Structure−Activity Relationships in Dendrimers Based on Triazines: Gelation Depends on Choice of Linking and Surface Groups

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ABSTRACT: A small library of dendrimers based on triazines was prepared by varying the surface and interior linking groups to study the relationship between structure and the ability of some of these dendrimers to gel in acidified organic solvents including chloroform, methylene chloride, and benzene. Convergent, divergent, and semiconvergent routes yielded eight molecules comprising *p*-aminobenzylamine or piperazine linking groups and piperidine or butylamine surface groups. Dendrimers that incorporate interior and surface groups capable of hydrogen bonding (*p*-aminobenzylamine or butylamine) gel at lower concentrations than those groups that offer no hydrogen-bonding protons (piperazine or piperidine). In some cases, these latter molecules do not form gels to the limit of solubility. Studies with competitive solvents corroborate hydrogen bonding, but neither IR nor NMR spectroscopy reveals signals that substantiate this hypothesis. TEM studies show fibers. Studies of these systems at concentrations below that required for gelation indicate the presence of aggregates in solution: an assay using gel permeation chromatography offers predictive ability for gelation.

Introduction

Our interest in dendrimers based on melamine stems from their synthetic accessibility,[1,2] opportunities for exercising exquisite control over their composition,[3] and their intrinsic potential for molecular recognition.[4] These characteristics make them an ideal class of macromolecules to explore structure−activity relationships. In the course of exploring their recognition potential, we serendipitously discovered that some dendrimers form gels in acidified organic solvents. To evaluate potential contributions that hydrogen bonding might have on gel formation, a library of eight molecules was prepared that varied in size and the choice of internal linking groups and surface groups. To further probe the limits of triazine chemistry, targets were prepared using convergent, semiconvergent, and divergent routes. We find that gelation depends on the composition of the gelator (dendrimer). The structure−activity trend corroborates the recognized importance of hydrogen-bonding networks in gel formation. We establish here that triazine-based dendrimers are readily amenable to structure−activity investigations based on inherent characteristics of their chemistry.

Dendrimers based on melamine offer a number of opportunities for pursuing structure−activity relationships and suggest to us that this system is a versatile model system for exploring a range of phenomena. First, melamine dendrimers incorporate, at minimum, two components: a triazine core from which branches radiate and diamine branches. Conceptually, a wealth of diamines can be incorporated into these architectures to provide structures with radial symmetry like those described here. Second, we have shown that the differential reactivity of triazines can be used to control the placement of different diamines within a generation. Third, structure−activity studies in this system are facilitated by reactions that proceed rapidly and chemoselectively and give high yields to provide products with excellent solubilities that are readily purified by conventional chromatographic methods.

Only a limited number of dendritic macromolecules that form gels have been described. Most examples are single component systems. Stupp and co-workers have incorporated a first-generation dendritic building block into a three domain molecule that gels.[5] Aida has described gelation of dipeptides functionalized with poly(benzyl ether) dendrons.[6] We are aware of only four dendrimers that gel, but these systems are not as amenable to structure−activity−relationship studies as our system. Both Newkome and Jorgensen have described "dumbell" shaped second generation dendrimers that form columnar fibers.[7,8] Caminade and Majoral have reported that phosphazine dendrimers gel aqueous solutions.[9] The rate of gelation is increased in the presence of various small molecules. Partridge and coworkers described gelation of poly(lysine) dendrimers in the presence of aliphatic diamines.[10] Small molecule gelators are more common.[11−18] Shirai and Shinkai have reported two-component, melamine-based systems with complementary hydrogen-bonding groups that gel.[13]

Experimental Section

Materials. Cyanuric chloride (99%, Acros), *p*-aminobenzylamine (99%, Aldrich), piperazine (99%, Acros), piperidine (99%, Aldrich), *n*-butylamine (99.5%, Acros), *N*,*N*-Diisopropylethylamine (98%, Acros) were used as received. Solvents $CDCl_3$, DMSO-d_6 (Cambridge Isotope Laboratories, Ins), $CHCl_3$, and THF (Mallinckrodt, HPLC grade) were used without further treatment. Chart 1 shows various compounds used in the paper.

NMR Spectroscopy. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Varian spectrometer.

MALDI Mass Spectrometry. Dry drop preparation was performed with 2,4,6-trihydroxyacetophenone (THAP) as a matrix. A 1:1 overlayer mixture of 1 μM aqueous analyte and 10 mg/mL THAP matrix in methanol was spotted in 1 μL aliquots on a Teflon coated plate. MALDI−TOF mass spectra were acquired in positive ion mode on a Voyager-DE STR mass spectrometer (Applied Biosystems, Framingham, MA) equipped with a pulsed nitrogen laser emitting at 337 nm. Samples were analyzed in linear mode using a delayed extraction time of ~500 ns and an accelerating voltage of 20

