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Synthesis and characterization of higher generation dendrons based on melamine using *p*-aminobenzylamine. Evidence for molecular recognition of Cu(II)

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Abstract—The difference in nucleophilicity between the amines of *p*-aminobenzylamine can be used to synthesize dendrimers based on melamine using a convergent, orthogonal approach. The resulting molecules comprise groups that donate and accept hydrogen-bonds, limiting synthetic accessibility due to intermolecular aggregation. Dendrons with molecular weights exceeding 10 kDa can be prepared by this strategy, but yields drop off significantly at the highest generation (D5) due to difficulties in purification. The addition of Cu(II) reduces the extent of aggregation as evident in SEC traces. UV–vis spectroscopy confirms recognition. © 2001 Elsevier Science Ltd. All rights reserved.

Our interest in dendrimers based on melamine stems from the potential structural diversity that can be introduced into these scaffolds by interconnecting the triazine cores with a variety of diamine linkers.[1] Initially, *p*-aminobenzylamine was chosen as a linking group because it offers an orthogonal, convergent route to these dendrimers.[2–5] We recognized, however, that *p*-aminobenzylamine could also limit the synthetic tractability of these architectures by facilitating aggregation. Newkome and co-workers reported similar difficulties with dendrimers containing diaminopyridine groups.[6] Evidence for aggregation was already suggested in dendrimers with molecular weights of ∼3 kDa.[1] Here, we report the limitations of *p*-aminobenzylamine as a linking group. Evidence for the recognition of Cu(II) by these molecules, and the use of these complexes during analysis is also described.

The synthetic route to these dendrons relies on iterative reactions between cyanuric chloride and *p*-aminobenzylamine (Scheme 1).[7–11] The difference in nucleophilicities between the aryl- and alkylamine groups of *p*-aminobenzylamine allows the reaction of *p*-aminobenzylamine with a monochlorotriazine to proceed with excellent selectivity and in high yield. The ^{1}H NMR spectra of dendrimers in DMSO-d_6 reveal the iterative nature of the synthesis (Fig. 1). For example, the positions and relative intensities of the benzylic protons of *p*-aminobenzylamine groups (**A**–**C**) reveal the extent of reaction. That is, lines from Boc-protected groups (**A**) are different from those of a free aniline (**B**), and from those of a *p*-aminobenzylamine group on the interior (**C**). Similar trends in the appearance of the aniline NH_2 groups (**D**) and the aromatic protons of the free aniline (**E**, **F**) are also evident.

Dendrons comprising *p*-aminobenzylamine can be prepared cleanly up to the fifth generation dendron, **10**, when repeated purification fails to remove traces (<5%) of **9** from the desired product. The starting material is apparent by NMR, mass spectrometry,[14] and size exclusion chromatography (Fig. 2). We attribute difficulties in purification to intermolecular aggregation. Indeed, the generation-dependent broadening that we attribute to aggregation can be significantly reduced by the addition of excess Cu(II).[13] The sharper peaks in the SEC traces suggest that Cu(II) coordinates to the dendrimer and interferes with intermolecular hydrogen-bonding between melamine groups. The coordination of Cu(II) is confirmed by the appearance of three absorption bands between 400 and 480 nm for these complexes with dendrons **2**, **4**, **6**, **8**, and **10** (stacked respectively in Fig. 2b). MALDI/TOF spectra show the ions corresponding to Cu(II) complexes for **2** and **4**.

While we have determined that the use of *p*-aminobenzylamine as an orthogonal linker is limited to medium-sized dendrons due to aggregation, we have uncovered a valuable technique for probing aggregation: the addi-

