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Dendrimers Based on Melamine. Divergent and Orthogonal, Convergent Syntheses of a G3 Dendrimer

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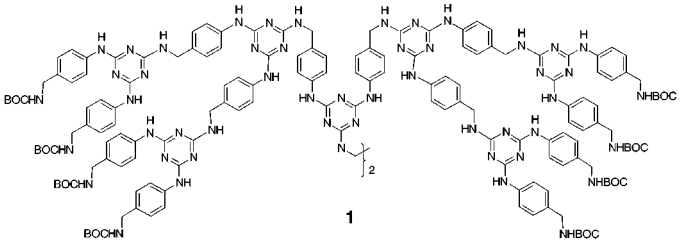
ABSTRACT

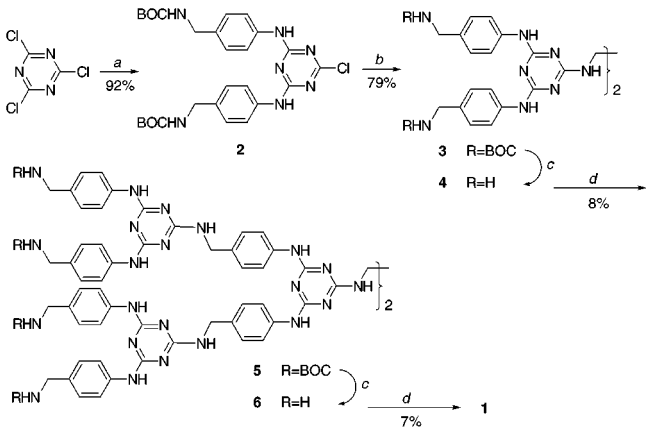


Both convergent and divergent strategies are used to synthesize 1, a dendrimer comprising triazines linked by diamines. The convergent approach is orthogonal; neither protecting groups nor functional group manipulations are required using the building blocks selected.

We report the convergent and divergent syntheses of **1**, a third generation (G3) dendrimer (MW > 5000) comprising melamine, which presents 16 carbamate groups on the periphery. Incorporating melamine groups into dendrimers[1] offers opportunities (i) to exploit the differential reactivity of triazines, (ii) to prepare dendrimers of significant structural diversity (based both on the number of diamines available and the ability to manipulate their placement within the structure), and (iii) to introduce domains for molecular recognition.[2,3] Molecule **1** was selected as a target because it is small enough to be prepared by both convergent[4] and divergent[5,6] methods. We find that **1** can be obtained in high yields and purity using the convergent method. The divergent method provides **1**, but upon separation from side products, less than 1% overall yield is realized.

The divergent synthesis of **1** (Scheme 1) relies on sequential additions of intermediate **2** to core structures (ethylenediamine, then **4**, then **6**). Only two reactions,

Scheme 1. Divergent Synthesis of **1**[a]



[a] Reagents and conditions: (a) Hunig's base; *p*-Boc-aminomethyl-aniline; 0−25 °C. (b) Hunig's base; ethylenediamine; 100 °C. (c) TFA. (d) Hunig's base; **2**; 80 °C.

(1) For recent reviews of dendrimer chemistry, see: (a) Newkome, G. R.; Moorefield, C. N.; Vogtle, F. *Dendritic Macromolecules*; VCH: New York, 1996. (b) Newkome, G. R.; He, E.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689. (c) Frechet, J. M. J. *Science* **1994**, *263*, 1710. (d) Fisher, M.; Vogtle, F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 4000. (e) Bosman, A. W.; Janssen, H. M.; Meijer, E. J. *Chem. Rev.* **1999**, *99*, 1665.

(2) For a review of molecular recognition using melamine, see: Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37 and references therein.

(3) Newkome and co-workers have incorporated 1,5-diaminopyridine units into dendrimers and examined the ability of these molecules to recognize barbituric acid derivatives: Newkome, G. R.; Woolsey, B. D.; He, E.; Moorefield, C. N.; Guther, R.; Baker, G. R.; Escamilla, G. H.; Merill, J.; Luftmann, H. *Chem. Commun.* **1996**, 2737.

