectively.

The coupling chemistry used in this particular implementation is CDMT/NMM.[12] The advantage of the CDMT/NMM system is the ease of the removal of unreacted coupling reagents and side products, which are soluble in acidic aqueous solutions. Thus, isolation of practically pure CBz-protected dendrons consists of their precipitation from reaction mixtures upon addition of water and washing of the solids with aqueous 0.1 M HCl.

The hydrogenolysis, employed in steps ii and iv, is clean and occurs quantitatively. However, it is difficult to remove the catalyst (Pd/C) from the products, as AG dendrons tend to support Pd/C particles in solution. It is, therefore, likely that using Boc instead of CBz protection would benefit these syntheses.

Both CBz-protected and unprotected G2 dendrons are soluble in DMF, pyridine, and DMSO and slightly soluble in hot EtOH, making it possible to purify CBzNH-AG[2]-OBu from unreacted amine **5** by washing it with cold EtOH. On the other hand, G3 dendrons show excellent solubility in most common organic solvents and can be purified by precipitation from CH_2Cl_2 solutions with ether or hexane.

The dendrimer assembly, shown in Scheme 2, is effective but relies on a two-step coupling/deprotection protocol. Shortening the synthesis by removing the deprotection step would benefit the entire scheme. This possibility is intrinsic to Fischer's haloacyl halide method, which could be extended to the synthesis of AG dendrimers themselves (Scheme 3).

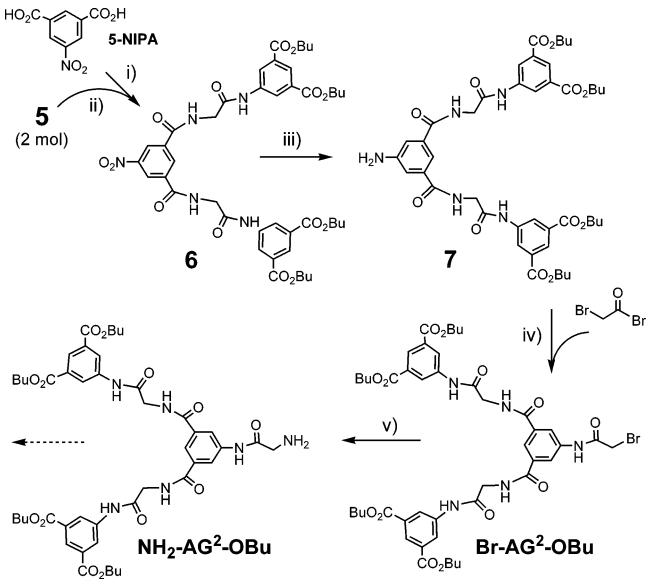
The key intermediate **7** in the synthesis of the G2 dendron H_2N-AG[2]-OBu can be obtained by coupling 5-nitroisophthalic dichloride with **5**, followed by the reduction of nitro derivative **6**. The following reactions replicate Scheme 1 and include the acylation of **7** with bromoacetyl bromide and the ammonolysis of the intermediate bromo derivative Br-AG[2]-OBu. Two molecules of the resulting G2 AG dendron can be further attached to 5-nitroisophthalic dichloride, and the sequence of reduction, acylation, and ammonolysis can be repeated to give the G3 dendron, etc. It is important to note that, in this pathway, dendrons with Br atoms in the focal points, e.g., Br-AG[2]-OBu, appear as intermediate products. These are useful for couplings to phenols by Williamson chemistry. On the other hand, given that the entire synthesis requires only 5-amino- and/or nitroisophthalic acid, bromoacetyl bromide, a chlorinating agent, e.g., $SOCl_2$, and ammonia, the AG dendrons appear to be among the least expensive and most practical dendrons described.

It is worth pointing out that the haloacyl halide method, employed in Schemes 1 and 3, can be naturally adopted to introduce various groups R′ (see Abstract Graphic) in place of the alkylamide hydrogens throughout the entire dendritic skeleton. This can be done by simply changing the nucleophile in the steps ii and vi (Scheme 1) or v (Scheme 3) from ammonia to an appropriate amine. Moreover, different functionalities can be included in the dendrimer interior using different amines at different stages of the synthesis. In addition, chiral centers can be placed throughout the dendrimer by using various α-haloacyl halides, a variety of which are readily available.

Finally, we would like to demonstrate how AG dendrons can be used to modify functional centers and how the peripheral groups on the AG dendrimers can be adjusted in accordance with the demands of an application.

Pt and Pd porphyrins, due to their long-living emissive triplet states, are commonly used as phosphorescent probes for oxygen measurements in biological systems.[13] When dissolved directly in the blood, hydrophobic porphyrin molecules tend to aggregate and bind to the cell surfaces, blood vessel walls, and biomacromolecules such as albumin and other proteins. To circumvent these problems, it has been suggested to encapsulate phosphorescent chromophors inside dendrimers.[5] The periphery of the dendrimers can be tuned to provide isolation of the phosphors from active components of biological systems and to simultaneously make them water soluble. On the other hand, the dendritic matrix, if appropriately chosen, folds in aqueous solutions, leading to more effective encapsulation of the core porphyrin and enabling control over the oxygen diffusion inside dendrimers.[5a,b]

Scheme 3. Synthesis of G2 AG Dendron Using Haloacyl Halide Method[a]



[a] Conditions: (i) $SOCl_2$, reflux, 1 h, (ii) CH_2Cl_2/DMF/pyridine, 61%; (iii) H_2, Pd/C, DMF, 88%; (iv) Na_2CO_3, DMF, 87%; (v) NH_3/MeOH, 90%.