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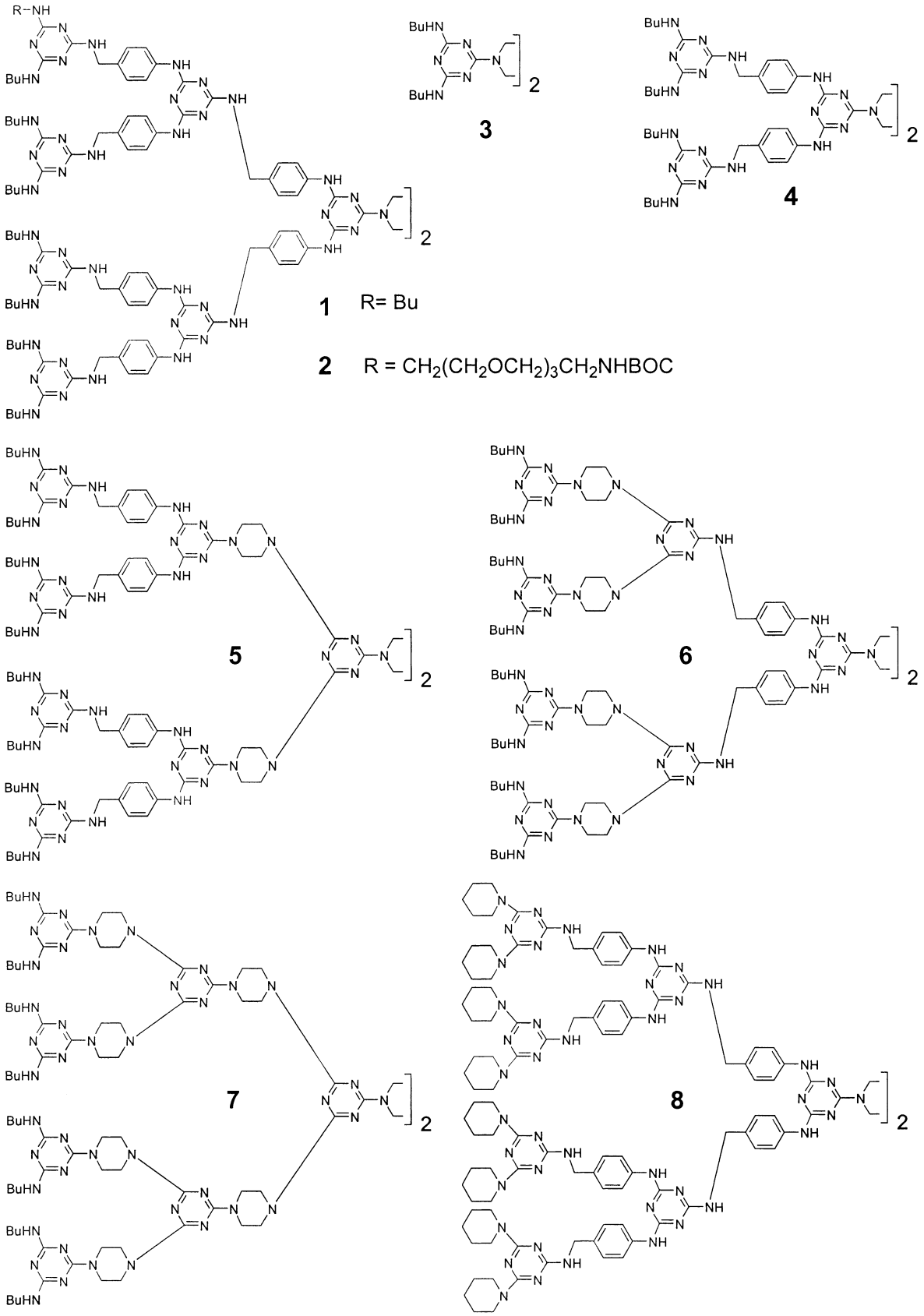
Chart 1



kV. Laser strength was adjusted to provide the optimal signal-to-noise ratio. All spectra were recorded as an average of 50−100 laser shots.

Gel Permeation Chromatography. Traces were obtained on a Waters 600 chromatograph system at room temperature by monitoring at λ = 254 nm with a Waters 2487 dual absorbance detector using a Waters Styragel HR 5E column (MW range 10^3−10^6). THF was used as the carrier solvent at a flow rate of 0.6 mL/min. All dendrimers were analyzed at 0.06 mM using an injection volume of 10 μL.

TEM Imaging. A portion of gel was smeared across a TEM grid and then placed in a sealed chamber with an open vessel

containing aqueous OsO_4 overnight. The grids were examined using a Ziess 10C instrument (80 kV).

General Dimerization Procedure (3). 2,4-Dibutylamino-6-chlorotriazine[3] (516 mg, 2 mmol) was dissolved in 10 mL of THF containing 0.4 mL of *N,N*-diisopropylethylamine (2.3 mmol) and piperazine (86 mg, 1 mmol). The solution was bubbled with nitrogen for 5 min and sealed in a Parr vessel before stirring at 80 °C for 12 h. Upon cooling, the solvent was removed, and the residue was purified by column chromatography on silica gel using $CH_2Cl_2-CH_3OH$ (50:1) to afford a white solid (508 mg, 96%). Mp: 155−156 °C. ^{1}H NMR ($CDCl_3$): δ 5.02 (br, 4H), 3.75 (br, 8H), 3.32 (m, 8H), 1.49 (m, 8H), 1.33 (m, 8H), 0.88 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 166.07, 165.24, 43.24, 40.57, 32.16, 20.26, 14.00. MS: calcd, 529 (M + H)$^+$; found ($^+$FAB/DP): 529 (M + H)$^+$.

General Cyanuric Chloride Protocol (13). Intermediate **12** (500 mg, 0.61 mmol) was dissolved in 10 mL of THF before triazine trichloride (57 mg, 0.31 mmol) and 0.2 mL of *N,N*-diisopropylethylamine (1.2 mmol) were added to the solution. After the reaction mixture was stirred at room temperature for 24 h, the solvent was removed and the residue was purified by column chromatography using $CH_2Cl_2-CH_3OH$ (30:1, 25:1, 20:1) to give a white solid (480 mg, 90%). ^{1}H NMR ($CDCl_3$): δ 7.38 (br, 4H), 7.21 (br, 4H), 5.62 (br, 4H), 5.11 (br, 8H), 4.50 (br, 4H), 3.76 (br,32H), 3.32 (br, 16H), 1.48 (br, 16H), 1.31 (m, 16H), 0.88 (t, 24H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.39, 165.36, 164.17, 136.37, 128.27, 121.84, 44.72, 43.23, 40.54, 32.15, 20.28, 14.06. MS: calcd, 1735.63 (M + H$^+$); found (MALDI−TOF): 1735.95 (M + H)$^+$, 1758.64 (M + Na)$^+$, 1774.22 (M + K)$^+$.