(4) Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

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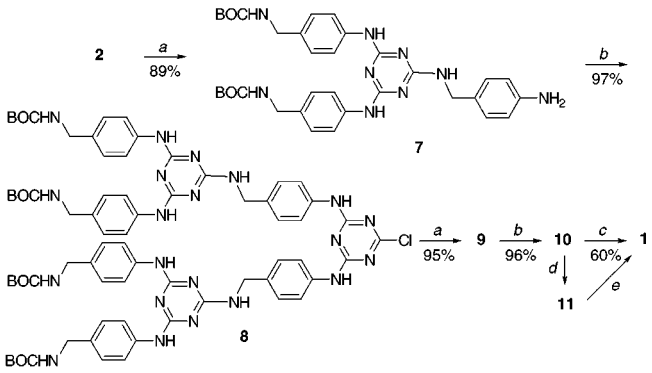
deprotection and coupling, are required for each new generation of dendrimers (G1 = **3**; G2 = **5**; G3 = **1**). However, as the generation number increases, our ability to (i) identify defects, (ii) separate the desired product from side products resulting from incomplete reactions, and (iii) obtain product in reasonable yields all become increasingly difficult.

The reactivities of these dendrimers differ with their size. Most noteworthy are the differences in the rates of deprotection of the BOC group as monitored by the disappearance of the *t*-Bu line in the ^{1}H NMR. Whereas the deprotection of **3** requires 2 h, deprotection of **5** requires 24 h under identical conditions (1:1 TFA/CH_2Cl_2). Complete deprotection of **1** requires 5 days. Molecules **1**, **3**, and **5** show excellent solubility in DMSO and mixtures of CH_3OH/CH_2Cl_2.

Although the presence of **1** can be confirmed by NMR, mass spectrometry, and size exclusion chromatography, we have been unsuccessful in developing strategies for its preparation on large scales because of low yields in the final steps of the synthesis.

The convergent route to **1** relies on adding *p*-aminobenzylamine and cyanuric chloride to the dendron in an iterative fashion (Scheme 2). The use of *p*-aminobenzylamine

Scheme 2. Convergent Synthesis of **1**[a]

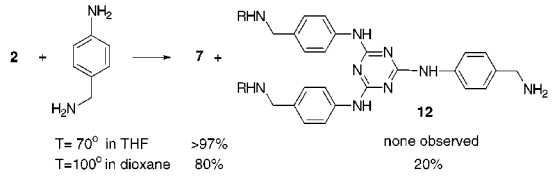


[a] Reagents and conditions: (a) Hunig's base; *p*-aminobenzylamine; 70 °C. (b) Hunig's base; $C_3N_3Cl_3$; 0−25 °C. (c) Ethylenediamine; Hunig's base; 100 °C. (d) Excess ethylenediamine; Hunig's base; 100 °C. (e) **10**; Hunig's base; 100 °C.

to connect triazine groups is noteworthy; differences in nucleophilicity of the two amino groups allow us to exploit reactivity to achieve an orthogonal, convergent synthesis of **1** instead of relying on functional group interconversions or protecting group manipulations. Only a limited number of orthogonal routes to dendrimers have been reported. In contrast to our strategy, these routes rely on orthogonal synthetic tranformations.[7,8]

Reaction of the benzylic amine (over the aniline NH_2) is further enhanced by performing these substitutions on the deactivated, disubstituted monochlorotriazine (Scheme 3). Only one product, **7**, is observed by ^{1}H NMR when *p*-aminobenzylamine is reacted with **2** at 70° C in THF. Performing this reaction at 100° C in dioxane leads to a 4:1 mixture of **7** and **12**.

