Macromolecules 1994, 27, 3464-3471

“Smart” Cascade Polymers.[1] Modular Syntheses of Four-Directional Dendritic Macromolecules with Acidic, Neutral, or Basic Terminal Groups and the Effect of pH Changes on Their Hydrodynamic Radii

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Received January 19, 1994; Revised Manuscript Received March 22, 1994®

ABSTRACT: Three series of cascade polymers possessing identical internal hierarchical architectures, but with either acidic, neutral, or basic terminal functionality, have been prepared. An iterative synthetic strategy was employed that involved amidation (via peptide coupling methods) of carboxylic acids with branched amines possessing the desired protected functionalities, followed by facile deprotection to give water-soluble cascade polymers (dendrimers). Diffusion ordered spectroscopy (^{1}H DOSY NMR) of these cascade polyamides revealed that some of these polymers swell or shrink in response to the stimulus of a pH change. These data are consistent with the hypothesis that the flexible internal architecture of these cascade molecules and coulombic repulsions between (charged) terminal groups account for this “smart” behavior. Consequently, the proposed uses of cascade (dendritic) polymers as size standards must be tempered by this pronounced pH dependence of the hydrodynamic radii.

We recently demonstrated (via SEC and DOSY NMR studies)[2] that the members of the carboxylic acid-terminated four-directional *Z*-cascade:methane[4]:(3-oxo-6-oxa-2-azapentylidyne)$^{G-1}$:propanoic acid[3] series exhibit a pronounced pH dependence of their hydrodynamic radii (Table 1). This behavior can be thought of as the nanoscale equivalent of that exhibited by pH sensitive “smart”[4] polymer gels.[5,6] The observed pH dependence of the hydrodynamic radii of this carboxylic acid family was attributed to repulsions between *charged* surface moieties. As a means to verify this hypothesis, alcohol- or amine-terminated cascades (dendrimers) that possessed internal architectures identical to the above series were prepared and examined.

Synthetic Aspects

While tetraacid[7] 1 and amines[8] 2 and 3 (Figure 1) were readily available in our laboratories,[9] the development of amine 4 enabled pursuit of the strategy illustrated by the retrosynthetic tree, shown in Figure 2. This divergent strategy, which involved attachment of a “module” (i.e., branched amine) to the appropriate acid-terminated dendrimer and is reminiscent of Michl's[10,11] molecular “Tinkertoy” approach to constructing miniature objects, gives facile access to nanoscale spheres with porous infrastructures.

Amine 4 was prepared from the branched trinitrile 5,[12] as shown in Scheme 1. Borane reduction of 5 gave (82%) triamine 6, as indicated by a loss of the nitrile (^{13}C NMR) resonance at 119.3 ppm and the appearance of a peak at δ 42.5 (CH_2NH_2) and a (^{1}H NMR) triplet (CH_2NH_2, J = 6.0 Hz, 6 H) at 2.65 ppm.[13] Treatment of triamine 6 with di-*tert*-butyl dicarbonate[14,15] and Et_3N in refluxing MeOH gave (87%), after workup and purification via column (SiO_2) chromatography, tricarbamate 7. The ^{13}C NMR spectrum of 7 possesses the expected seven peaks; signals at 28.3 (CH_3), 79.1 (CMe_3), and 156.0 ($C{=}O$) ppm correspond to the *tert*-butoxycarbonyl (Boc) moieties. Catalytic reduction (T-1 Raney[16] Ni, H_2, 55 psi, 65 °C, 12 h) of 7 gave (92%) amine 4; reduction was confirmed by a shift (^{13}C NMR) of the quaternary carbon resonance from 94.2 to 52.8 ppm.

The preparations of dodeca-*tert*-butyl ester 10, dodecaacid 11, 36-*tert*-butyl ester 16, 36-acid 17, 108-*tert*-butyl ester 22, and 108-acid 23 have previously been described;[2] complete synthetic details are given in the Experimental Section. Syntheses of the first generation dodecaalcohol 9, -acid 11, and -amine 13 are depicted in Scheme 2. In each case, the tetraacid core 1 was amidated with the branched amine building block via standard dicyclohexylcarbodiimide[17,18]/1-hydroxybenzotriazole[19] (DCC/1-HBT) peptide coupling conditions, before facile removal of the protecting group. The second (Z = 36) and third (Z = 108) generation alcohol-terminated cascades (“arborols”[20,21]) and amine-terminated cascades were similarly prepared from dodecaacid 11 (Scheme 3) and the second tier 36-acid 17, respectively.

Three generations of the alcohol-terminated cascade polyamides were prepared.[22] Coupling of tetraacid 1 with amine 3 via treatment with DCC/1-HBT in DMF at 25 °C provided (47%) dodecaacetate 8, which was characterized by eleven (^{13}C NMR) resonances. Two (^{1}H NMR) triplets at 2.37 (CH_2CONH) and 3.63 (OCH_2) ppm and a singlet at 3.31 ($4°C_{core}CH_2O$) ppm, which were attributed to the core of 8, gave proper integration relative to each other and to each of the resonances of the twelve exterior branches. Base-catalyzed transesterification of 8, followed by purification via dialysis, gave (36%)[23] dodecaalcohol 9, as evidenced by the loss of the (^{1}H and ^{13}C) NMR resonances and IR stretches attributed to the acetyl moieties. Coupling amine 3 to dodecaacid 11 produced (50%) 36-acetate 14, which was characterized by resonances (^{13}C NMR) at 57.7 and 57.8 ppm attributed to the two different side chain quaternary carbons and at 45.1

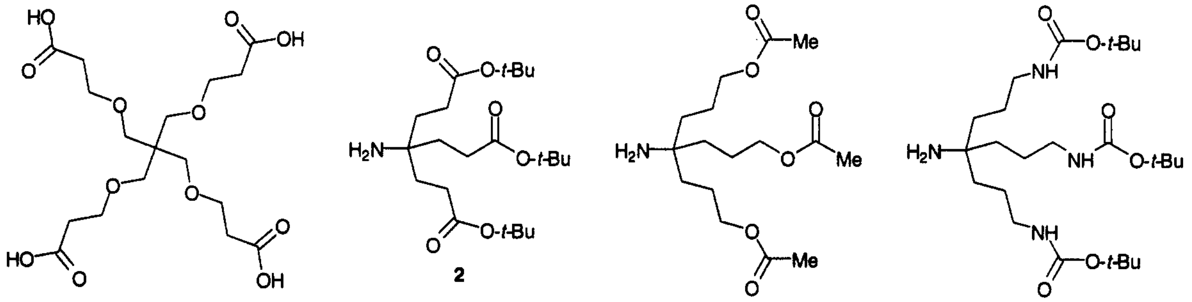
® Abstract published in *Advance ACS Abstracts,* May 1, 1994.

0024-9297/94/2227-3464$04.50/0

Table 1. Observed Diffusion Coefficients and Calculated Hydrodynamic Radii for the Four-Directional Cascade Polymers

generation (G)	no. of terminal groups (Z)	terminal functionality	fw	[cascade] (mM)	D (cm^2 s^{-1})/hydrodynamic Radius (Å)		
					acidic pH	neutral pH	basic pH
1	12	$-CO_2H^a$ **10**	1341	1.00	2.41×10^{-6}/8.24	1.62×10^{-6}/12.3	1.68×10^{-6}/11.8
		$-CH_2OH^b$ **9**	1174	1.00	2.30×10^{-6}/8.64	2.33×10^{-6}/8.53	2.35×10^{-6}/8.46
		$-CH_2NH_2{}^c$ **13**	1162	1.00	1.68×10^{-6}/11.8	1.75×10^{-6}/11.4	1.92×10^{-6}/10.3
2	36	$-CO_2H^a$ **17**	4092	1.00	1.74×10^{-6}/11.4	1.15×10^{-6}/17.3	1.26×10^{-6}/15.8
		$-CH_2OH^b$ **15**	3589	1.00	1.57×10^{-6}/12.7	1.56×10^{-6}/12.7	1.60×10^{-6}/12.4
		$-CH_2NH_2{}^c$ **19**	3553	1.00	1.09×10^{-6}/18.2	1.20×10^{-6}/16.6	1.44×10^{-6}/13.8
3	108	$-CO_2H^a$ **23**	12345	1.00	1.15×10^{-6}/17.3	8.32×10^{-7}/23.9	9.09×10^{-7}/21.9
		$-CH_2OH^b$ **21**	10834	0.50	1.30×10^{-6}/15.3	1.28×10^{-7}/15.5	1.28×10^{-7}/15.5
		$-CH_2NH_2{}^c$ **25**	10728	1.00	7.90×10^{-7}/25.2	8.50×10^{-7}/23.4	1.07×10^{-6}/18.6
4	324	$-CO_2H^a$ **27**	37102	0.97	8.79×10^{-7}/22.6	6.01×10^{-7}/33.1	6.87×10^{-7}/28.9
5	972	$-CO_2H^a$ **29**	111373	0.34	7.83×10^{-7}/25.4	5.35×10^{-7}/37.1	6.17×10^{-7}/32.3

[a] Solution pH ranged 3.16–3.64, 7.01–7.04, and 13.24–13.33 for the acidic, neutral, and basic solutions, respectively. [b] Solution pH ranged 2.28–4.74, 6.89–7.44, and 12.18–13.18 for the acidic, neutral, and basic solutions, respectively. [c] Solution pH ranged 2.60–3.77, 7.04–7.10, and 12.10–12.69 for the acidic, neutral, and basic solutions, respectively.



