Amphiphilic Dendrimers with Both Octyl and Triethylenoxy Methyl Ether Chain Ends

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ABSTRACT: Tertiary amine dendrimers with both hydrophilic and hydrophobic chains on every end were synthesized from poly(propyleneimine) dendrimers DAB-*dendr*-$(NH_2)_n$ (n = 8, 32, and 64) using sequential amidations and $LiAlH_4$ reductions. The tertiary amine dendrimers were quaternized completely with methyl iodide and converted to quaternary ammonium chlorides by ion exchange. The quaternary ammonium chloride dendrimers are soluble in both organic solvents and water. ^{13}C NMR spin−lattice relaxation time (T_1) measurements show that the conformations of the dendrimers depend on solvent. The quaternary ammonium chloride dendrimers solubilize lipophilic compounds, such as pyrene and Reichardt's dye, in aqueous solution. The limiting solubility corresponds to one pyrene per dendrimer molecule. The rates of the decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid in aqueous solutions of the cationic dendrimers were up to 500 times faster than in water alone.

Introduction

The term unimolecular micelles was used for amphiphilic dendrimers first by Newkome,[1] and many examples have been reported.[2−14] Most commonly, amphiphilic dendrimers have carboxylate anions or ammonium cations as end groups and a hydrophobic core. Low molar mass surfactants form micelles in water only when their concentration exceeds the critical micelle concentration (cmc), which depends on the ionic strength and temperature.[15] In contrast, dendritic unimolecular micelles retain their colloidal structure regardless of concentration, ionic strength, or temperature. As catalysts, dendritic quaternary ammonium ions are active even at very low concentrations and high ionic strength.[16] Amphiphilic dendrimers can solubilize lipophilic compounds in aqueous solutions.[1,17−21] These properties may enable applications of dendritic unimolecular micelles in the areas of molecular encapsulation,[22] drug delivery, and nanoscopic transport.[23]

Other amphiphilic dendrimers, different from those resembling conventional micelles, also are attractive for such applications. Dendritic inverse micelles have been made by amidating the primary amine end groups of poly(propyleneimine) dendrimers such as DAB-*dendr*-$(NH_2)_{64}$ with fatty acids[24] and by creating alcohol functionality in the core of an aryl benzyl ether dendrimer having tetradecyl chain ends.[25] Unimolecular micellar dendrimers have been made by linking dendrons with hydrophobic and hydrophilic end groups to the same core.[26] Stimuli responsive hybrid star macromolecular amphiphiles can change conformations as the solvent polarity is varied.[27,28]

Poly(propyleneimine) dendrimers have been studied extensively and are commercial.[14] In this study, we report their modification with both hydrophilic triethylenoxy methyl ether (TEO) and hydrophobic octyl chains at every end and their conversion to quaternary ammonium ion dendrimers by total methylation.[29] The quaternary ammonium chloride dendrimers are soluble in both organic solvents and water, solubilize lipophilic compounds in water, and speed the rate of decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion up to 500 times the rate in water.

Results and Discussion

Synthesis of Amphiphilic Polyamine Dendrimers. The synthesis of the tertiary amine dendrimer G_4(TAn32) (generation 4 tertiary amine with 32 end groups) (**5**) was achieved in four steps from poly(propyleneimine) dendrimer DAB-*dendr*-$(NH_2)_{32}$ (**1**) as shown in Scheme 1. The hydrophobic octyl arms were introduced by an amidation of the surface NH_2 groups with octanoyl chloride to give polyamide-terminated dendrimer **2**, which was isolated by extraction and purified by chromatography. Amide **2** was reduced to secondary amine **3** by $LiAlH_4$, and the hydrophilic TEO arms were introduced by the corresponding acid chloride to give amide **4**. Another $LiAlH_4$ reduction afforded polyamine dendrimer **5**. The formation of the amide groups and their subsequent conversions to amine groups were monitored by FT-IR of the amide carbonyl band at 1640−1650 cm^{-1}.

Generation 2 dendrimer G_2(TAn8) (**10**) with eight terminal amines and generation 5 dendrimer G_5(TAn64) (**15**) with 64 terminal amines were synthesized from DAB-*dendr*-$(NH_2)_8$ (**6**) and DAB-*dendr*-$(NH_2)_{64}$ (**11**), by the same method.