Scheme 3. Regioselective Reaction of *p*-Aminobenzylamine



Dendrons **2** and **7**−**11** are soluble in a range of common organic solvents, thus allowing purification by silica gel chromatography. Compared with the divergent approach, this route provides large amounts of pure material and has become our method of choice for preparing dendrimers.

Molecule **1** can be obtained from **10** directly, or indirectly through **11.** Intermediate **11** can be isolated and characterized by NMR and size exclusion chromatography. Both routes proceed in very similar yields, and accordingly, we prefer the one-pot method.

Consistent with our previous experience, the ^{1}H NMR spectra of polymelamines in $CDCl_3$ provides little useful information because of the existence of rotational isomers.[2] In DMSO-d_6, however, lines, especially the benzylic lines, can be used to watch the iterative process. Three different types of benzylic groups are seen (peripheral, close to BOC; internal with a monochlorotriazine; internal with a free aniline).

The ^{13}C NMR is more useful. The shifts of the aromatic carbons of both the *p*-aminobenzylamine and the triazine groups are dependent on the substitution pattern of the triazine.[9] Thus, the monochlorotriazines **2**, **8**,[10] and **10**[10] show spectra different than those of amines **7**, **9**, and **11** (Figure 1).

Most useful to us are the carbons "f" and "c" of the *p*-aminobenzylamine group. When attached to a monochlorotriazine (i.e., **2**), these lines appear close together (136 and 137 ppm). When attached to a trisubstituted triazine (i.e., **7**), these lines separate to 134 and 138 ppm). Thus, intermediate **8**, which has one monochlorotriazine and two trisubsituted triazines, shows both features in approximately a 2:1 ratio. The inner pair of lines disappears in **9**, as the chlorine atom is replaced with *p*-aminobenzylamine. These lines reappear in **10**, but in a 6:1 ratio reflecting the ratio of trisubstituted triazines to monochlorotriazine groups.

(5) Tomalia, D. A.; Durst, H. D. *Top. Curr. Chem.* **1993**, *165*, 193.
(6) Moorefield, C. N.; Newkome, G. R.; Baker, G. R. *Aldrichimica Acta* **1992**, *25*, 31.
(7) Zimmerman employs alternating Mitsunobu esterifications and Sonogashira couplings (of terminal acetylenes with aryl iodides) to build G4 and G6 dendrimers; see: Zeng, F.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996**, *118*, 5326.
(8) Frechet's strategy relies on alternating carboxylate alkylations and DCC-mediated esterifications to build G4 dendrimers; see: (a) Spindler, R.; Frechet, J. M. J. *J. Chem. Soc., Perkins Trans. 1* **1993**, 913. (b) Freeman, A. W.; Frechet, J. M. J. *Org. Lett.* **1999**, *1*, 685.
(9) Spectra were obtained on a 400 MHz Varian instrument using typical ^{13}C parameters. DMSO-d_6 is the solvent for all molecules except **9**. The spectrum of **9** in $CDCl_3$ is shown to illustrate the generality of the pattern of lines; slight deviations in chemical shift can be seen.
(10) Lines corresponding to "a" for both **8** and **10** are not discernible in Figure 1. These peaks both appear at 169 ppm.