1 **2** **3** **4**

Figure 1. Building block "modules" for cascade synthesis.

and 30.9 ppm corresponding to the core quaternary carbon and the terminal methyl groups, respectively. Proper integration (^{1}H NMR) was obtained for the three core methylene resonances relative to the interior methylene signals at 1.91 and 2.19 ppm, the exterior methylene resonances at 1.52, 1.68, and 4.00 ppm, and the terminal methyl group signal at 2.02 ppm. Transesterification of **14** provided (72%) 36-alcohol **15**, as a hygroscopic white solid. Amidation of the second generation 36-acid with amine **3**, to provide (69%) 108-acetate **20**, was confirmed by a shift of the carboxylic acid carbonyl resonance (^{13}C NMR) from 179.7 to 172.5 ppm and by the proper integration of the core methylene signals relative to the internal methylene, terminal methylene, and terminal methyl resonances. Transesterification of **20** gave (71%) 108-alcohol **21**, which was characterized by the loss of the (^{1}H and ^{13}C) NMR resonances and IR stretches attributed to the acetyl moieties.

Three generations of amine-terminated cascade polyamides[24] were prepared in a manner similar to that for the corresponding alcohols. Coupling amine **4** to tetraacid **1** gave (56%) dodecaurethane **12**, which was hydrolyzed in formic acid (95%) at 25 °C. The formate salt was treated with dilute aqueous HCl and dialyzed to provide (37%)[23] dodecaamine **13** as its hydrochloride salt. The ^{13}C NMR spectrum exhibited the expected nine resonances. The second generation 36-carbamate **18** and third generation 108-carbamate **24** were similarly prepared and deprotected to give 36-amine **19** and 108-amine **25**, respectively. The ^{1}H NMR spectra (D$_2$O) of **19** and **25** contained core methylene signals at 2.38, 3.21, and 3.54 ppm that gave proper integration relative to each other and to resonances at 1.73 and 2.16 ppm, attributed to the interior methylenes, and at 1.44, 1.58, and 2.82 ppm, corresponding to the methylene groups of the exterior branches.

Pulsed Field Gradient NMR Studies

D$_2$O solutions containing an alcohol- or amine-terminated cascade polymer were examined by means of diffusion ordered 2D-NMR spectroscopy (DOSY).[25] This method, which makes use of pulsed field gradient NMR (PFG-NMR), displays chemical shifts in one direction and diffusion coefficients in the other. Complete details about the DOSY method have been published elsewhere.[25,26] As previously reported for the acid-terminated polymer,[2] the diffusion dimension revealed only the HOD peak and a single polymer peak; therefore, data acquisition and analysis were focused on the polymer peaks. In principle, the complete DOSY experiment requires no more time than a PFG-NMR experiment for one peak; however, the nuclear relaxation time T_1 is much longer for HOD than for the polymers and the repetition time required for acquisition of the complete DOSY data set is determined by the longest T_1 in the sample. Thus, to obtain the maximum signal to noise ratio, the experimental param-

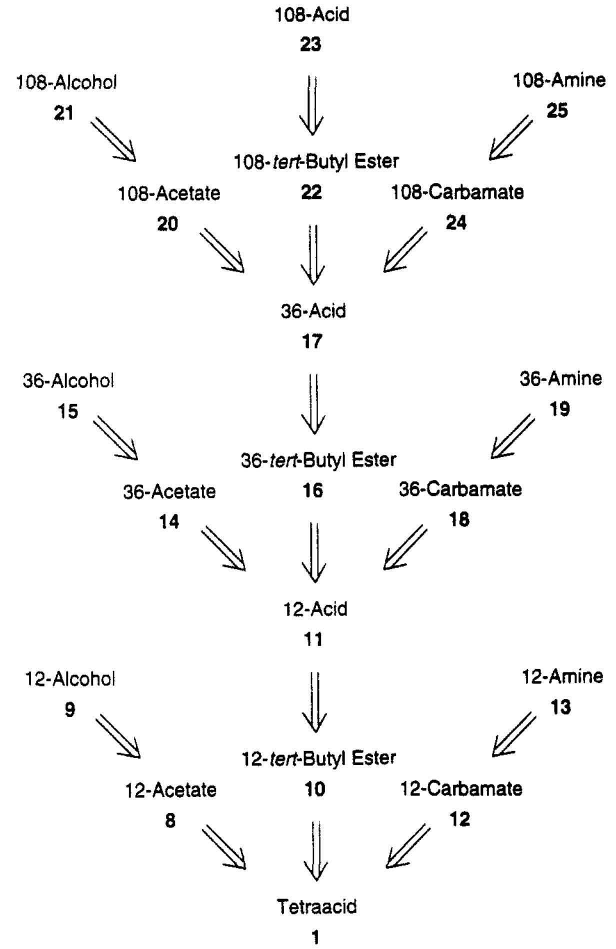


Figure 2. Retrosynthetic tree illustrating the derivation of alcohol-, acid-, and amine-terminated cascade polymers.

eters were optimized for the polymer peaks at the expense of the uninteresting HOD signal.

All experiments were performed with the longitudinal-eddy-current delay pulse sequence (LED) shown in Figure 3 to minimize distortions resulting from eddy currents and the effects of J-modulation.[27] An actively shielded gradient coil set was also used to minimize pulse induced eddy currents.[28] The DOSY data sets were acquired and analyzed as previously described.[25,26] Diffusion coefficients were obtained for each generation of the water-soluble alcohol- and amine-terminated polyamides at ca. 1 mM concentration by using only the integral A of the major polymer peaks. A typical ^{1}H 250-MHz data set is shown in Figure 4 for the 108-amine cascade polymer; the observed linear relationship indicates that the sample is pure and monodisperse within the limits of detection. Similar results were obtained from the PFG-NMR analyses of the other amine- and alcohol-terminated cascade polymers. The integrals of the polymer peaks were fit by nonlinear regression to the Stejskal–Tanner equation:[29]

$$A = A_0 \exp[-K^2(\Delta - \delta/3)D] \qquad (1)$$

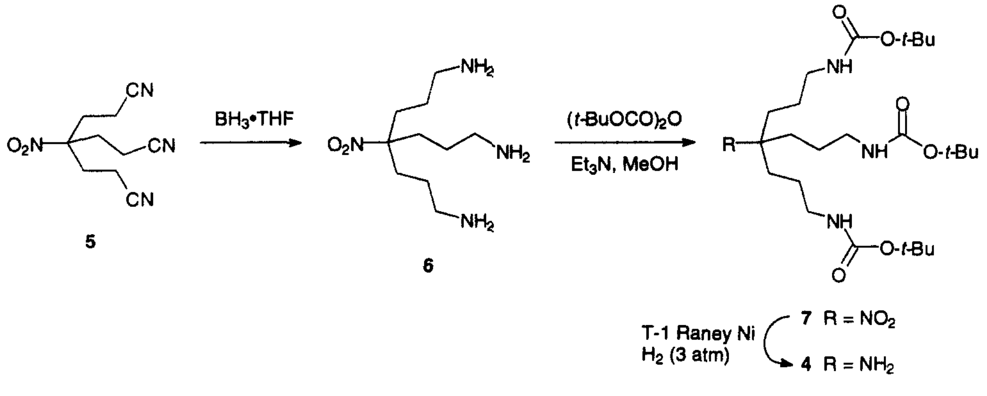
with A_0 and the tracer diffusion coefficient D as free parameters. In eq 1, $K = \gamma g \delta$, where γ is the magnetogyric ratio, g and δ are the amplitude and duration of the gradient pulses, respectively, and Δ is the diffusion time (i.e., the time between the leading edges of the gradient pulses). In these experiments Δ = 100.0 ms and δ = 1.00 ms. Also, the rf pulse pair separation was τ = 1.60 ms and the eddy current delay period was T_e = 20.0 or 25.0 ms. Effective hydrodynamic radii were calculated from measured D values with the Stokes–Einstein equation, $R_H = k_B T/(D6\pi\eta)$, where k_B is the Boltzmann constant, T is the absolute temperature, and η = 1.098 cP is the viscosity of D_2O at 298 K.[30]

The pH of the NMR samples was adjusted by injection of small quantities of 0.1 N HCl or NaOH, followed by measurement of the solution pH. The cascade polymers were 1.0 mM or less and no additional salt was added; thus, the ionic strengths were low but not accurately measured. Preliminary SEC studies varying the ionic strength at constant pH show that the smallest apparent size (radius) occurs at low ionic strength for the 108-acid cascade **23**; however, all observed size variations due to ionic strength are small relative to variations due to pH changes.[2] Since the ionic strength also affects the molecular radius, additional studies are indicated.