We also converted **6** to a secondary amide by reaction with the acid chloride $CH_3O(CH_2CH_2O)_2CH_2COCl$ (**16**). The product was soluble only in water and alcohols and could not be purified by silica chromatography or dissolved into an ether solvent for reduction with $LiAlH_4$. On the other hand, the octyl modified-DAB-*dendr*-$(NH_2)_n$ (n = 8, 32, and 64) dendrimer amides G_2-(Am32) (**2**), G_4(Am8) (**7**), and G_5(Am64) (**12**) were insoluble in 0.1 M aqueous HCl solution. Only the dendrimers with both octyl and TEO chain ends were soluble in both organic solvents and acidic aqueous solutions. The octyl arms must be introduced first because solubilities of the octyl-modified dendrimers in organic solvents facilitate the subsequent $LiAlH_4$ reduction, amidation, and purification.

Preparation of Water-Soluble Amphiphilic Polyammonium Dendrimers. The water-insoluble tertiary amine dendrimers **5** and **10** were fully quaternized with excess methyl iodide to give the corresponding polyammonium iodide dendrimers G_4(PM**I**32) (**5a**) and

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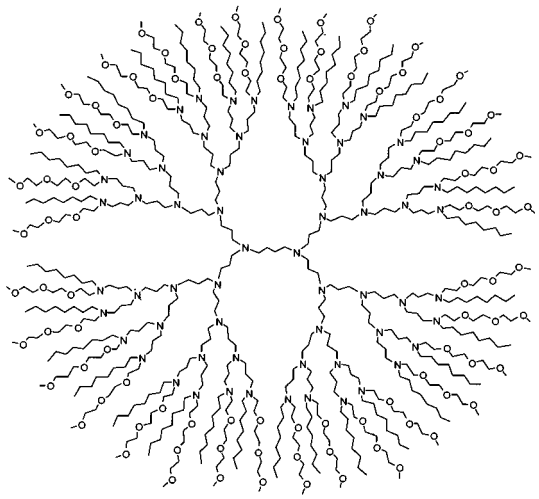

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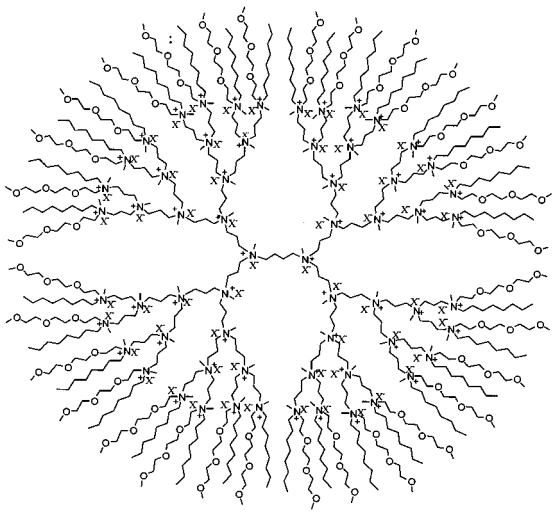
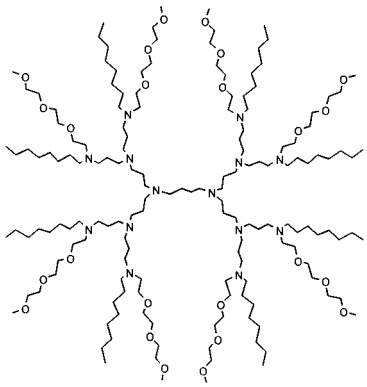


5a X=I
5b X=Cl



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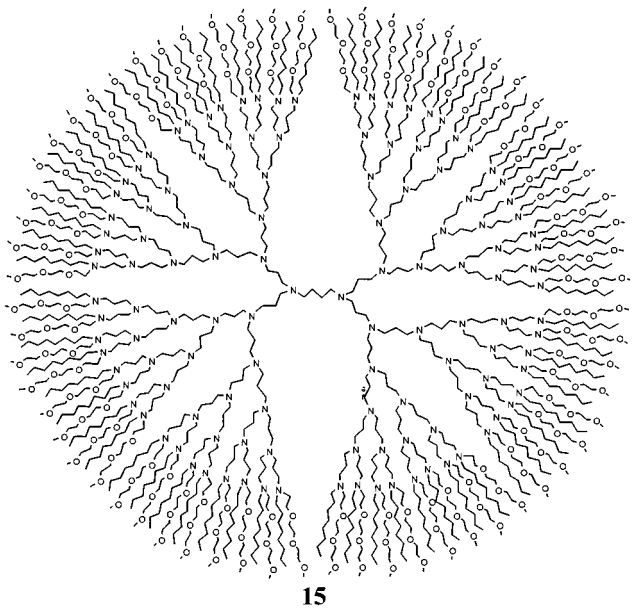