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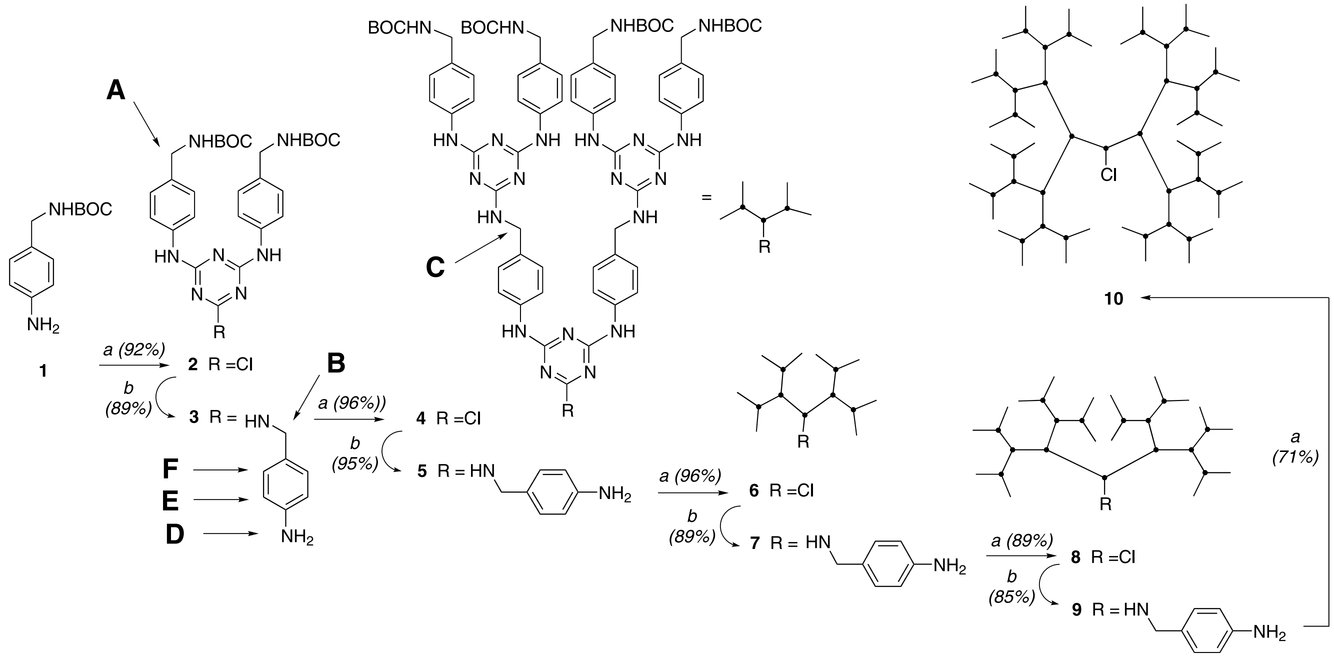

Scheme 1. Synthesis of dendrons. Large dendrons are shown schematically. *Reagents and conditions*: *a*. $C_3N_3Cl_3$, THF, 0–25°C, DIPEA. *b*. *p*-aminobenzylamine, THF, 80°C, DIPEA.[12]