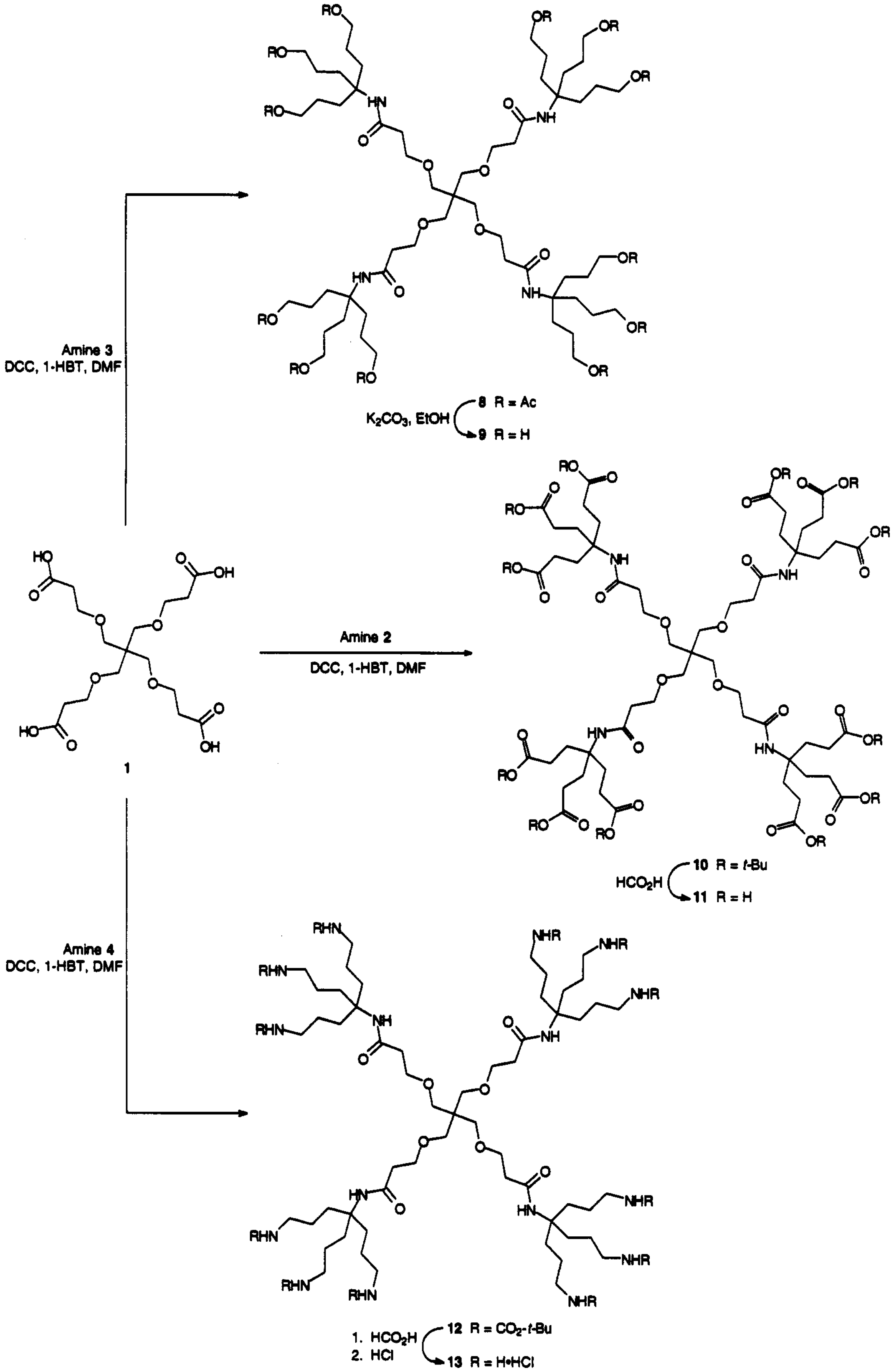
The measured diffusion coefficients and calculated hydrodynamic radii for the alcohol- and amine-terminated cascade polyamides are listed in Table 1. Unlike their acid-terminated parents, the alcohol-terminated cascades exhibited to appreciable pH dependence of their hydrodynamic radii. In contrast, the amine-terminated polyamides exhibited a pH size dependence that is approximately equal, but opposite to, that displayed by the corresponding polyacids. The amines are "expanded" at acidic pH and "contracted" at basic pH, while the corresponding acids are largest ("expanded") at neutral pH and smallest ("contracted") at acidic pH (Figure 2). *Remarkably, the third generational 108-acid and 108-amine each undergo a maximum 35% change in hydrodynamic radius.*

In conclusion, the branched amines **2**–**4** were used to prepare water-soluble cascade polymers, possessing identical internal hierarchical architectures, but with either acidic, neutral, or basic terminal functional groups. The availability of these complementary series allowed an initial examination of the dependence of macromolecular

Scheme 1. Synthesis of Branched Amine Module 4



Scheme 2. Synthesis of the First Generation Cascade Polyamides

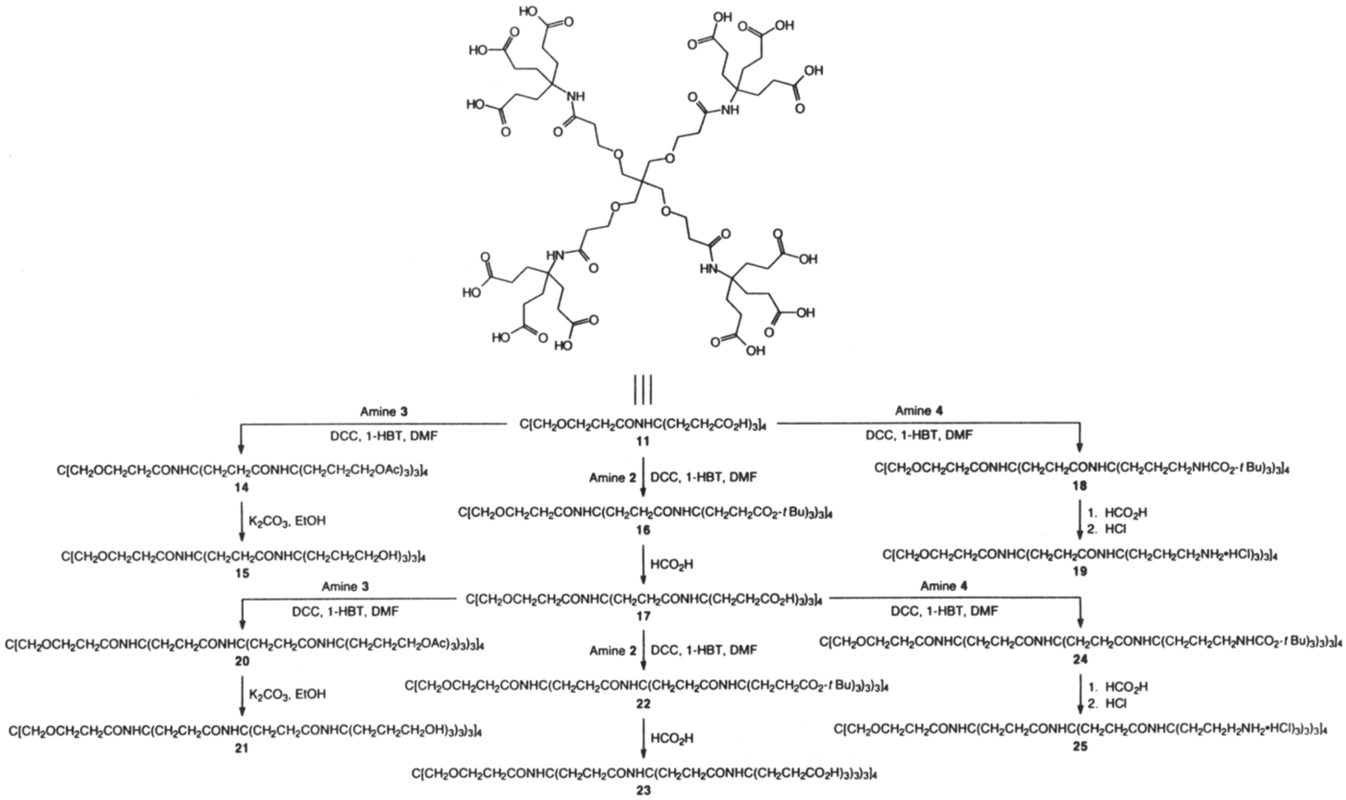


properties on the nature of the cascade terminal group. The PFG-NMR results are consistent with the supposition that size variations arise from coulombic repulsions between charged terminal moieties, which are formed as a function of pH. These findings should be general in that dendritic macromolecules with other internal branching architectures and functional group linkages should also be smart, provided their interior branches are relatively flexible. *As a consequence, the use of cascade polymers as size standards in aqueous solution must account for this pronounced pH dependence.*[31]

Experimental Section

General Comments. Melting point data were obtained in capillary tubes with a Gallenkamp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$, except where noted, with Me_4Si as the internal standard (δ 0 ppm), and recorded at 360 MHz. Infrared spectra (IR) were obtained (KBr pellet, unless otherwise noted) and recorded in

Scheme 3. Synthesis of the Second and Third Generation Cascade Polyamides



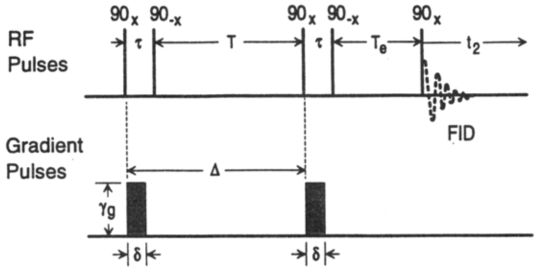


Figure 3. Basic LED pulse sequence. The gradient pulses shown represent the last two pulses in a train of five matched and equally spaced pulses. Phase cycling and sometimes homospoil pulses during T_e are used to suppress secondary echoes.