15

G_2(PM**I**8) (**10a**). The ^{1}H NMR spectra of **5a** and **10a** show the absence of the NCH_2 and NCH_2CH$_2$O peaks of **5** and **10** at 2.40 and 2.62 ppm. The water-soluble polyammonium chloride dendrimers G_4(PM**Cl**32) (**5b**) and G_2(PM**Cl**8) (**10b**) were obtained via ion exchange. The conversion was confirmed by the ^{1}H NMR integration of a newly formed OCH_2CH$_2$N$^+$Cl$^-$ peak of **5b** at 4.32 ppm with respect to the alkyl CH_3 peak at 0.84 ppm (OCH_2CH$_2$N$^+$Cl$^-$/CH_3 2/3 area ratio).

All new dendrimer amides and amines were purified using flash chromatography on basic aluminum oxide, and the purity was checked by TLC on silica gel plates pretreated with trimethylamine. The products were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR analysis, and the products from DAB-*dendr*-$(NH_2)_8$ were also characterized by ESI-MS analysis. Figure 1 shows the ^{13}C NMR spectrum of dendrimer **10**.

Elemental analysis was obtained only for polyammonium chloride **5b**. Even after extensive drying its carbon content was about 4% less than the calculated value. However, analysis showed excellent agreement of experimental C/N and Cl/N mol ratios with the calculated values, which suggests that the impurity causing low C, N, and Cl content was water. The iodine content was <0.10%, indicating that all iodide was replaced by chloride.

Solubilities of the Polyamine and Polyammonium Dendrimers. The solubilities are reported in Table 1. The tertiary amine dendrimers **5**, **10**, and **15** are soluble in organic solvents but insoluble in water despite the TEO (triethyleneoxy methyl ether) end groups. Amine **5** is not even soluble in 0.1 M aqueous HCl. Thus, the octyl end groups control the solubilities of the tertiary amine dendrimers. The polyammonium iodide dendrimers **5a** and **10a** are only slightly soluble in water and very soluble in organic solvents. The polyammonium chloride dendrimers **5b** and **10b** are readily soluble in both organic solvents and water and can be extracted quantitatitively from water by dichloromethane and chloroform.

NMR Spectra. The dendrimers with both hydrophilic and hydrophobic chain ends change the conformations of their end groups with change of solvent polarity according to both ^{1}H NMR line widths and ^{13}C NMR T_1 measurements.[29] ^{13}C spin−lattice relaxation in large organic molecules is usually through a dipolar mechanism. When molecular motion in solution slows down, there is more motion at the Larmor frequency, which increases the relaxation rate and decreases T_1.[30] The data in Table 2 show that the T_1 values of the TEO arms increase, and the T_1 values of the octyl arms decrease, when the solvent changes from chloroform to methanol. Thus, the octyl chains have greater freedom of motion in chloroform, and the TEO chains have more freedom