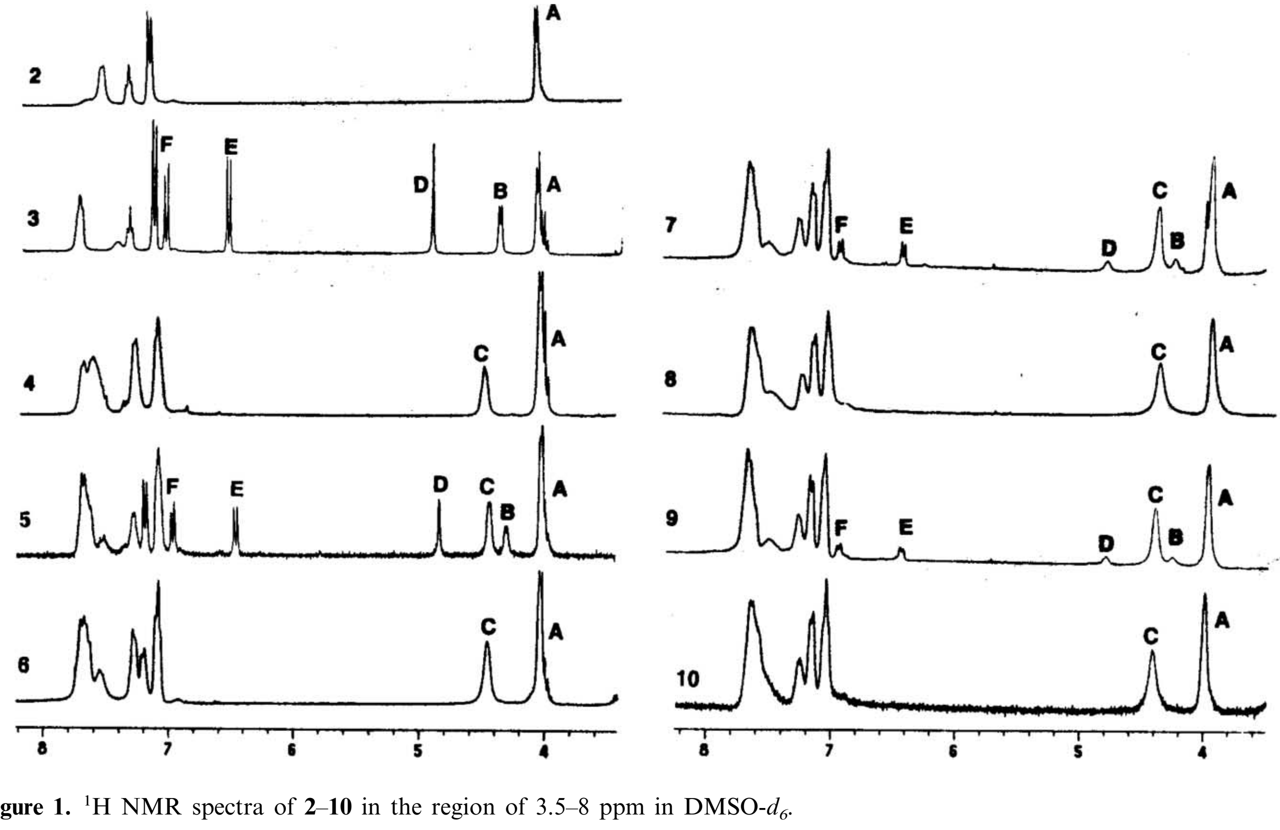

Figure 1. ^1H NMR spectra of **2**–**10** in the region of 3.5–8 ppm in DMSO-d_6.

tion of Cu(II) leads to sharpening of SEC traces. Dendritic structures based on triazines have recently been shown to be useful scavengers of protons and amines.[15] The ability of the reported molecules to sequester copper ions is not unique to these dendrons, but offers potential application of melamine-based architectures.[16–22]

Acknowledgements

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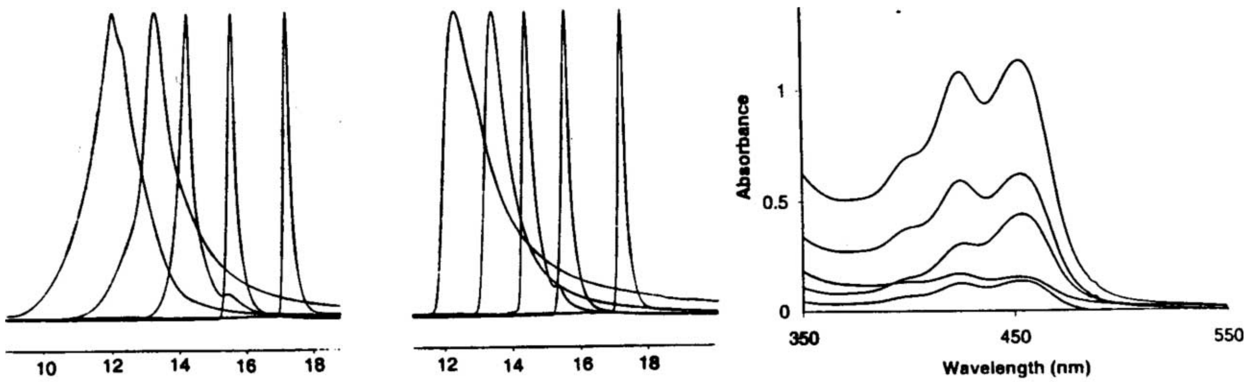

Figure 2. The SEC traces of dendrons **10**, **8**, **6**, **4**, and **2** (left) and the respective Cu(II) complexes (middle) with the associated UV–vis spectra. Times for the SEC are reported in minutes.