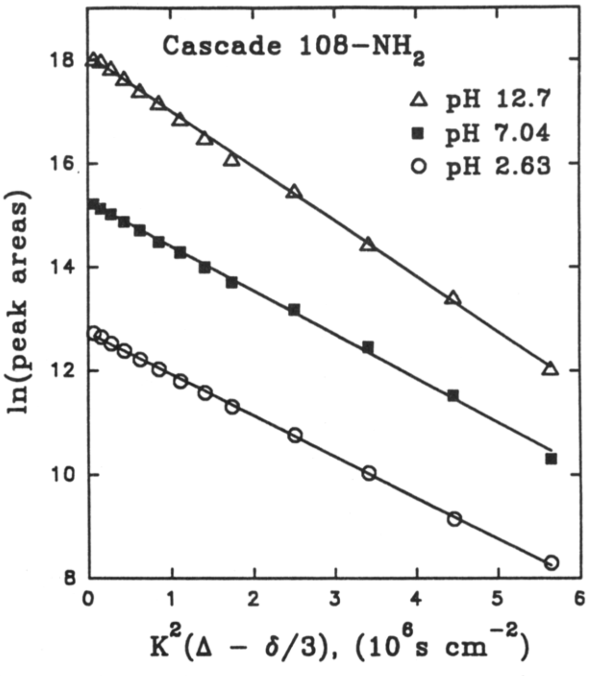


Figure 4. Area of the major polymer peaks versus $K^2(\Delta - \delta/3)$ for the cascade 108-amine polymer in acidic, neutral, and basic solutions at 298 K.

a Perkin-Elmer 621 grating infrared spectrometer. Mass spectral (MS) data were obtained by Burt Wolf (FSU) at 79 eV on a Finnigan 4510 GC–mass spectrometer and are reported as (assignment, relative intensity). Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Dialysis. Purification of the water-soluble acid-, alcohol-, and amine-terminated cascade polymers with molecular weights greater than 1000 was accomplished via dialysis (H_2O, 4 L, 12 h) using Spectra/Por 6 molecularporous dialysis membranes (1000 MWCO). In a typical procedure for the cascade polyacids, 5 g of crude polyacid were dissolved in water (50 mL) using 10% NaOH to assist in the dissolution. Additional base was added, resulting in a yellow solution at approximately pH 7. The solution was poured into the appropriate length of dialysis membrane so that, upon sealing, the membrane tube was flaccid. The filled membrane was dialyzed against 4 L of stirred deionized water for 12 h, with replacement of the water at least once during that time. During dialysis the solution changed from a deep to pale yellow color, an insoluble white suspension appeared in the solution, and the membrane tube became rigid. The contents of the tube were filtered and the water was removed in vacuo to provide the poly(sodium carboxylate) cascade as a white solid.

The alcohol cascades were dissolved in deionized water with no pH adjustment. The crude amine formate salts were dissolved in 2% HCl, and each resulting solution was poured into a dialysis membrane, which was sealed and placed in water as quickly as possible to minimize degradation of the cellulose tubing that may occur under these acidic conditions.

Preparative HPLC. Small portions of the polyacids were subjected to preparative scale HPLC using an Isco Model 2350 HPLC pump, Isco Model 2361 gradient programmer, Isco V^4 absorbance detector, Spectra-Physics SP-4600 integrator, Cygnet fraction collector, and a DuPont Zorbax ODS (C_{18}, octyldecylsilyl 21.2 mm × 25 cm) column. The dialyzed polyacid was dissolved in water (ca. 75 mg/mL), titrated with 10% HCl to pH 3–4, and filtered through a 0.02μm Anotop alumina matrix filter before injection (2 mL). The gradient conditions were 2 min of water followed by a 15-min linear ramp of 60/40 H_2O/CH_3CN.

The retention time for the product was approximately 10 min at a flow rate of 20 mL/min, which corresponded to an operating pressure of 1400 psi.

1,7-Diamino-4-(3-aminopropyl)-4-nitroheptane (6) was prepared as previously reported.[13]

1,7-Bis[*N*-(*tert*-butoxycarbonyl)amino]-4-[3-(*N*-(*tert*-butoxycarbonyl)amino)propyl]-4-nitroheptane (7). A mixture of triamine 6 (4.06 g, 17.5 mmol), Et_3N (5.56 g, 54.9 mmol), and di-*tert*-butyl dicarbonate (12.00 g, 55.0 mmol) in MeOH (60 mL) was refluxed for 2 h before the solvent was removed in vacuo. The resulting residue was column chromatographed (SiO_2) eluting with 10% MeOH in EtOAc to provide (87%) tricarbamate 7, as a slightly hygroscopic white solid: 8.05 g; mp 48–51 °C; ^{1}H NMR δ 1.44 (s, CH_3 and $CH_2CH_2CH_2$, 33 H), 1.90 (t, $J = 7.2$ Hz, $^{4\circ}CCH_2$, 6 H), 3.10 (t, $J = 5.0$ Hz, CH_2NH, 6 H), 4.72 (br, N*H*, 3 H); ^{13}C NMR δ 24.2 ($CH_2CH_2CH_2$), 28.3 (CH_3), 32.6 ($^{4\circ}CCH_2$), 40.1 (CH_2-NH), 79.1 (*C*Me_3), 94.2 ($^{4\circ}CNO_2$), 156.0 (*C*O); IR 3358 (NH), 1687 (C═O), 1543 (NO_2), 1172 (C—O) cm^{-1}. Anal. Calcd for $C_{25}H_{48}N_4O_8$: C, 56.37; H, 9.08; N, 10.52. Found: C, 56.76; H, 8.84; N, 10.50. MS: *m/e* 533.2 ($M^+ + 1$, 26).

1,7-Bis[*N*-(*tert*-butoxycarbonyl)amino]-4-[3-(*N*-(*tert*-butoxycarbonyl)amino)propyl]-4-aminoheptane (4). A slurry of nitro tricarbamate 7 (8.06 g, 15.1 mmol), T-1 Raney Ni (10 g), and absolute EtOH (300 mL) was hydrogenated at 55 psi and 60 °C for 12 h. The solution was *cautiously* filtered through Celite, to remove the catalyst, and the solvent removed in vacuo to give (92%) the amino tricarbamate 4, as a hygroscopic white solid: 7.60 g; ^{1}H NMR δ 1.33 (m, $CH_2CH_2CH_2$, 6 H), 1.44 (s, CH_3 and $^{4\circ}CCH_2$, 33 H), 3.10 (br, CH_2NH, 6 H), 4.77 (br, CON*H*, 3 H); ^{13}C NMR δ 24.1 ($CH_2CH_2CH_2$), 28.3 (CH_3), 36.9 ($^{4\circ}CCH_2$), 40.9 (CH_2-NH), 52.8 ($^{4\circ}CNH_2$), 79.0 (*C*Me_3), 155.9 (*C*O); IR (neat) 3355 (NH_2, NH), 1694 (C═O), 1170 (C—O) cm^{-1}. Anal. Calcd for $C_{25}H_{50}N_4O_6$: C, 59.73; H, 10.02; N, 11.14. Found: C, 59.63; H, 9.85; N, 10.95. MS: *m/e* 503.3 ($M^+ + 1$, 25).

12-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): *tert*-butyl Propanoate (10). General Procedure A. A mixture of tetraacid 1 (9.73 g, 23 mmol), amine **2** (40.00 g, 96 mmol), dicyclohexylcarbodiimide (DCC: 19.80 g, 96 mmol), and 1-hydroxybenzotriazole (1-HBT: 13.00 g, 96 mmol) in DMF (350 mL) was stirred at 25 °C for 24 h. After filtration to remove dicyclohexylurea, the solvent was evaporated in vacuo to give a residue, which was dissolved in EtOAc (200 mL), and then sequentially washed with *cold* aqueous HCl (10%), water, aqueous $NaHCO_3$ (10%), and brine. The organic phase was dried ($MgSO_4$), concentrated in vacuo, and chromatographed (SiO_2 column), eluting with 10% EtOAc in CH_2Cl_2 to furnish (70%) the desired 12-cascade ester **10**, as a spongy white solid: 32.33 g; mp 68–72 °C; ^{1}H NMR δ 1.43 (s, CH_3, 108 H), 1.96 (t, $J = 7.2$ Hz, CH_2CH_2COO, 24 H), 2.22 (t, $J = 7.2$ Hz, CH_2COO, 24 H), 2.38 (t, $J = 5.7$ Hz, CH_2CONH, 8 H), 3.34 (s, CH_2O, 8 H), 3.67 (t, $J = 5.7$ Hz, OCH_2, 8 H), 6.38 (s, N*H*, 4 H); ^{13}C NMR δ 28.1 (CH_3), 29.7 (CH_2CH_2COO), 37.4 (CH_2CONH), 45.4 ($^{4\circ}C_{core}$), 57.3 ($^{4\circ}CNH$), 67.7 (CH_2O), 68.9 (OCH_2), 80.4 (*C*Me_3), 170.7 (*C*ONH), 172.7 (CO_2); IR 3310 (NH), 1733 (ester C═O), 1664 (amide C═O), 1157 (ester C—O) cm^{-1}. Anal. Calcd for $C_{105}H_{184}N_4O_{32}$; C, 62.60; H. 9.20; N, 2.78. Found: C, 62.82; H, 9.14; N, 2.91.