Scheme 1

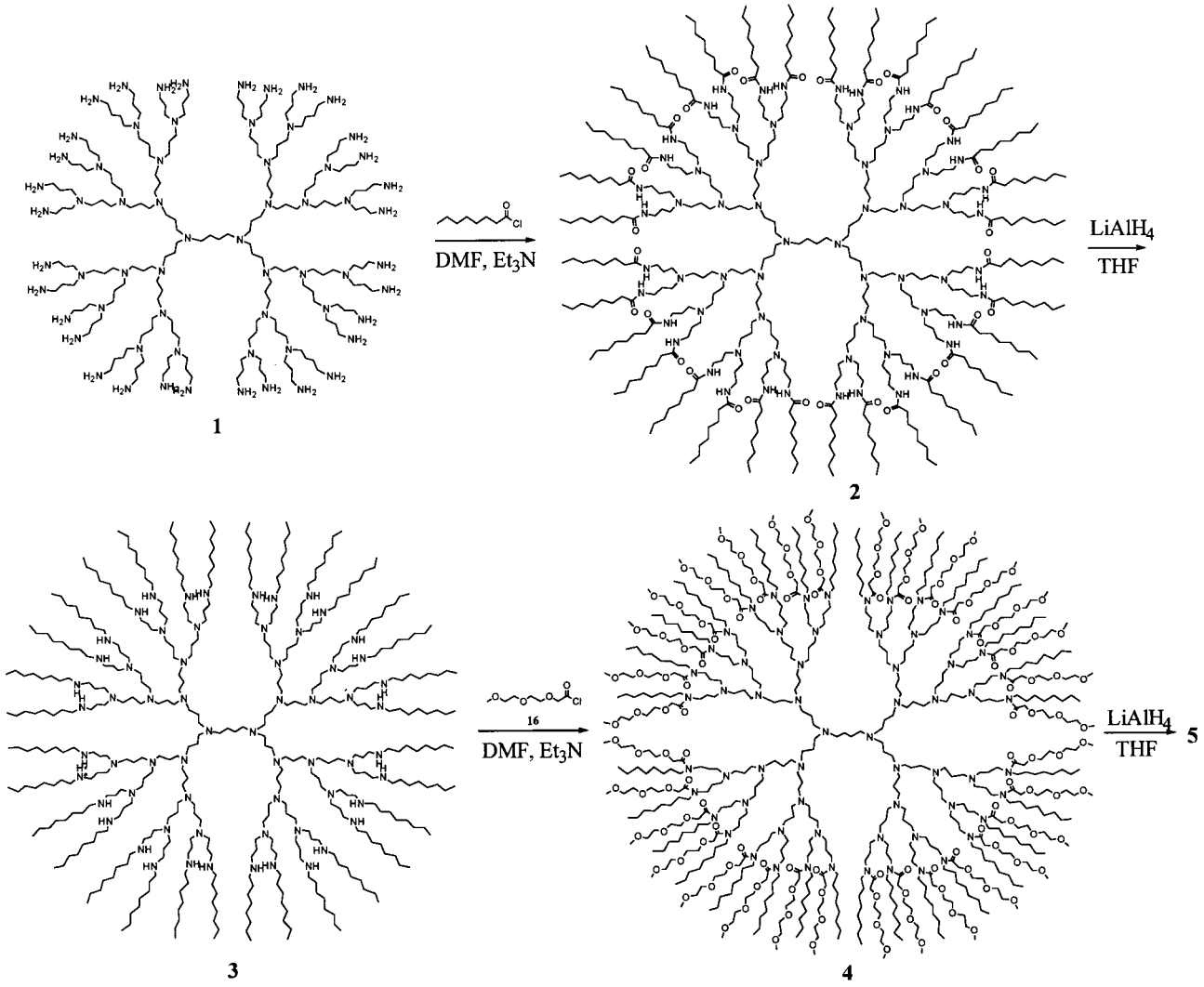


Table 1. Solubilities of Generation 2, 4, and 5 Polyamine, Polyammonium Iodide, and Chloride Dendrimers[a]

dendrimers	MeOH, EtOH, THF, CH_2Cl_2, $CHCl_3$, acetone	toluene	diethyl ether	H_2O
5, **10**, **15**	soluble	soluble	soluble	insoluble
5a, **10a**	soluble	insoluble[b]		slightly soluble
5b, **10b**	soluble	insoluble[b]		soluble

[a] Solubilities were tested by adding 4−5 mg of sample into 1.0 mL of solvent in a 4 mL vial and stirring magnetically for 15 min. The sample was judged soluble if a clear solution formed, slightly soluble if a cloudy solution formed, and insoluble if the oil or solid remained unchanged. [b] Not tested.

of motion in methanol. Greater motional freedom is due to solvent molecules rather than dendrimer chains as nearest neighhbors. In both chloroform and methanol the T_1 values of TEO chain ends of the quaternary ammonium ions **5a** and **5b** are significantly less than those in tertiary amine **5**, which suggests that motion of both the octyl and the TEO arms is slowed by crowding of the added methyl groups and counterions.