General Deprotection Protocol (16). Intermediate **15** (120 mg, 0.122 mmol) was dissolved in 3 mL of CH_2Cl_2−TFA (1:1) and stirred for 12 h. After solvent was removed, the residue was dissolved in water and the solution was adjusted to pH 11 by adding 1 M NaOH. A white solid was collected by filtration (70 mg, 98%). Mp: 215 °C dec. ^{1}H NMR (CD_3OD): δ 3.91 (m, 16H), 3.67 (m, 8H), 3.10 (m, 16H), 3.23 (t, 16H). ^{13}C NMR (CD_3OD): δ 165.43, 43.28, 40.01. MS: calcd, 581 (M + H)$^+$; found (+FAB/DP), 581 (M + H)$^+$.

General 4-Aminobenzylamine Protocol (20). Intermediate **19** (2.00 g, 7.10 mmol) was dissolved in 100 mL of THF, and 4-aminobenzylamine (3.47 g, 28.4 mmol) was added. The solution was stirred at 80 °C for 12 h. Upon cooling, the precipitate was removed by filtration and the solvent was evaporated. Column chromatography (9:1 $CH_2Cl_2-CH_3OH$) provided a yellow oil (1.95 g, 75%). Mp: 120−123 °C. ^{1}H NMR ($CDCl_3$): δ 1.55−1.64 (m, 12 H), 3.71 (br, 8H), 4.45 (d, J = 5.7 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 25.41, 26.21, 44.36, 44.75, 1115.26, 129.24, 130.11, 145.50, 165.26, 166.48. ESI-MS: calcd, 367.49 (M + H)$^+$; found 368.24 (M + H)$^+$.

Dendrimers 1 and 2 have been reported previously.[3]

Dendrimer 3. Described in the general dimerization procedure.

Dendrimer 4. After the general dimerization procedure was employed, chromatography on silica gel was performed using $CH_2Cl_2-CH_3OH$ (50:1, 25:1) to afford the product as a white solid (370 mg, 92%). Mp: 192−194 °C. ^{1}H NMR (300 MHz, DMSO): δ 9.18 (br, 4H), 7.67 (br, 8H), 7.42 (br, 4H), 7.22 (d, J = 11.5, 8H), 7.05 (br, 8H), 4.41 (br, 8H), 3.86 (br, 8H), 3.23 (br, 16H), 1.45 (br, 16H), 1.29 (br, 16H), 0.88 (br, 24H). ^{13}C NMR ($CDCl_3$): δ 164.74, 139.43, 134.00, 128.21, 120.44, 43.38, 40.00, 32.02, 20.29, 14.44. MS: calcd, 1609.05 (M + H$^+$); found (MALDI−TOF), 1609.81 (M + H)$^+$, 1631.95 (M + Na).$^+$

Dendrimer 5. Intermediates **11** (274 mg, 0.34 mmol) and **16** (25 mg, 0.043 mmol) and 0.2 mL of *N,N*-diisopropylethylamine (0.86 mmol) were dissolved in 8 mL of THF. The solution was bubbled with nitrogen for 5 min and was sealed in a Parr vessel before stirring for 36 h at 80 °C. Upon cooling, the solvent was evaporated, and the residue was purified by column chromatography using $CH_2Cl_2-CH_3OH$ (30:1, 20:1) to give the product as a white solid (131 mg, 84%). Mp: 177−178 °C. ^{1}H NMR (DMSO-d_6): δ 9.13 (br, 8H), 7.62 (br, 16H), 7.18 (br, 16H), 7.10−6.00 (br, 24H), 4.35 (br, 16H), 3.81 (br, 40H), 3.16(br, 32H), 1.40 (br, 32H), 1.25 (m, 32H), 0.82 (m, 48H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.42, 165.20, 164.75, 139.15, 128.50, 127.83, 120.38, 43.48, 38.88, 32.29, 20.32, 14.45. MS: calcd, 3626.32 (M$^+$); found (MALDI−TOF): 3627.45 (M + H)$^+$, 3650.04 (M + Na)$^+$.

Dendrimer 6. After the general dimerization procedure was employed, column chromatography was performed using $CH_2Cl_2-CH_3OH$ (20:1, 16:1) to afford the product as a white solid (353 mg, 82%). Mp: 190−192 °C. ^{1}H NMR ($CDCl_3$): δ 7.39 (br, 8H), 7.16 (br, 8H), 5.75 (br, 4H), 5.00 (br, 16H), 4.47 (br, 8H), 3.74 (br, 72H), 3.29 (br, 32H), 1.44 (m, 32H), 1.29 (m, 32H), 0.87 (m, 48H). ^{13}C NMR (DMSO): δ 164.26, 163.26, 162.31, 136.06, 132.03, 126.07, 118.30, 42.21, 41.10, 38.35, 29.95, 18.08, 11.86. MS: calcd, 3484.34 (M + H)$^+$; found (MALDI−TOF) 3507.60 (M + Na)$^+$.