12-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): propanoic Acid (11). General Procedure B. A solution of dodecaester **10** (30.00 g, 15 mmol) in 95% formic acid (100 mL) was stirred at 25 °C for 12 h. After concentration, toluene (50 mL) was added and the solution was again evaporated in vacuo to azeotropically remove residual formic acid. The crude solid was dissolved in a water (200 mL)/acetone (10 mL) mixture and then sequentially washed with CH_2Cl_2 (50 mL) and EtOAc (50 mL). The aqueous phase was boiled with activated charcoal (0.5 g), filtered through Celite, and then concentrated in vacuo to furnish the acid as a white solid, which was purified via dialysis and preparative reversed-phase HPLC to give (72%) dodecaacid **11**, as a white solid: 14.38 g; mp 64–66 °C; ^{1}H NMR (D_2O/*p*-dioxane/3.54 ppm) δ 1.76 (t, $J = 7.5$ Hz, CH_2CH_2COO, 24 H), 2.04 (t, $J = 7.5$ Hz, CH_2COO, 24 H), 2.24 (br, CH_2CONH, 8 H), 3.15 (br, CH_2O, 8 H), 3.44 (br, OCH_2, 8 H); ^{13}C NMR (D_2O/*p*-dioxane/66.4 ppm) δ 29.7 (CH_2CH_2COO), 30.1 (CH_2COO), 37.0 (CH_2-CONH), 45.0 ($^{4\circ}C_{core}$), 57.8 ($^{4\circ}CNH$), 67.6 (CH_2O), 69.8 (OCH_2), 173.0 (*C*ONH), 179.2 (CO_2H); IR 3366 (br, acid OH), 1720 (acid C═O), 1645 (amide C═O) cm^{-1}. Anal. Calcd for $C_{57}H_{88}N_4O_{32}$: C, 51.04; H, 6.61; N, 4.18. Found: C, 50.89; H, 6.83; N, 4.38.

36-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): (3-oxo-2-azapentylidyne):*tert*-butyl propanoate (16) was prepared (57%), as a spongy white solid, from dodecaacid **11** (5.63 g, 4.2 mmol), amine **2** (21.98 g, 52.9 mmol), DCC (10.89 g, 52.9 mmol), 1-HBT (7.14 g, 52.9 mmol), and DMF (250 mL) via procedure A: 14.55 g; mp 67–70 °C; ^{1}H NMR δ 1.42 (s, CH_3, 324 H), 1.95, 2.20 (m, CH_2CH_2CO, 192 H), 2.37 (t, $J = 5.7$ Hz, OCH_2CH_2CO, 8 H), 3.32 (s, CH_2O, 8 H), 3.66 (t, $J = 5.7$ Hz, OCH_2, 8 H), 6.36 (s, N*H*, 16 H); ^{13}C NMR δ 28.1 (CH_3), 29.7 (CH_2CH_2CO), 37.4 (OCH_2CH_2CO), 45.4 ($^{4\circ}C_{core}$), 57.3 ($^{4\circ}CNH$), 67.7 (CH_2O), 68.9 (OCH_2), 80.4 (*C*Me_3), 170.7 (*C*ONH), 172.6 (CO_2); IR 3311 (NH), 1730 (ester C═O), 1661 (amide C═O), 1157 (ester C—O) cm^{-1}. Anal. Calcd for $C_{321}H_{556}N_{16}O_{92}$: C, 63.08; H, 9.17; N, 3.67. Found: C, 63.18; H, 8.89; N, 3.79.

36-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): (3-oxo-2-azapentylidyne):propanoic acid (17) was prepared (77%) by hydrolysis of 36-ester **16** (13.55 g, 2.22 mmol) via procedure B: 6.95 g; mp 132–134 °C; ^{1}H NMR (5% NaOD/*p*-dioxane/3.54 ppm) δ 1.75, 1.99 (br, CH_2CH_2CO, 192 H), 2.32 (br, OCH_2CH_2CO, 8 H), 3.19 (br, CH_2O, 8 H), 3.48 (br, OCH_2, 8 H); ^{13}C NMR (5% NaOD/*p*-dioxane/66.4 ppm) δ 29.7, 30.1 (CH_2CH_2-CO), 37.0 (OCH_2CH_2CO), 45.0 ($^{4\circ}C_{core}$), 57.9, 58.1 ($^{4\circ}CNH$), 67.7 (CH_2O), 69.9 (OCH_2), 173.1 (*C*ONH), 179.7 (CO_2); IR 3363 (br, acid OH), 1718 (acid C═O), 1648 (amide C═O) cm^{-1}. Anal. Calcd for $C_{177}H_{288}N_{16}O_{92}$: C, 51.95; H, 6.60; N, 5.48. Found: C, 51.74; H, 6.71; N, 5.30.

108-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): (3-oxo-2-azapentylidyne)^2:*tert*-butyl propanoate (22) was prepared (48%), as a spongy white solid, from 36-acid **17** (2.63 g, 643 μmol), amine **2** (10.10 g, 24.3 mmol), DCC (5.00 g, 24.3 mmol), 1-HBT (3.28 g, 24.3 mmol), and DMF (150 mL) via procedure A: 5.68 g; mp 103–108 °C; ^{1}H NMR δ 1.43 (s, CH_2, 972 H), 1.95, 2.19 (br, CH_2, 624 H); ^{13}C NMR δ 28.1 (CH_3), 29.7 (CH_2CH_2), 57.3 ($^{4\circ}CNH$), 80.3 (*C*Me_3), 170.8 (*C*ONH), 172.7 (CO_2); IR 3366 (NH), 1730 (ester C═O), 1645 (amide C═O), 1160 (ester C—O) cm^{-1}. Anal. Calcd for $C_{969}H_{1672}N_{52}O_{272}$: C, 63.24; H, 9.16; N, 3.96. Found: C, 63.06; H, 8.89; N, 4.23.

108-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): (3-oxa-2-azapentylidyne)^2:propanoic acid (23) was prepared (70%) by hydrolysis of 108-ester **22** (5.68 g, 309 μmol) via procedure B: 2.65 g; mp 136–139 °C; ^{1}H NMR (5% NaOD/*p*-dioxane/3.54 ppm) δ 1.71, 1.92 (br, CH_2CH_2CO, 624 H), 2.34 (br, OCH_2CH_2CO, 8 H), 3.22 (br, CH_2O, 8 H), 3.48 (br, OCH_2, 8 H); ^{13}C NMR (5% NaOD/*p*-dioxane/66.4 ppm) δ 31.0, 31.4 (br, CH_2CH_2CO), 58.3 (br, $^{4\circ}CNH$), 174.8 (*C*ONH), 181.8 (CO_2); IR 3361 (br, acid OH), 1718 (acid C═O), 1647 (amide C═O) cm^{-1}. Anal. Calcd for $C_{537}H_{808}N_{52}O_{272}$: C, 52.25; H, 6.60; N, 5.90. Found: C, 52.06; H, 6.71; N, 5.76.

324-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): (3-oxo-2-azapentylidyne)^3:*tert*-butyl propanoate (26) was prepared (42%), as a spongy white solid, from 108-acid **23** (5.39 g, 437 μmol), amine **2** (20.00 g, 48.1 mmol), DCC (9.91 g, 48.1 mmol), 1-HBT (6.50 g, 48.1 mmol), and DMF (250 mL) via procedure A: 10.20 g; mp 135–141 °C; ^{1}H NMR δ 1.39 (s, CH_3, 2916 H), 1.93–2.17 (m, CH_2, 1920 H); ^{13}C NMR δ 28.1 (CH_3), 29.6 (CH_2CH_2), 57.2 ($^{4\circ}CNH$), 80.1 (*C*Me_3), 170.8 (*C*ONH), 172.6 (CO_2); IR 3368 (NH), 1728 (ester C═O), 1658 (amide C═O), 1160 (ester C—O) cm^{-1}. Anal. Calcd for $C_{2913}H_{5020}N_{160}O_{812}$: C, 63.29; H, 9.15; N, 4.05. Found: C, 63.47; H, 8.99; N, 4.16.

324-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): (3-oxo-2-azapentylidyne)^3:propanoic acid (27) was prepared (72%), as a white solid, by hydrolysis of 324–ester **26** (5.00 g, 90.4 μmol) via procedure B: 2.42 g; mp 138–142 °C; ^{1}H NMR (5% NaOD/*p*-dioxane/3.54 ppm) δ 1.71–1.93 (br, CH_2CH_2CO, 1920 H), 2.38 (br, OCH_2CH_2, 8 H), 3.22 (br, CH_2O, 8 H), 3.48 (br, OCH_2, 8 H); ^{13}C NMR (5% NaOD/*p*-dioxane/66.4 ppm) δ 29.7, 30.8 (br, CH_2CH_2CO), 57.4 ($^{4\circ}CNH$), 174.3 (*C*ONH), 182.0 (CO_2H); IR 3361 (br, acid OH), 1720 (acid C═O), 1648 (amide C═O) cm^{-1}. Anal. Calcd for $C_{1617}H_{2428}N_{160}O_{812}$: C, 52.35; H, 6.60; N, 6.04. Found: C, 52.42; H, 6.60; N, 6.05.