The line widths in both ^1H and ^{13}C NMR spectra increase with increasing dendrimer size of both the tertiary amines and the quaternary ammonium iodides. This is expected from slower overall tumbling of the larger molecules in solution. The ^{13}C T_1 data of the octyl and TEO chains as a function of the tertiary amine dendrimer size are given in Figure 2. The decrease of T_1 values with increasing size of the dendrimer must be due to more motion at the Larmor frequency, from molecular rotational diffusion and rotation about single bonds. All of the T_1 values are in the motional narrowing regime, which indicates good solvation of all chain ends by chloroform. This is important for applications such as molecular extraction and homogeneous catalysis, because solutes may need to permeate to the interior of the dendrimer.

The proton NMR signals of the secondary amide $C_7H_{15}CO\mathbf{NH}-$ end groups of **2**, **7**, and **12** shifted downfield with increasing size of the dendrimer as reported for fatty acid amides of the same parent dendrimers.[24] This indicates increased strength of intramolecular hydrogen bonding with increasing size, which is likely due to closer packing of chain ends.

Molecular Inclusion. The quaternary ammonium chloride dendrimers are soluble in a wide range of solvents, and they can host lipophilic substrates from aqueous solutions through hydrophobic interactions. Reichardt's dye, a pyridinium-*N*-phenoxide betaine, has a λ_{max} at 576 nm in an aqueous solution of dendrimer **5b**, which is similar to its λ_{max} values in cetyltrimethylammonium chloride micelles and in benzyl alcohol.[29]

The limiting solubility of pyrene (as measured by UV−vis spectra) in a 9.16×10^{-4} M aqueous solution

Table 2. ^{13}C T_1 Values of the Chain Ends of 5, 5a, and 5b in $CDCl_3$ and CD_3OD[a]

	5		5a		5b	
	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD
CH_3OCH_2	1.48	1.90	0.43	0.42	0.62	0.71
OCH_3	4.31	5.88	1.66	2.73	2.43	3.00
CH_3CH_2	2.07	1.79	1.54	1.63	1.42	1.84
CH_3	3.04	2.19	2.35	2.43	2.43	3.02

[a] ^{13}C T_1 data at 75 MHz were collected by the inversion−recovery method using 126 mg of **5**, 108 mg of **5a**, and 101 mg of **5b** in 0.8 mL of the solvents at 22 °C. Estimated errors are ±5% of the reported values.

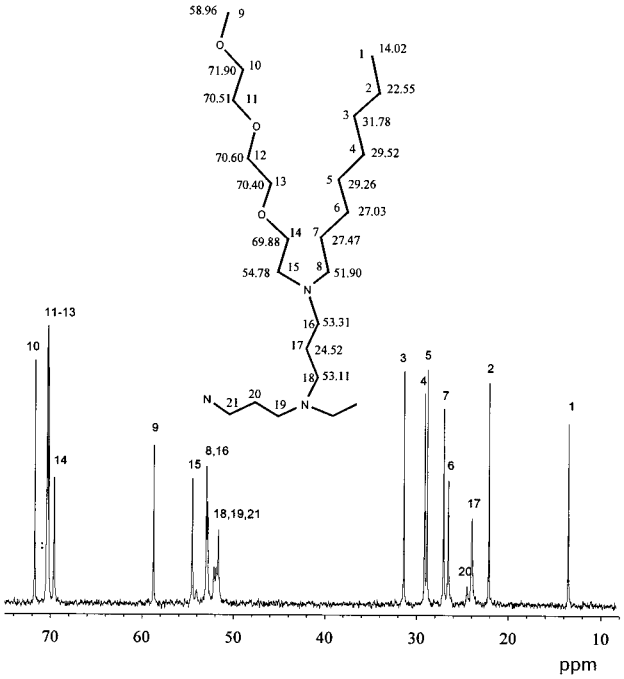


Figure 1. The 75 MHz ^{13}C NMR chemical shift assignments of dendrimer **10**.