Dendrimer 7. Intermediate **18** (55 mg, 0.035 mmol) was dissolved in 8 mL of THF before **9** (145 mg, 0.56 mmol) and 0.20 mL of *N,N*-diisopropylethylamine (1.2 mmol) were added. The solution was bubbled with nitrogen for 5 min and was sealed in a Parr vessel before stirring for 36 h at 80 °C. Upon cooling, the solvent was evaporated, and the residue was purified by column chromatography using $CH_2Cl_2-CH_3OH$ (30:1, 20:1) to give a white solid (82 mg, 70%). Mp: 240−241 °C. ^{1}H NMR ($CDCl_3$): δ 5.60−5.00 (br,16H), 3.81 (br, 104H), 3.36 (m, 32H), 1.52 (m, 32H), 1.37 (m., 32H), 0.91 (m, 48H). ^{13}C NMR ($CDCl_3$): δ 165.66, 43.38, 40.68, 31.98, 20.25, 14.00. MS: calcd, 3338.32 (M + H)$^+$; found (MALDI−TOF): 3339.96 (M + H)$^+$.

Dendrimer 8. Intermediate **22** (15 mg, 0.008 mmol) was dissolved in 1.5 mL of THF, and *N,N′*-diisopropylethylamine (0.25 mL, 1.4 mmol) was added to the reaction mixture in a Parr vessel. Intermediate **23** (15 mg, 0.008 mmol) was added, and the reaction was stirred for 24 h at 80 °C. After removal of the solvent, column chromatography (40:1 $CH_2Cl_2-CH_3OH$) provided a white solid (20 mg, 68%). ^{1}H NMR (in DMSO-d_6, 300 MHz): δ 1.49−1.87 (br, 96H), 3.59 (br, 64H), 3.77 (br, 8H), 4.30 (br, 16H), 4.43 (br, 8H), 7.19 (br, 24H), 7.64 (br, 24H). ^{13}C (DMSO-d_6): δ 25.02, 26.01, 43.86, 44.21, 79.18, 79.63, 120.43, 134.56, 128.15, 139.36, 164.71, 166.40. MS: calcd, 3964.91 (M + H)$^+$; found (ESI-TOF) 3965.34 (M + H)$^+$.

Intermediates 9, 10, and **11** have been reported previously.[3]

Intermediate 12. After intermediate **9** (1.50 g, 5.81 mmol) was dissolved in 20 mL of THF, piperazine (1.25 g, 14.5 mmol) was added to the solution. The reaction was stirred at 75 °C for 12 h in a Parr vessel. Upon cooling, solid materials were filtered, and the solvent was evaporated. The residue was redissolved in 150 mL of $CHCl_3$ and washed three times with water. The organic phase was dried over Na_2SO_4. After evaporation of the solvent, the residue (1.50 g, 4.87 mmol) was redissolved in 10 mL of THF. Triazine trichloride (448 mg, 2.44 mmol) and 1.0 mL of *N,N*-diisopropylethylamine (5.7 mmol) were added to the solution. After the reaction was stirred for 12 h, the solvent was removed, and the residue was redissolved in 150 mL $CHCl_3$. The organic phase was washed three times with water and dried over Na_2SO_4. Removal of the solvent provided a residue (1.70 g, 2.34 mmol) that was redissolved in 15 mL of THF before *p*-aminobenzylamine (0.71 g, 5.9 mmol) was added. After bubbling with nitrogen, the mixture was sealed in a Parr vessel and stirred at 75 °C for 12 h. The solid that appeared was filtered, and the solvent was removed. The residue was purified by column chromatography using $CH_2Cl_2-CH_3OH$ (30:1, 25:1, 20:1) to give the product (1.81 g, 95%) as a white solid. Mp: 110−111 °C. ^{1}H NMR ($CDCl_3$): δ 7.11 (d, J = 11.5 Hz, 2H), 6.61 (d, J = 12 Hz, 2H), 5.16 (t, 1H), 4.87 (br, 2H), 4.45 (d, J = 8.0 Hz, 2H), 3.78 (br, 16H), 3.34 (m, 8H), 1.52 (m, 8H), 1.34 (m, 8H), 0.92 (t, 12H). ^{13}C NMR ($CDCl_3$): δ 166.49, 165.58, 165.43, 145.71, 129.79, 129.18, 115.32, 44.66, 43.26, 40.58, 32.21, 20.30, 14.07. MS: calcd, 811.5670 (M + H$^+$); found (ESI/TOF) 812.5752 (M + H)$^+$, 406.7947 (M + 2H)$^{2+}$.

Intermediate 13. Described in the general cyanuric chloride protocol.

Intermediate 14. After the general cyanuric chloride procedure was employed, a white solid was recovered (3.6 g, 92%). Mp: 115−116 °C. ^{1}H NMR($CDCl_3$): δ 3.75 (br, 8H), 3.44

(br, 8H), 1.46 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 169.72, 164.58, 154.83, 80.43, 43.58, 28.59. MS: calcd, 484 $(M + H)^+$; found (+FAB/DP), 484 $(M + H)^+$.

Intermediate 15. After the general dimerization procedure was employed, column chromatography using CH_2Cl_2−CH_3OH (50:1) afforded the product as a white solid (466 mg, 95%). Mp: 235−237 °C. ^{1}H NMR ($CDCl_3$): δ 3.77 (br, 8H), 3.71 (br, 16H), 3.42 (br, 16H), 1.45 (s, 36H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.42, 155.03, 80.08, 43.31, 28.63. MS: calcd, 981 $(M + H)^+$; found (+FAB/DP), 982 $(M + H)^+$.

Intermediate 16. Described in the general deprotection protocol section.