972-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne): (3-oxo-2-azapentylidyne)^4:*tert*-butyl propanoate (28) was prepared (45%), as a spongy white solid, from 324–acid **27** (5.40 g, 146 μmol), amine **2** (20.00 g, 48.1 mmol), DCC (9.91 g, 48.1

mmol), 1-HBT (6.50 g, 48.1 mmol), and DMF (250 mL) via procedure A: 10.87 g; mp 138–142 °C; ^{1}H NMR δ 1.39 (s, CH_3, 8748 H), 1.93–2.17 (m, CH_2, 5808 H); ^{13}C NMR δ 28.0 (CH_3), 29.5 (CH_2CH_2), 57.4 ($^{4\circ}$CNH), 80.4 (CMe_3), 170.4 (CO_2), 172.6 (CONH); IR 3310 (NH), 1730 (ester C=O), 1645 (amide C=O), 1155 (ester C—O) cm^{-1}. Anal. Calcd for $C_{8745}H_{15064}N_{484}O_{2432}$: C, 63.31; H, 9.15; N, 4.09. Found: C, 63.47; H, 9.31; N, 4.04.

972-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne)^4:propanoic acid (29) was prepared (68%), as a white solid, by hydrolysis of 972-ester **28** (9.50 g, 57.3 μmol) via procedure B: 4.34 g; mp 144–149 °C; ^{1}H NMR (5% NaOD/*p*-dioxane/3.54 ppm) δ 1.38–3.50 (br, CH_2CH_2); ^{13}C NMR (5% NaOD/*p*-dioxane/66.4 ppm) δ 28.4, 29.5 ($CH_2CH_2CO_2H$), 56.5 ($^{4\circ}$CNH), 172.3 (CONH), 174.8 (CO_2); IR 3419 (br, acid OH), 1718 (acid C=O), 1638 (amide C=O) cm^{-1}. Anal. Calcd for $C_{4857}H_{7288}N_{484}O_{2432}$: C, 52.38; H, 6.60; N, 6.09. Found: C, 52.24; H, 6.70; N, 6.03.

12-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):1-acetoxypropane (8). General Procedure C. A mixture of tetraacid 1 (433 mg, 1.02 mmol), 1-HBT (562 mg, 4.16 mmol), and DCC (858 mg, 4.16 mmol) in DMF (20 mL) was stirred at 0 °C for 1 h. Amine 3 (1.38 g, 4.16 mmol) in DMF (10 mL) was added to the mixture, which was then stirred at 25 °C for an additional 23 h. After filtration of dicyclohexylurea, the solvent was removed in vacuo to give an oily residue, which was column chromatographed (SiO_2), eluting with MeOH/EtOAc (5:95) to give (47%) dodecaester 8 was a fruity-smelling, hygroscopic, waxy, white solid: 811 mg; ^{1}H NMR δ 1.57 (m, $CH_2CH_2CH_2$, 24 H), 1.74 (t, J = 7.3 Hz, $^{4\circ}$CNHCH_2, 24 H), 2.05 (s, CH_3, 36 H), 2.37 (t, J = 5.8 Hz, CH_2CONH, 8 H), 3.31 (s, $^{4\circ}C_{core}CH_2O$, 8 H), 3.63 (t, J = 5.8 Hz, OCH_2CH_2, 8 H), 4.04 (t, J = 6.3 Hz, CH_2OAc, 24 H), 5.92 (s, NH, 4 H); ^{13}C NMR δ 20.9 ($CH_2CH_2CH_2$), 22.6 ($^{4\circ}$CNHCH_2), 31.0 (CH_3), 37.5 (CH_2CONH), 45.4 ($^{4\circ}C_{core}$), 57.8 ($^{4\circ}$CNH), 64.4 (CH_2OAc), 67.7 ($^{4\circ}C_{core}CH_2$), 69.2 (OCH_2CH_2CONH), 170.3 (CONH), 171.0 (COO); IR (neat) 3397 (NH), 1738 (ester C=O), 1643 (amide C=O), 1245 (ester C—O) cm^{-1}. Anal. Calcd for $C_{81}H_{136}N_4O_{32}$: C, 57.98; H, 8.17; N, 3.34. Found: C, 58.06; H, 8.35; N, 3.37.

12-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):propanol (9). General Procedure D. A stirred slurry of dodecaester 8 (600 mg, 358 mmol) and K_2CO_3 (100 mg, 723 mmol) in absolute EtOH was refluxed. After 12 h, the solution was filtered and the solvent removed in vacuo to give a residue, which was dissolved in water (20 mL) and dialyzed (H_2O, 4 L, 12 h) using a 1000 MWCO Spectra/Por 6 molecularporous membrane. Removal of the water in vacuo gave (36%) dodecaalcohol **9** as a clear, colorless, waxy solid: 149 mg; ^{1}H NMR (D_2O/*p*-dioxane/3.54 ppm) δ 1.29 (br, $CH_2CH_2CH_2$, 24 H), 1.51 br, $^{4\circ}$CNHCH_2, 24 H), 2.26 (br, CH_2CONH, 8 H), 3.20 (s, $^{4\circ}C_{core}CH_2$, 8 H), 3.44 (br, CH_2OAc, 24 H), 3.48 (br, OCH_2CH_2CONH, 8 H); ^{13}C NMR (D_2O/*p*-dioxane/66.4 ppm) δ 25.4 ($CH_2CH_2CH_2$), 30.6 ($^{4\circ}$CNHCH_2), 36.9 (CH_2CONH), 45.1 ($^{4\circ}C_{core}$), 58.6 ($^{4\circ}$CNH), 61.9 (CH_2OAc), 67.7 ($^{4\circ}C_{core}CH_2$), 69.4 (OCH_2CH_2CONH), 172.8 (CONH); IR (neat) 3343 (OH), 1648 (amide C=O), 1059 (C—O) cm^{-1}. Anal. Calcd for $C_{57}H_{112}N_4O_{20}$: C, 58.34; H, 9.62; N, 4.77. Found: C, 58.39; H, 9.54; N, 4.59.

36-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne):3-acetoxypropane (14) was prepared (50%), as a fruity-smelling, hygroscopic, waxy, white solid, from dodecaacid **11** (456 mg, 340 μmol), amine **3** (1.38 g, 4.16 mmol), DCC (858 mg, 4.16 mmol), 1-HBT (562 mg, 4.16 mmol), and DMF (30 mL) via procedure C: 867 mg; ^{1}H NMR δ 1.52 (br, $CH_2CH_2CH_2$, 72 H), 1.68 (br, $CH_2CH_2CH_2$, 72 H), 1.91, 2.19 (br, $^{4\circ}$CNHCH_2CH_2CONH, 48 H), 2.02 (s, CH_3, 108 H), 2.34 (br, OCH_2CH_2CONH, 8 H), 3.28 (s, $^{4\circ}C_{core}CH_2O$, 8 H), 3.58 (br, OCH_2CH_2, 8 H), 4.00 (t, J = 6.2 Hz, CH_2OAc, 72 H); ^{13}C NMR δ 20.9 ($CH_2CH_2CH_2$), 22.5 ($^{4\circ}$CNHCH_2), 30.9 (CH_3), 31.4 ($^{4\circ}$CNHCH_2CH_2CONH), 37.4 (OCH_2CH_2CONH), 45.1 ($^{4\circ}C_{core}$), 57.7, 57.8 ($^{4\circ}$CNH), 64.4 (CH_2OAc), 67.8 ($^{4\circ}C_{core}CH_2$), 69.4 (OCH_2CH_2CONH), 171.4 (COO), 172.6 (CONH); IR (neat) 3376 (NH), 1738 (ester C=O), 1658 (amide C=O), 1247 (ester C—O) cm^{-1}. Anal. Calcd for $C_{249}H_{412}N_{16}O_{92}$: C, 58.62; H, 8.14; N, 4.39. Found: C, 58.53; H, 8.33; N, 4.49.

36-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne):propanol (15) was prepared (72%), as a hygroscopic white solid, from 36-ester **14** (700 mg, 137 μmol) via procedure D: 492 mg; mp 58–60 °C; ^{1}H NMR (D_2O/*p*-dioxane/3.54 ppm) δ 1.25 (br, $CH_2CH_2CH_2$, 72 H), 1.48 (br, $CH_2CH_2CH_2$, 72 H), 1.72 (br, $^{4\circ}$CNHCH_2CH_2CONH, 24 H), 1.95 (br, $^{4\circ}$CNHCH_2CH_2CONH, 24 H), 2.27 (br, OCH_2CH_2CONH, 8 H), 3.16 (br, $^{4\circ}C_{core}CH_2$, 8 H), 3.36 (br, CH_2OH, 72 H), 3.46 (br, OCH_2CH_2CONH, 8 H); ^{13}C NMR (D_2O/*p*-dioxane/66.4 ppm) δ 25.3 ($CH_2CH_2CH_2$), 30.4 ($CH_2CH_2CH_2$), 30.8 ($^{4\circ}$CNHCH_2CONH), 36.7 (OCH_2CH_2CONH), 45.0 ($^{4\circ}C_{core}$), 57.8, 58.4 ($^{4\circ}$CNH), 61.8 (CH_2OH), 67.8 ($^{4\circ}C_{core}CH_2$), 69.2 (OCH_2CH_2CONH), 174.5 (COHN); IR 3394 (OH), 1651 (amide C=O), 1059 (C—O) cm^{-1}. Anal. Calcd for $C_{177}H_{340}N_{16}O_{56}$: C, 59.24; H, 9.55; N, 6.24. Found: C, 59.54; H, 9.38; N, 5.99.