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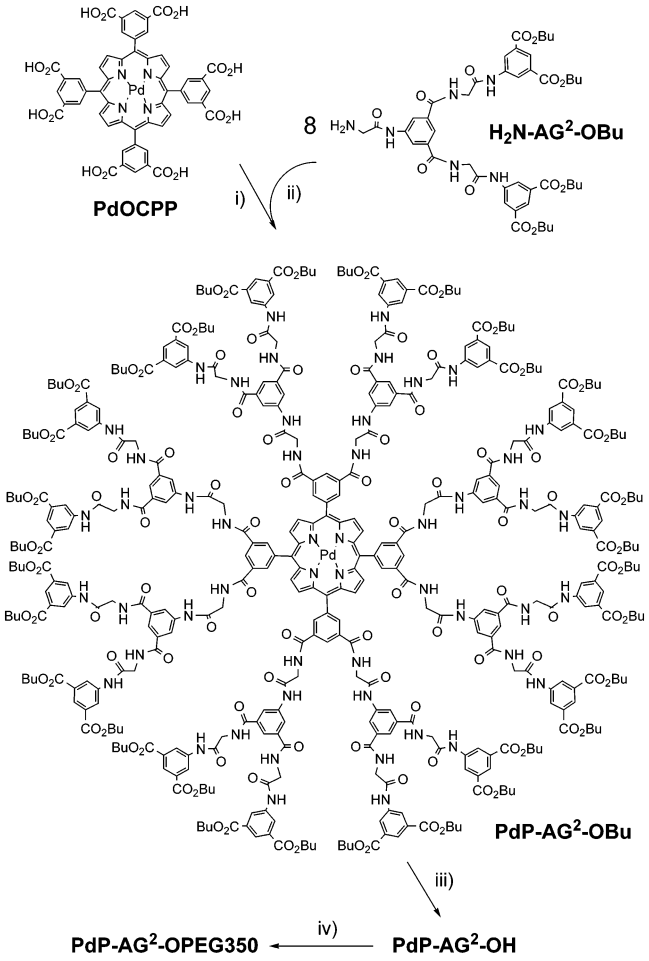
Scheme 4. Synthesis of G2 Pd Porphyrin-AG Dendrimer[a]



[a] Conditions: (i) CDI, DMF, 12 h; (ii) H_2N-AG^2-OBu, rt, 48 h; 68%; (iii) NaOH, THF/MeOH, rt, 1.5 h, 95%; (iv) PEG350, DCC/BtOH/*sym*-collidine, rt, 72 h, 80%.

A modification of Pd octacarboxyporphyrin with eight AG dendrons is shown in Scheme 4. Coupling of H_2N-AG^2-OBu dendrons to PdOCPP was accomplished in a two-step, one-pot synthesis using carbonyldiimidazol (CDI) chemistry. The product, PdP-AG^2-OBu, could be isolated in about 70% yield after purification by GPC. The dendrimer is well soluble in organic solvents (e.g., CH_2Cl_2, THF) due to the 64 peripheral butoxycarbonyl groups, and its UV−vis spectra indicate no intermolecular aggregation. On the other hand, the ^{1}H NMR spectra in $CDCl_3$ reveal quite significant restraints within the dendrimer, which are expected due to the folding of the dendritic matrix.

The hydrolysis of the peripheral butoxycarbonyl groups leads to the water-soluble polyacid PdP-AG^2-OH. The rate of oxygen diffusion in this dendrimer, reflected by the value of the phosphorescence oxygen quenching constant (k_q),[5] i.e., $k_q = 125$ mmHg^{-1} s^{-1}, was found to be about 30 times less than that for the parent PdOCPP, which reveals a substantial protection offered by the G2 AG dendrons to the core porphyrin.

For biological applications, it is necessary that the sensor molecules are uncharged while retaining good water solubility. The periphery of PdP-AG^2-OH could be esterified by monomethoxypoly(ethylene glycol)s (av MW 350) (PEG350) using DCC/BtOH coupling chemistry, yielding a neutral, water-soluble dendrimer PdP-AG^2-PEG350 with excellent phosphorescent characteristics. Its oxygen quenching constant was found to be decreased even further (k_q = 93 mmHg^{-1} s^{-1}) due to the bulk effect of 32 PEG peripheral groups.

In conclusion, a versatile method of synthesis of arylamide dendrimers with flexible linkers is developed. The method has a broad scope and allows for convenient introduction of functional groups at the dendrimer interior and periphery. The aryl-glycine dendrons are very useful for encapsulation of functional luminescent centers.

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Supporting Information Available: Synthetic details and characterization of all new compounds, as well as details of oxygen quenching experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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