Intermediate 17. Intermediate **14** (44 mg, 0.076 mmol) was dissolved in 5 mL of THF before **16** (293 mg, 0.61 mmol) and 0.15 mL of *N*,*N*-diisopropylethylamine (0.86 mmol) were added to the solution. The solution was bubbled with nitrogen for 5 min and sealed in a Parr vessel. The mixture was heated to 80 °C under stirring for 36 h. Upon cooling, the solvent was evaporated, and the residue was purified by column chromatography using CH_2Cl_2−CH_3OH (30:1, 25:1) to afford the product as a white solid (135 mg, 75%). Mp: 242−243 °C. ^{1}H NMR ($CDCl_3$): δ 3.81 (br, 40H), 3.75 (br, 32H), 3.44 (br, 32H), 1.48 (s, 72H). ^{13}C NMR ($CDCl_3$): δ 165.44, 155.06, 80.11, 43.37, 28.65. MS: calcd, 2369.43 $(M + H)^+$; found (MALDITOF), 2369.99 $(M + H)^+$.

Intermediate 18. After the general deprotection protocol was employed, the residue was extracted twice with CH_2Cl_2−CH_3OH (1:1). After solvent was removed, a white solid was obtained (64 mg, 96%). Mp: 218 °C dec. ^{1}H NMR (CD_3OD): δ 3.78(br, 64H), 2.84 (m, 40H) ^{13}C NMR (75 MHz, CD3OD): δ 165.53, 45.24, 43.76, 43.06. MS: calcd, 1569.93 $(M + H)^+$; found (+FAB/DP), 1569.85 $(M + H)^+$.

Intermediate 19. After the general cyanuric chloride procedure was employed, the residue was dissolved in 150 mL of CH_2Cl_2 and washed twice with water and sodium bicarbonate. After drying over Na_2SO_4, the solvent was removed. Recrystallization from 150 mL of ethanol yielded a white solid (2.60 g, 85%). Mp: 117−119 °C.^{1}H NMR ($CDCl_3$): δ 1.52−1.67 (m, 12 H), 3.71 (t, J = 5.4 Hz, 8H). ^{13}C NMR ($CDCl_3$): δ 25.03, 26.05, 44.76, 164.22, 169.57. MS calcd, 281.78 $(M + H)^+$; found (ESI-TOF), 282.14 $(M + H)^+$.

Intermediate 20. Described in the general 4-aminobenzylamine protocol.

Intermediate 21. After the general cyanuric chloride protocol was employed, the residue was redissolved in CH_2Cl_2 and washed with sodium bicarbonate. Column chromatography (9:1 CH_2Cl_2−CH_3OH, with 1% THF) provided a yellow solid (1.45 g, 77%). Mp: 213-216 °C. ^{1}H NMR ($CDCl_3$): δ 1.44−1.75 (m, 24 H), 3.69−3.77 (m, 16H), 4.56−4.58 (br, 4H), 7.23−7.42 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 25.34, 26.10, 26.18, 44.39, 121.72, 128.43, 136.18, 137.19, 163.85, 165.15, 166.45. MS: calcd, 846.47 $(M + H)^+$; found (ESI−TOF), 846.47 $(M + H)^+$.

Intermediate 22. After the general *p*-aminobenzylamine protocol was employed, column chromatography (9:1 CH_2Cl_2−CH_3OH) provided a yellow solid (0.67 g, 47%). Mp: 150 °C dec. ^{1}H NMR ($CDCl_3$): δ 1.44−1.91 (m, 24H), 3.71−3.77 (br, 16H), 4.43−4.49 (m, 6H), 6.56 (d, J = 9 Hz, 2H), 7.06−7.31 (br, 10H). ^{13}C NMR ($CDCl_3$): δ 25.38, 25.99, 26.20, 44.37, 44.85, 115.39, 120.38, 120.79, 128.35, 128.86, 128.96, 134.38, 137.95, 145.78, 165.22, 166.51, 166.51. MS: calcd, 932.18 $(M + H)^+$; found (ESI/TOF), 932.57 $(M + H)^+$.

Intermediate 23. After the general cyanuric chloride protocol was employed, column chromatography (40:1 CH_2Cl_2−CH_3OH) provided a white solid (0.40 g, 86%). ^{1}H NMR ($CDCl_3$): δ 1.50−1.88 (br, 48H), 3.73 (br, 32H), 4.44 (br, 12H), 7.11−7.32 (br, 24H). ^{13}C NMR (DMSO): δ 25.02, 26.01, 43.86, 44.22, 120.65, 128.19, 134.62, 139.39, 140.21, 164.65, 164.82. MS: calcd, 1976.10 $(M + H)^+$; found (MALDI−TOF), 1976.01 $(M + H)^+$.

Intermediate 24. Intermediate **23** (20 mg, 0.010 mmol) was dissolved in 3 mL of THF, and piperazine (40 mg, 0.51 mmol) was added. After reaction was stirred for 16 h, the solvent was removed, and column chromatography (40:1 CH_2Cl_2−CH_3OH) provided a white powder (17 mg, 83%). ^{1}H NMR ($CDCl_3$): δ 1.50−1.80 (br, 48 H), 2.77 (br, 4H), 4.42 (br, 12H), 7.10 (br, 12H), 7.32 (br, 12H). ^{13}C NMR (DMSO-d_6): δ 25.25, 26.20, 44.14, 120.38, 125.54, 128.07, 128.69, 134.74, 139.15, 139.85, 152.05, 164.52, 165.01, 166.35. MS: calcd, 2025.20 $(M + H)^+$; found (MALDI−TOF), 2025.77 $(M + H)^+$.

Results and Discussion

Synthesis. The syntheses of **1** and **2** proceed convergently[19,20] by relying on iterative reactions with cyanuric chloride and *p*-aminobenzylamine as previously described.[1,3,4] Dendrimers **3** and **4** were prepared using the same strategy as illustrated in Scheme 1 commencing with intermediate **9**. Compound **9** also serves as the starting material for convergent synthesis of **6**, a radially symmetric target presenting piperazine and *p*-aminobenzylamine layers.