108-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne)^2:1-acetoxypropane (20) was prepared (69%), as a fruity-smelling, hygroscopic waxy, white solid, from 36-acid 17 (405 mg, 99.0 μmol), amine **3** (1.24 g, 3.74 mmol), DCC (771 mg, 3.74 mmol), 1-HBT (505 mg, 3.74 mmol), and DMF (30 mL) via procedure C: 1.05 g; ^{1}H NMR δ 1.56 (br, $CH_2CH_2CH_2$, 216 H), 1.72 (br, $CH_2CH_2CH_2$, 216 H), 2.05 (s, CH_3, 324 H), 4.03 (br, CH_2OAc, 216 H); ^{13}C NMR δ 20.9 ($CH_2CH_2CH_2$), 22.5 ($^{4\circ}$CNHCH_2), 30.8 (CH_3), 31.4 ($^{4\circ}$CNHCH_2CH_2CONH), 37.4 (OCH_2CH_2CONH), 57.8 ($^{4\circ}$CNH), 64.5 (CH_2OAc), 67.8 ($^{4\circ}C_{core}CH_2$), 69.4 (OCH_2CH_2CONH), 171.1 (COO), 172.5 (CONH); IR (neat) 3376 (OH), 1738 (ester C=O), 1661 (amide C=O), 1244 (ester C—O) cm^{-1}. Anal. Calcd for $C_{753}H_{1240}N_{52}O_{272}$: C, 58.83; H, 8.13; N, 4.74. Found: C, 58.81, H, 8.24; N, 4.51.

108-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne)^2:propanol (21) was prepared (71%), as a hygroscopic white solid, from 108-ester **20** (750 mg, 48.8 μmol) via procedure D: 374 mg; mp 71–76 °C; ^{1}H NMR (D_2O/*p*-dioxane/3.54 ppm) δ 1.27 (br, $CH_2CH_2CH_2$, 216 H), 1.49 (br, $CH_2CH_2CH_2$, 216 H), 1.70 (br, $^{4\circ}$CNHCH_2CH_2CONH, 96 H), 1.96 (br, $^{4\circ}$CNHCH_2CH_2CONH, 96 H), 2.31 (br, OCH_2CH_2CONH, 8 H), 3.20 (br, $^{4\circ}C_{core}CH_2$, 8 H), 3.38 (br, CH_2OH, 216 H), 3.49 (br, $OCHH_2CH_2$CONH, 8 H); ^{13}C NMR (D_2O/*p*-dioxane/66.4 ppm) δ 25.3 ($CH_2CH_2CH_2$), 30.4 ($CH_2CH_2CH_2$), 30.8 ($^{4\circ}$CNHCH_2CONH), 36.7 (OCH_2CH_2CONH), 57.8, 57.7 ($^{4\circ}$CNH), 61.8 (CH_2OH), 67.8 ($^{4\circ}C_{core}CH_2$), 69.2 (OCH_2CH_2CONH), 174.6 (CONH); IR 3343 (OH), 1653 (amide C=O), 1059 (C—O) cm^{-1}. Anal. Calcd for $C_{537}H_{1024}N_{52}O_{164}$: C, 59.53; H, 9.53; N, 6.72. Found: C, 59.37; H, 9.43; N, 6.79.

12-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):*N*-(*tert*-butoxycarbonyl)propylamine (12). General Procedure E. A mixture of tetraacid 1 (458 mg, 1.08 mmol), 1-HBT (612 mg, 4.53 mmol), and DCC (934 mg, 4.53 mmol) in DMF (20 mL) was stirred at 25 °C for 1 h. Amine 4 (2.28 g, 4.54 mmol) in DMF (10 mL) was added to the mixture, which was stirred for 12 h. Additional DCC (300 mg, 1.46 mmol) was added and the mixture was stirred for another 12 h. After filtration of dicyclohexylurea, the solvent was removed in vacuo to give a residue, which was dissolved in EtOAc (50 mL), sequentially washed with cold aqueous HCl (10%), water, saturated $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), concentrated in vacuo, and chromatographed (SiO), eluting with 10% MeOH in EtOAc to furnish (56%) dodecacarbamate **12**, as a spongy white solid: 1.43 g; mp 87–89 °C; ^{1}H NMR δ 1.41 (s, CH_3 and $CH_2CH_2CH_2$, 132 H), 1.67 (br, HN$^{4\circ}$CCH_2, 24 H), 2.35 (br, OCH_2CH_2, 8 H), 3.05 (br, CH_2NHBoc, 24 H), 3.33 (br, $^{4\circ}CCH_2O$, 8 H), 3.64 (br, OCH_2, 8 H), 5.06 (s, NHBoc, 12 H), 6.37 (very br, CONH, 4 H); ^{13}C NMR δ 23.6 ($CH_2CH_2CH_2$), 28.4 (CH_3), 32.2 (HN$^{4\circ}$CCH_2), 37.5 (OCH_2CH_2), 40.8 (CH_2NHBoc), 58.2 ($^{4\circ}$CNH), 67.9 ($^{4\circ}CCH_2O$), 69.5 (OCH_2), 78.9 (CMe_3), 156.1 (NHCOO), 170.8 (CONH); IR 3353 (NH), 1694 (C=O), 1456, (C—N), 1175 (C—O) cm^{-1}. Anal. Calcd for $C_{117}H_{220}N_{16}O_{32}$: C, 59.47; H, 9.38; N, 9.48. Found: C, 59.36; H, 9.23; N, 9.30.

12-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):propylamine Hydrochloride (13). General Procedure F. A solution of dodecacarbamate **12** (1.28 g, 542 μmol) in 95% formic acid (10 mL) was stirred at 25 °C for 12 h. After concentrating in vacuo, toluene (10 mL) was added and the solution was again evaporated in vacuo to remove azeotropically any residual formic acid. The crude formate salt was dissolved in aqueous 2% HCl (10 mL) and dialyzed (H_2O, 1 L, 12 h) using a 1000 MWCO Spectra/Por 6 molecularporous membrane. Removal of the water in vacuo gave (37%) dodecaamine hydrochloride **13**, as a hygroscopic, light yellow, glassy solid: 322 mg; ^{1}H NMR (D_2O/

p-dioxane/3.54 ppm) δ 1.43 (br, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2}$, 24 H), 1.56 (br, $\mathrm{HN^{4^\circ}CC}\mathit{H}_2$, 24 H), 2.36 (br, $\mathrm{C}\mathit{H}_2\mathrm{CONH}$, 8 H), 2.81 (br, $\mathrm{C}\mathit{H}_2\mathrm{NH_2}$, 24 H), 3.20 (s, $\mathrm{OC}\mathit{H}_2$, 8 H), 3.48 (br, $\mathrm{^{4^\circ}C_{core}C}\mathit{H}_2\mathrm{O}$, 8 H); ^{13}C NMR δ 20.7 ($\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 30.8 ($\mathrm{HN^{4^\circ}C}\mathit{C}\mathrm{H_2}$), 36.4 ($\mathit{C}\mathrm{H_2CONH}$), 39.4 ($\mathit{C}\mathrm{H_2NH_2}$), 44.9 ($\mathit{C}_{\mathrm{core}}$), 58.0 ($^{4^\circ}\mathit{C}\mathrm{NH}$), 67.8 ($\mathrm{^{4^\circ}C_{core}}\mathit{C}\mathrm{H_2}$), 69.7 ($\mathrm{O}\mathit{C}\mathrm{H_2}$), 173.0 ($\mathit{C}\mathrm{O}$); IR 3448 ($\mathrm{NH_3^+}$), 2057 ($\mathrm{NH_3^+}$ overtone), 1648 (C═O), 1550 ($\mathrm{NH_3^+}$ bend), 1100 (C—$\mathrm{NH_3^+}$) cm^{-1}.