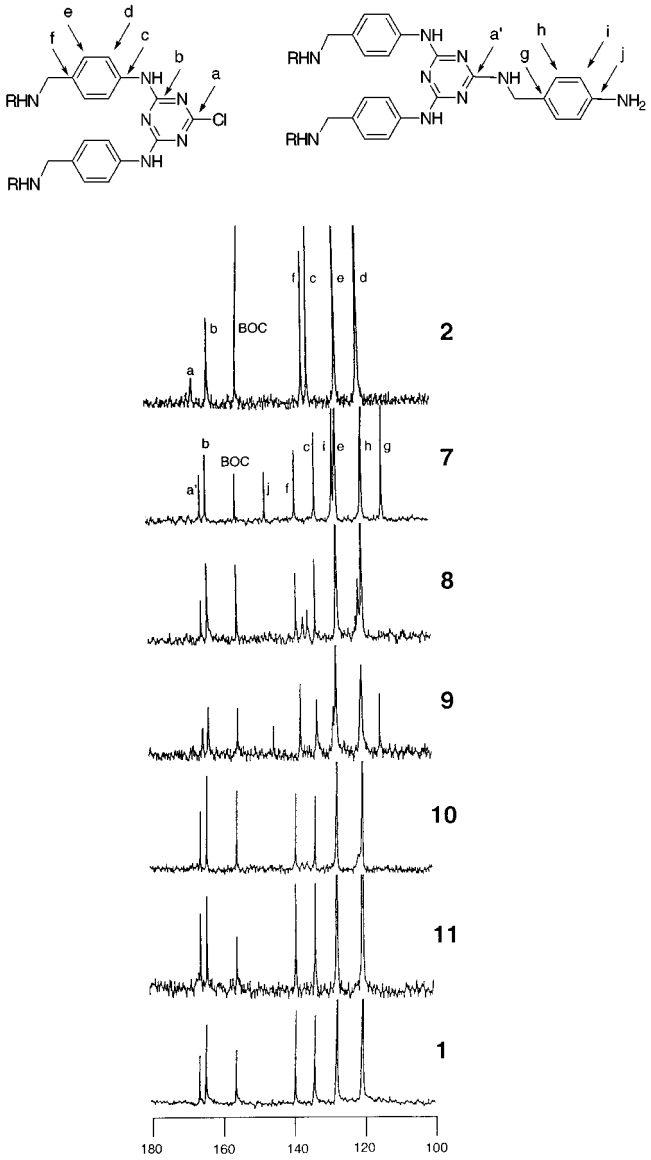


Figure 1. The ^{13}C NMR of **1** and intermediates.

Figure 2 shows the traces of the three generations of dendrimers. The width of each peak increases with increasing size of the molecule. Impurities can be identified in the trace produced by size exclusion chromatography at the G2 (**5**) stage (indicated with an arrow in Figure 2). These impurities can be removed with chromatography to provide material that shows a single ion by mass spectrometry and appears pure by ^{13}C NMR.

If impurities are present in the trace of **1** (obtained through the convergent method, not from **5**), they cannot be identified. However, the tailing of the trace toward longer retention times is highly suggestive of their presence. Polydispersity

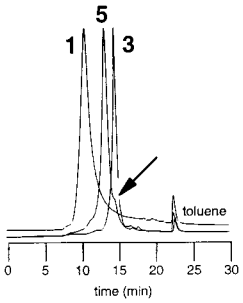


Figure 2. Traces were obtained on an HPLC apparatus equipped with a Jordi gel column (divinylbenzene, 500 Å pore size) using THF as a solvent (1.5 mL/min.) The retention times are 11.1 min (**1**), 13.9 min (**5**), 15.2 min (**3**).

measurements are consistent with these observations and are 1.08, 1.16, and 1.80 for **3**, **5**, and **1**, respectively. Beyond the tailing of **1** by SEC, we have no evidence for the existence of impurities in samples derived using the convergent strategy. The potential impurities of **1**, molecules **10** and/or **11**, give different retention times by SEC. They appear between **5** and **1**, so their presence cannot be discounted solely using this technique. Both ^{13}C NMR and mass spectrometry suggest that **1** is pure within the detection limits of these techniques. Also noteworthy is that **10**, **11**, and **1** are separable by silica gel chromatography.

We are left with three explanations for the observed tailing in the size exclusion traces: trace impurities not identified with the available techniques; aggregation events on the column; absorption events on the column. We are examining the behavior of these molecules as a function of concentration and solvent and cannot yet eliminate these possibilities.

All molecules gave satisfactory mass spectra. With the exception of **1**, little fragmentation of the molecular ion was observed. The fragmentation pattern produced by **1**, which appears to be loss of BOC followed by reaction of the resulting amine, is under investigation.

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Supporting Information Available: Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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