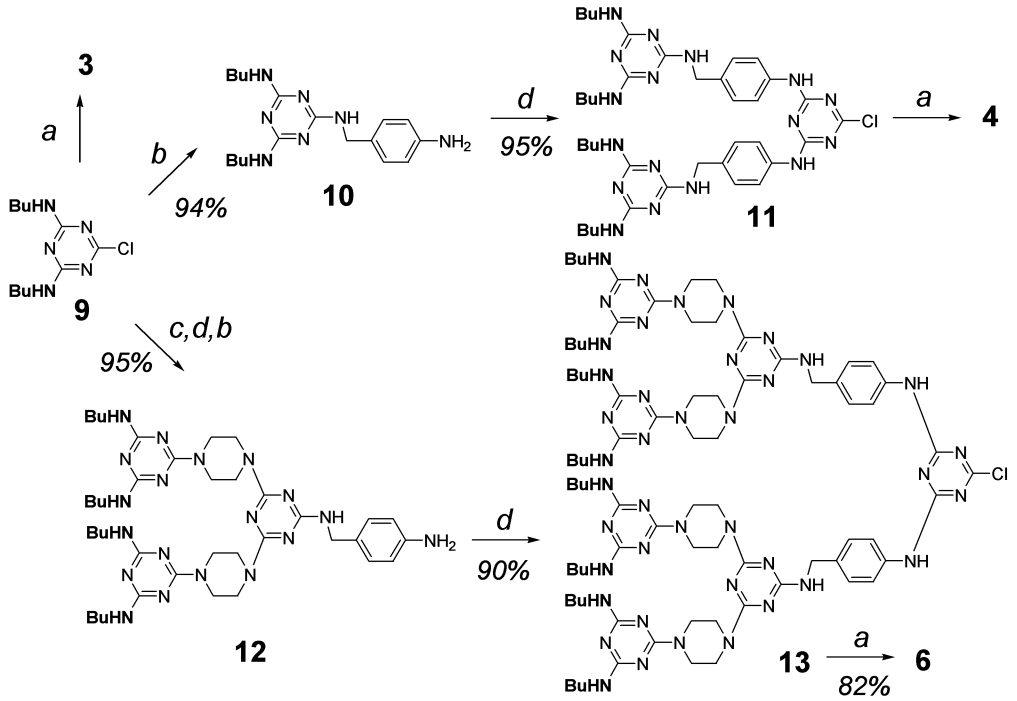
Previously described efforts for the divergent syntheses[21] of dendimers based on melamine were relatively unsuccessful for reasons that we attribute primarily to low reactivity of the *p*-aminobenzylamine groups on the periphery.[3] Targets **5** and **6** offered an opportunity to readdress both divergent and semiconvergent routes to these molecules while taking advantage of the enhanced nucleophilicity of the constrained secondary amines of piperazine groups when compared with benzylic amines. Indeed, the divergent and semiconvergent approaches proceed in high yields (Scheme 2). From common intermediate **16**, reaction with the generation two dendron **11** yields **5** in 84% overall yield. Further divergent growth from **16** proceeds in lower yields, 75%, to provide **7**, but such yields far exceed those previously described (<10%) for the divergent synthesis of dendrimers comprising solely *p*-aminobenzylamine groups.

The final target, **8**, was prepared using a convergent approach (Scheme 3) which remains the best strategy for the preparation of these dendrimers in our hands. From **21**, the unoptimized synthesis is completed in seven linear steps in 12% overall yield.

Throughout the syntheses of these architectures, the reactions can be monitored readily by thin-layer chromatography: most reactions proceed spot-to-spot. The iterative nature of these reactions is reflected in the NMR spectra of these materials. Figure 1 shows the ^{13}C NMR spectra for the intermediates and product of the divergent synthesis of **7**. The trace of **14** reveals three lines in the far downfield region of the spectra corresponding to the chlorinated (a) and aminated (b) carbons of the monochlorotriazine, and the carbonyl group of the BOC protecting group (c). This line and others that belong to the BOC group (d, f) oscillate (**14**, **15**, and then **17**) in appearance as would be predicted by the synthesis. Only one type of piperazine signal (e) is apparent when both nitrogens are functionalized (BOC or triazine). However, upon deprotection to **16**, two signal appears upfield of the solvent signal (CD_3OD) corresponding to carbons proximal to the free amine (g) and those proximal to the *N*-triazine groups (h and i). These peaks reappear in the trace of **18**, but the chemical shift dispersion is notably reduced. Installation of the bis(butylamino)monochlorotriazine group on the periphery leads to the disappearance of the these signals and the reappearance of signal (i). The butyl lines are evident.

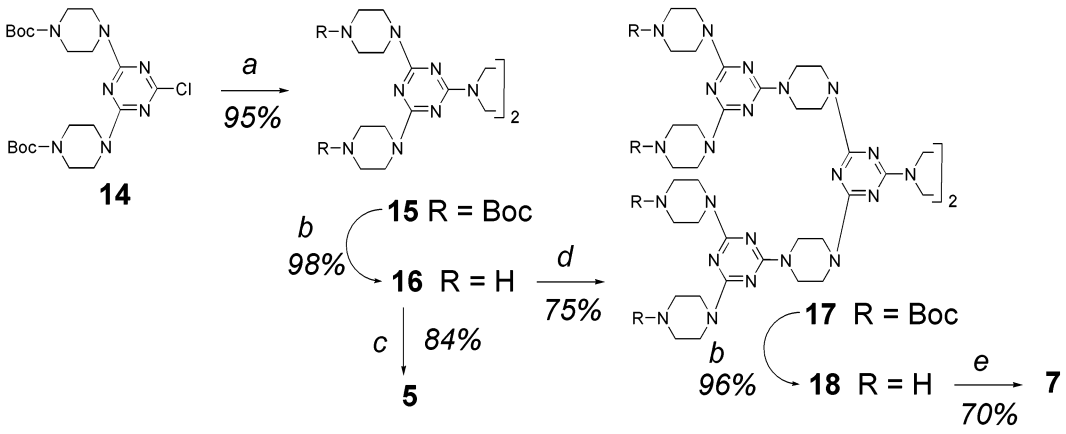
Gelation. Gelation was first observed when solutions of **1** were prepared in $CDCl_3$ for NMR analysis. At 10 mM **1**, a colorless, transparent gel was obtained within minutes. The gel is stable to temperatures exceeding 70 °C. Melting and dilution established that gels form at concentrations of **1** as low as 2 mM. This observation