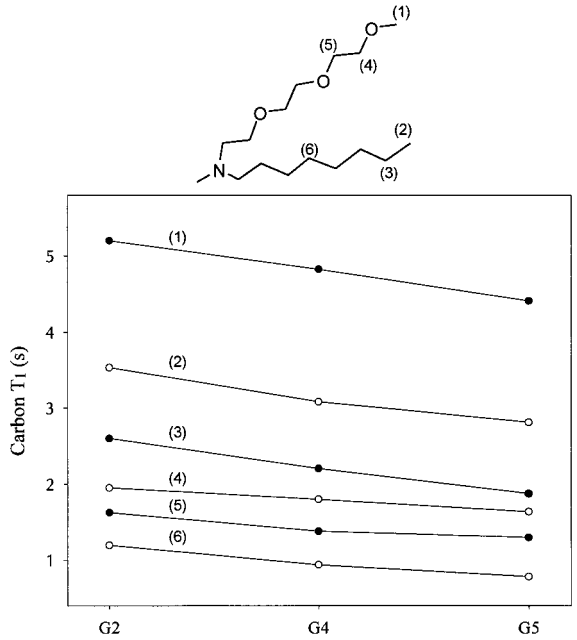


Figure 2. The 75 MHz ^{13}C NMR T_1 values of polyamine dendrimers **5**, **10**, and **15** in $CDCl_3$ at 22 °C as a function of generation. Signal (6) is from the central carbons of the octyl chain.

of **5b** is 1.04×10^{-3} M, which is 1300 times higher than in pure water (8×10^{-7} M) and corresponds to one pyrene per dendrimer molecule. In spectra with increasing pyrene concentrations, which are recorded in Figure 3, the λ_{max} values are concentration-independent, and the absorbance increases linearly with concentration, which implies that pyrene does not aggregate and lies in the same hydrophobic region of the dendrimer over the entire range of concentration.

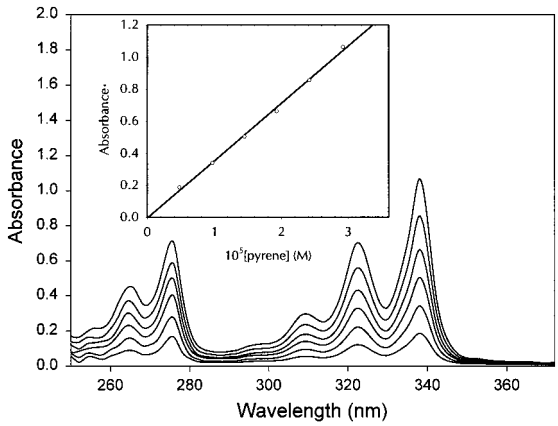


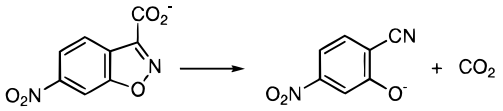
Figure 3. UV−vis absorption spectra of pyrene in 9.16×10^{-4} M aqueous dendrimer **5b** with increasing pyrene concentrations (0.48, 0.97, 1.45, 1.93, 2.42, and 2.90×10^{-5} M). The inset shows that absorbance at 338 nm obeys Beer's law.

Table 3. Molecular Diameters of Generation 2, 4, and 5 Dendrimers

dendrimer	modeling (Å)[a]	DLS (Å)[b]
G_2(TAn8) (**10**)	21.5	
G_4(TAn32) (**5**)	35.4	34.7
G_5(TAn64) (**15**)	44.1	42.4

[a] Insight II. [b] Dynamic light scattering.

Scheme 2



Molecular Size. The diameters of the dendrimers were measured by dynamic light scattering (DLS) in methanol at 20 °C. The data in Table 3 show that the measurements agree closely with the diameters estimated by molecular simulation using Insight II. Therefore, the polyamines are not aggregated in methanol.

Rates of Decarboxylation of 6-Nitrobenzisoxazole-3-carboxylate. The internal quaternary ammonium ions of a dendrimer can be active sites for phase transfer or polyelectrolyte catalysis. One particularly useful reaction to probe the microenvironment of polymers and colloids is the unimolecular concerted decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion, which is shown in Scheme 2.[16,31−33] Hydrogen bonding of solvent to the carboxylate anion reduces the rate, and dipolar aprotic solvents increase the rate of decarboxylation. The quaternary ammonium chloride dendrimers **5b** and **10b** increase the rate by 200−500 times the rate in pure water.