36-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne):*N*-(*tert*-butoxycarbonyl)propylamine (18) was prepared (68%), as a spongy white solid, from dodecaacid 11 (483 mg, 360 μmol), amine 4 (2.28 g, 4.54 mmol), 1-HBT (612 mg, 4.54 mmol), DCC (934 mg/300 mg, 4.53 mmol/1.46 mmol), and DMF (30 mL) via procedure E: 1.76 g; mp 109–112 °C; ^{1}H NMR δ 1.43 (s, $\mathrm{C}\mathit{H}_3$, and $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2}$, 396 H), 1.66 (br, $\mathrm{C}\mathit{H}_2\mathrm{CH_2CH_2}$, 72 H), 1.94 (br, $\mathrm{HN^{4^\circ}CC}\mathit{H}_2\mathrm{CH_2CONH}$, 24 H), 2.15 (br, $\mathrm{HN^{4^\circ}CCH_2C}\mathit{H}_2\mathrm{CONH}$, 24 H), 2.35 (br, $\mathrm{OCH_2C}\mathit{H}_2$, 8 H), 3.05 (br, $\mathrm{C}\mathit{H}_2\mathrm{NHBoc}$, 72 H), 3.29 (br, $\mathrm{^{4^\circ}C_{core}C}\mathit{H}_2\mathrm{O}$, 8 H), 3.63 (br, $\mathrm{OC}\mathit{H}_2$, 8 H), 5.33 [very br, $\mathrm{N}\mathit{H}\mathrm{Boc}$, 28 H (exchange)]; ^{13}C NMR δ 23.7 ($\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 28.5 ($\mathit{C}\mathrm{H_3}$), 31.9 (br, $\mathrm{HN^{4^\circ}C}\mathit{C}\mathrm{H_2}\mathit{C}\mathrm{H_2CONH}$), 32.2 ($\mathit{C}\mathrm{H_2CH_2CH_2}$), 37.6 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_2}$), 40.9 ($\mathit{C}\mathrm{H_2NHBoc}$), 58.1 ($^{4^\circ}\mathit{C}\mathrm{NH}$), 68.0 ($\mathrm{^{4^\circ}C_{core}}\mathit{C}\mathrm{H_2O}$), 69.6 ($\mathrm{O}\mathit{C}\mathrm{H_2}$), 78.9 ($\mathit{C}\mathrm{Me_3}$), 156.2 ($\mathrm{NH}\mathit{C}\mathrm{OO}$), 171.1 ($\mathit{C}\mathrm{ONH}$); IR 3350 (NH), 1697 (C═O), 1455 (C—N), 1172 (C—O) cm^{-1}. Anal. Calcd for $\mathrm{C_{357}H_{664}N_{52}O_{92}}$: C, 59.91; H, 9.35; N, 10.18. Found: C, 59.97; H, 9.19; N, 9.99.

36-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne):propylamine hydrochloride (19) was prepared (49%), as a hygroscopic, light yellow, glassy solid, from 36-carbamate 18 (1.61 g, 225 μmol) via procedure F: 530 mg; mp >182 °C dec; ^{1}H NMR ($\mathrm{D_2O}$/*p*-dioxane/3.54 ppm) δ 1.43 (br, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2}$, 72 H), 1.57 (br, $\mathrm{C}\mathit{H}_2\mathrm{CH_2CH_2}$, 72 H), 1.74 (br, $\mathrm{HN^{4^\circ}CC}\mathit{H}_2\mathrm{CH_2CONH}$, 24 H), 2.05 (br, $\mathrm{HN^{4^\circ}CCH_2C}\mathit{H}_2\mathrm{CONH}$, 24 H), 2.37 (br, $\mathrm{OCH_2C}\mathit{H}_2$, 8 H), 2.81 (br, $\mathrm{C}\mathit{H}_2\mathrm{NH_3^+}$, 72 H), 3.23 (br, $\mathrm{^{4^\circ}C_{core}C}\mathit{H}_2\mathrm{O}$, 8 H), 3.50 (br, $\mathrm{OC}\mathit{H}_2$, 8 H); ^{13}C NMR ($\mathrm{D_2O}$/*p*-dioxane/66.4 ppm) δ 20.8 ($\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 30.8 (br, $\mathit{C}\mathrm{H_2CH_2CH_2}$ and $\mathrm{HN^{4^\circ}}\mathit{C}\mathrm{H_2}\mathit{C}\mathrm{H_2CONH}$), 36.5 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_2}$), 39.6 ($\mathit{C}\mathrm{H_2NH_3^+}$), 44.9 ($\mathrm{^{4^\circ}C_{core}}$), 58.1 ($^{4^\circ}\mathit{C}\mathrm{NH}$), 67.9 ($\mathrm{^{4^\circ}C_{core}}\mathit{C}\mathrm{H_2O}$), 69.6 (br, $\mathrm{O}\mathit{C}\mathrm{H_2}$), 173.1 ($\mathrm{OCH_2CH_2}\mathit{C}\mathrm{ONH}$), 175.3 ($\mathit{C}\mathrm{ONH}$); IR 3448 ($\mathrm{NH_3^+}$), 2054 ($\mathrm{NH_3^+}$ overtone), 1646 (C═O), 1548 ($\mathrm{NH_3^+}$ bend), 1098 (C—$\mathrm{NH_3^+}$) cm^{-1}.

108-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne)^2:*N*-(*tert*-butoxycarbonyl)propylamine (24) was prepared (70%), as a spongy white solid, from 36-acid 17 (491 mg, 120 μmol), amine 4 (2.28 g, 4.54 mmol), 1-HBT (612 mg, 4.54 mmol), DCC (934 mg/300 mg, 4.53 mmol/1.46 mmol), and DMF (30 mL) via procedure E: 1.81 g, mp 119–123 °C; ^{1}H NMR δ 1.43 (s, $\mathrm{C}\mathit{H}_3$ and $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2}$, 1188 H), 1.66 (br, $\mathrm{C}\mathit{H}_2\mathrm{CH_2CH_2}$, 216 H), 3.06 (br, $\mathrm{C}\mathit{H}_2\mathrm{NHBoc}$, 216 H), 5.33 (very br, $\mathrm{N}\mathit{H}\mathrm{Boc}$, exchange); ^{13}C NMR δ 23.7 ($\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 28.5 ($\mathit{C}\mathrm{H_3}$), 31.9 (br, $\mathrm{HN^{4^\circ}C}\mathit{C}\mathrm{H_2}\mathit{C}\mathrm{H_2CONH}$), 32.2 ($\mathit{C}\mathrm{H_2CH_2CH_2}$), 40.9 ($\mathit{C}\mathrm{H_2}$-NHBoc), 58.1 (br, $^{4^\circ}\mathit{C}\mathrm{NH}$), 78.9 ($\mathit{C}\mathrm{Me_3}$), 156.2 ($\mathrm{NH}\mathit{C}\mathrm{OO}$), 173.0 (br, $\mathit{C}\mathrm{ONH}$); IR 3337 (NH), 1698 (C═O), 1455 (C—N), 1170 (C—O) cm^{-1}. Anal. Calcd for $\mathrm{C_{1077}H_{1996}N_{160}O_{272}}$: C, 60.05; H, 9.34; N, 10.40. Found: C, 60.11; H, 9.16; N, 10.32.

108-Cascade:methane[4]:(3-oxo-6-oxa-2-azaheptylidyne):(3-oxo-2-azapentylidyne)^2:propylamine Hydrochloride (25) was prepared (53%), as a hygroscopic, light yellow, glassy solid, from 108-carbamate 24 (1.66 g, 77.1 μmol) via procedure F: 593 mg; mp >198 °C dec; ^{1}H NMR ($\mathrm{D_2O}$/*p*-dioxane/3.54 ppm) δ 1.44 (br, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2}$, 216 H), 1.58 (br, $\mathrm{C}\mathit{H}_2\mathrm{CH_2CH_2}$, 216 H), 1.73 (br, $\mathrm{HN^{4^\circ}CC}\mathit{H}_2\mathrm{CH_2CONH}$, 96 H), 2.05 (br, $\mathrm{HN^{4^\circ}CCH_2C}\mathit{H}_2\mathrm{CONH}$, 96 H), 2.38 (br, $\mathrm{OCH_2C}\mathit{H}_2$, 8 H), 2.82 (br, $\mathrm{C}\mathit{H}_2\mathrm{NH_3^+}$, 216 H), 3.21 (br, $\mathrm{^{4^\circ}C_{core}C}\mathit{H}_2\mathrm{O}$, 8 H), 3.49 (br, $\mathrm{OC}\mathit{H}_2$, 8 H); ^{13}C NMR ($\mathrm{D_2O}$/*p*-dioxane/66.4 ppm) δ 20.8 ($\mathrm{CH_2}\mathit{C}\mathrm{H_2CH_2}$), 30.8 (br, $\mathit{C}\mathrm{H_2CH_2CH_2}$ and $\mathrm{HN^{4^\circ}}\mathit{C}\mathrm{H_2}\mathit{C}\mathrm{H_2CONH}$), 36.5 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_2}$), 39.6 ($\mathit{C}\mathrm{H_2NH_3^+}$), 45.4 (br, $^{4^\circ}\mathit{C}_{\mathrm{core}}$), 58.1 (br, $^{4^\circ}\mathit{C}\mathrm{NH}$), 68.0 (br, $\mathrm{^{4^\circ}C_{core}}\mathit{C}\mathrm{H_2O}$), 69.7 (br, $\mathrm{OCH_2}$), 175.4 ($\mathit{C}\mathrm{ONH}$); IR 3438 ($\mathrm{NH_3^+}$), 2060 ($\mathrm{NH_3^+}$ overtone), 1646 (C═O), 1545 ($\mathrm{NH_3^+}$ bend), 1103 (C–$\mathrm{NH_3^+}$) cm^{-1}.

Acknowledgment. This work was supported in part by the National Science Foundation (C.S.J., CHE-922590; G.R.N., DMR-8906792, DMR-9217331, and DMR-9208925), by the Army Research Office (G.R.N., DAAHO4-93-G-0448), and by a North Carolina Biotechnology Grant (C.S.J., 9212-ARG-0901).

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(23) The relatively low yields for these materials are probably due to losses during dialysis. The formula weights of these materials are close to the molecular weight cutoff (MWCO) rating of the dialysis membrane.
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