Scheme 1. Synthesis of Dendrimers 3, 4, and 6 Using a Convergent Approach



[a] Piperazine (0.5 equiv), Hunig's base. [b] *p*-Aminobenyzlamine, Hunig's base. [c] Excess piperazine. [d] $C_3N_3Cl_3$, Hunig's base.

Scheme 2. Divergent Syntheses of 5 and 7



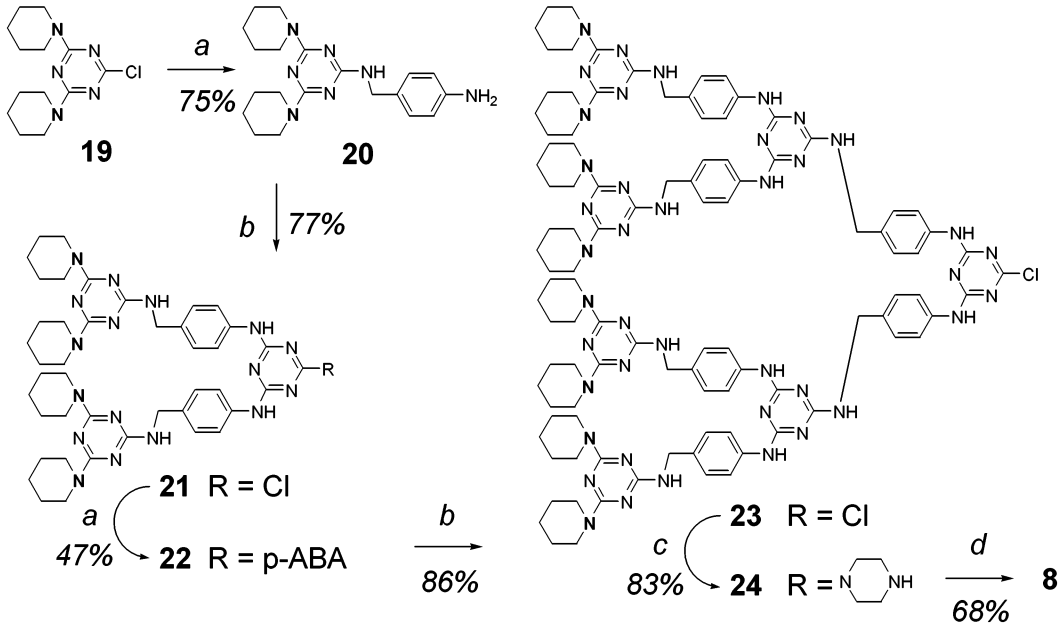
[a] Piperazine (0.5 equiv), Hunig's base. [b] Trifluoroacetic acid. [c] Intermediate **11**, Hunig's base. [d] Intermediate **14**, Hunig's base. [e] Intermediate **9**, Hunig's base.

was not surprising to us. While gel formation is serendipitous, we had previously observed that larger generation dendrons (third or greater) based on *p*-aminobenzylamine aggregate, presumably through the formation of networks of hydrogen bonds between the nitrogen atoms of the triazine and the melamine N*H* group.[4] The importance of acid was realized when gelation was not observed in $CHCl_3$. Indeed, $CDCl_3$ showed acid content on performing an acidity test.[22] Addition of gaseous HCl to $CHCl_3$ or CH_2Cl_2 or benzene led to gelation upon addition of **1**. Neutral organic solvents did not provide gels. Material recovered from samples that were acidified showed no perceptible change by NMR spectroscopy or MS spectrometry suggesting that decomposition of the sample was not occurring to any measurable extent.

The importance of hydrogen bonding was corroborated by the observation that the addition of as little as 1% EtOH to solutions of chloroform prevents gelation. Other competitive hydrogen-bonding solvents including methanol, 2-propanol, and DMSO provided solutions. On standing, solutions of **1** yielded precipitates from ethanol and 2-propanol at room temperature. This observation is consistent with a hypothesis which has been invoked with similar experimental observations; gels are a metastable state resulting from a kinetic trap of molecules en route to precipitation.[23,24]

While the pH dependence of gelation is not unique,[24,25] the observation that relatively small changes in composition of these macromolecules greatly affects gelation is surprising to us (Figure 2). Dendrimer **2**, a macromolecule that is structurally similar to **1**, gels under similar conditions. Gelation does not occur with smaller generation dendrimers **3** and **4** in acidified organic solvents. Instead, **3** forms a precipitate on standing, while **4** forms turbid solutions. Molecules **5** and **6** replace hydrogen bond donating groups of *p*-aminobenzylamine with piperazines. Both compounds form gels only at higher concentrations with respect to **1** or **2**. Replacing all the *p*-aminobenzylamine groups with

Scheme 3. Convergent Synthesis of 8



[a] *p*-Aminobenyzlamine, Hunig's base. [b] $C_3N_3Cl_3$, Hunig's base. [c] Excess piperazine. [d] Intermediate **23**, Hunig's base.