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7. Molecules **1**–**6** have been described in Ref. 1. The use of ^{13}C NMR is also described.
8. Data for compound **7**: ^1H NMR (300 MHz, DMSO) δ 9.07 (br, 7H), 9.00 (br, 7H), 7.73 (m, 28H), 7.55 (br, 6H), 7.32 (m, 8H), 7.21 (m, 12H), 7.12 (br, 16H), 6.98 (d, $J=11.5$ Hz, 2H), 6.46 (d, $J=12$ Hz, 2H), 4.86 (s, 2H), 4.48 (br, 12H), 4.34 (br, 2H), 4.05 (br, 16H), 1.39 (s, 72H). ^{13}C NMR (75 MHz, DMSO) δ 166.47, 164.77, 156.47, 148.02, 139.58, 133.98, 128.69, 127.73, 120.43, 114.38, 78.35, 43.73, 28.93. MS: Calcd, 3158.55 (M^+); Found (MALDITOF), 3156.23.
9. Data for compound **8**: ^1H NMR (300 MHz, DMSO) δ 9.07 (s, 15H), 9.00 (s, 15H), 7.70 (m, 60H), 7.58 (br, 14H), 7.30 (br, 16H), 7.20 (d, $J=11.5$ Hz, 28H), 7.10 (br, 32H), 4.46 (br, 28H), 4.05 (br. 32H), 1.38 (s, 144H). ^{13}C NMR (75 MHz, DMSO) δ 166.48, 164.77, 156.49, 139.60, 133.99, 127.76, 120.44, 78.38, 43.74, 28.97. MS: Calcd, 6428.57 (M^+); Found (MALDITOF): 6429.92.
10. Data for compound **9**: ^1H NMR (300 MHz, DMSO) δ 9.06 (br, 15H), 8.98 (br, 15H), 7.71 (m, 60H), 7.56 (br, 14H), 7.30 (m, 16H), 7.20 (m, 28H), 7.09 (br, 32H), 6.98 (d, $J=11.5$ Hz, 2H), 6.48 (d, $J=12$ Hz, 2H), 4.83 (br, 2H), 4.46 (br, 28H), 4.36 (br, 2H), 4.05 (br, 32H), 1.38 (s, 144H). ^{13}C NMR (75 MHz, DMSO) δ 166.48, 164.78, 156.49, 148.00, 139.61, 133.99, 128.73, 127.76, 120.43, 114.39, 78.39, 43.74, 28.97. MS: Calcd, 6514.28 (M^+); Found (MALDITOF): 6520.96.
11. Data for compound **10**: ^1H NMR (300 MHz, DMSO) δ 9.08 (s, 32H), 9.03 (s, 32H), 7.69 (m, 124H), 7.61 (br, 30H), 7.28 (br, 32H), 7.18 (m, 60H), 7.08 (br, 64H), 4.45 (br, 60H), 4.03 (br, 64H), 1.36 (s, 288H). ^{13}C NMR (75 MHz, DMSO) δ 166.10, 164.56, 156.48, 139.44, 134.15, 127.78, 120.53, 78.39, 43.74, 28.96. MS: Calcd, 13140.16 (M^+); Found (MALDITOF): 13142.81.
12. DIPEA is *N*,*N*-diisopropylethylamine.
13. The complexes were prepared by the reactions of dendrons with $CuCl_2·2H_2O$ in refluxing CH_2Cl_2–CH_3OH. Titrations with this salt or with $Cu(OAc)_2$ were unsuccessful suggesting a weaker association between copper ions and the dendrons than the counterions.
14. The line corresponding to molecular ions for some of these dendrons is broad, and has a position that is highly dependent ±0.1% on the conditions of ionization. Accordingly, some of the mass spectra of these dendrons, especially **9**, deviate from the predicted mass. Subsequent molecules prove satisfactory, however, and isotope distribution patterns match the predicted pattern. The origins of these shifts, and the development of an effective protocol for obtaining accurate masses of these polymers is currently underway with Dr. David Russell and the Laboratory for Biological Mass Spectrometry, Texas A&M University.
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