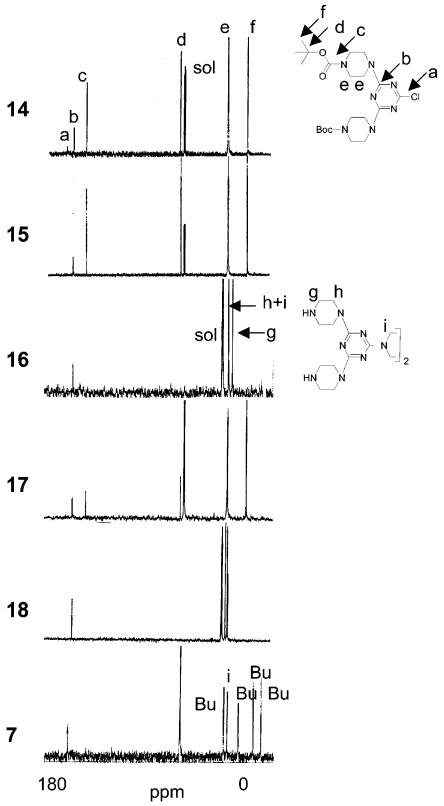


Figure 1. ^{13}C NMR spectra (75 MHz) from the divergent synthesis of **7** showing the iterative nature of the synthesis. See text for details. Spectra were recorded in $CDCl_3$ (**14**, **15**, **17**) and CD_3OD (**16**, **18**).

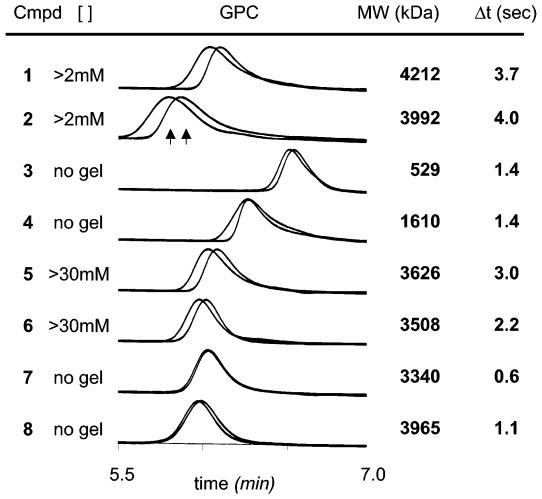


Figure 2. Concentrations required for the gelation of dendrimers **1**−**8**, an overlay of the GPC traces of the dendrimers derived from acidified and neutral chloroform (toluene standard), their molecular weights from mass spectrometry, and the difference in retention time (indicated with arrows for **2**) when constituted in acidified vs neutral solvents.[26] The acidified sample always eluted before the neutral sample.

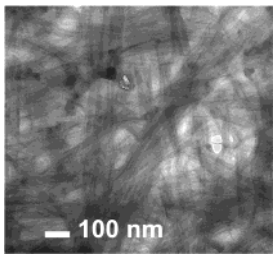


Figure 3. TEM image of the gel. The scale bar represents 100 nm.

piperazines, **7**, precludes gelation, as does replacing surface butylamines with piperidine groups, **8**.

Transmission electron micrographs of gels of **1** were obtained after exposure of the gel-coated EM grids to vapors of OsO_4. These micrographs reveal the typical network morphology with fiber dimensions of approximately 50 nm (Figure 3).[25] No fine structure in these fibrils could be seen, thus precluding us from proposing a model for structure of the gel.

With this set of compounds in hand, we questioned whether evidence for self-recognition (aggregation) could be obtained by other techniques at concentrations below that required for gelation. IR spectroscopy of samples of **1** in neutral and acidified chloroform showed no

differences that could be attributed to hydrogen bonding or other recognition events. Light-scattering experiments could not be executed on samples that gel. Solutions remained turbid to concentrations at which our light-scattering apparatus would no longer produce reliable data. Gas-phase computational models did not show dramatic differences in the shapes of these molecules: globular structures resulted for all targets due to low energetic barriers between piperazine conformers.

Traces from gel permeation chromatography, however, proved interesting (Figure 2). In general, the retention time for dendrimers that form gels is significantly different when the samples are prepared in acidified vs neutral chloroform (the GPC mobile phase is THF). Acidified samples elute first, an observation consistent with higher molecular weight species in solution. This trend is most pronounced in molecules **1** and **2**, which gel at the lowest concentrations.[26] Dendrimers **5** and **6** show smaller differences in retention times that are consistent with the requirement for higher concentrations to form gels. For the smaller generation molecules **3** and **4**, the peaks elute at very similar times, as with **7** and **8** which did not form gels up to the 100 mM.

Conclusions

The opportunity to execute structure−activity studies in dendrimers based on melamine by changing the diamine component of this two component dendrimer system suggests to us that these architectures are an excellent scaffold for phenomonological inquiries in a range of areas. The gelation event described is interesting in that it represents one of few dendrimers reported to gel. The pH dependence of gelation, while not unique, is curious: gelators previously reported to show strong pH dependence have carboxylic acid groups. pH dependence often arises when carboxylic acid groups are present. The affect of protonation state has been attributed to mediating hydrogen bonding or ionic interactions[25] or a destabilizing electrostatic repulsion that precludes gelation.[24] The strong acid conditions required do not appear to affect the integrity of the molecules as judged from characterization of the re-isolated compounds after neutralization. Presumably, addition of acid leads to protonation of the triazine ring to facilitate aggregation, but the details of the aggregation event beyond our observation of fibrils by TEM are unavailable.

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Supporting Information Available: Figures showing NMR assignments, IR spectra, and computational models (16 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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