Scheme 3

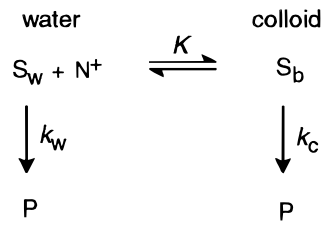


Table 4. Binding Constants and Intrinsic Rate Constants for Decarboxylation of 6-Nitrobenzisoxazole-3-carboxylic Acid in Aqueous 5b and 10b at 25.0 °C

dendrimer	$10^3\,k_c$ (s^{-1})[a]	k_c/k_w[b]	K (M^{-1})
G_4(PMCl32) (**5b**)	1.75	564	2442
G_2(PMCl8) (**10b**)	1.00	323	2043
PE-TMA36[c]	0.08	25	1700

[a] k_c = intrinsic rate constant in the dendrimer pseudophase. [b] (Rate constant in dendrimer)/(rate constant in water). [c] A dendrimer catalyst with 36 alkyltrimethylammonium ions on the surface.[16]

Using the single site binding model of Scheme 3, which is similar to the Michaelis−Menten model of enzyme kinetics and the Menger−Portnoy kinetic model for catalysis by surfactant micelles,[34,35] we assume that the substrate distributes between the aqueous phase and the dendrimer and that substrate binding is reversible. From Scheme 3, the observed rate constant (k_{obsd}) depends on the rate constants in water (k_w) and in the dendrimer (k_c) and on the fraction of total substrate S_t bound to the dendrimer (eq 1). K is the binding constant (eq 2), and the dependence of k_{obsd} on the concentration of quaternary ammonium ions [N^+] in the dendrimer is given by eq 3.

$$k_{obsd} = k_w[S]_w/[S]_t + k_c[S]_b/[S]_t \quad (1)$$

$$K = [S]_b/[S]_w[N^+] \quad (2)$$

$$k_{obsd} = (k_w/K + k_c[N^+])/(1/K + [N^+]) \quad (3)$$

The calculated binding constants K and catalytic rate constants k_c are shown in Table 4, and the plots of data used to determine K and k_c by regression analysis are shown in Figure 4.

Previously, we reported catalysis of this reaction by a dendrimer (PE-TMA36) having 36 terminal alkyltrimethylammonium iodide groups, a core containing no quaternary ammonium ions, and branch points derived from pentaerythritol.[16] The earlier result is compared with the new results in Table 4. Dendrimers **5b** and **10b** give much higher values of k_c and slightly greater values of K. The small difference in binding constants K is surprising because the earlier dendrimer's iodide counterions were expected to be bound much more strongly than chloride and therefore more difficult for the reactant anion to displace. The much larger k_c values in the dendrimers having both octyl and TEO chain ends than in dendrimers having only methyl chain ends were expected because the more hydrophobic quaternary ammonium ions should have fewer water molecules available to stabilize the reactant ground state by hydrogen bonding.

The fourth generation dendrimer **5b** gives faster rates of decarboxylation than the second generation dendrimer **10b**. Therefore, the substrate must be less hydrated in **5b** than in **10b**. We predict a still faster rate in G_5(PMCl64) (**15b**), but we did not complete the synthesis of **15b**.

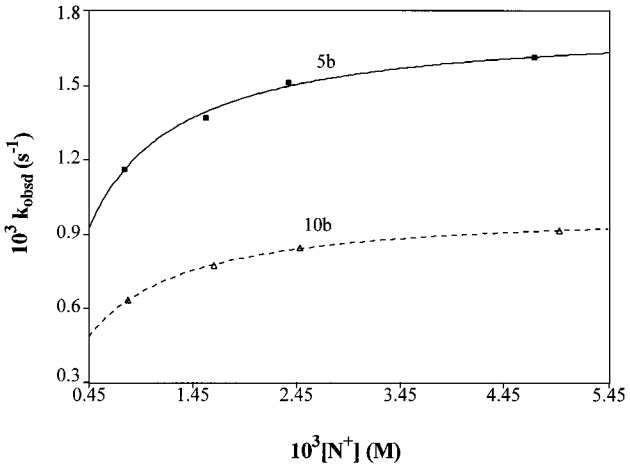


Figure 4. Pseudo-first-order rate constants for decarboxylation of 7.82×10^{-5} M 6-nitrobenzisoxazole-3-carboxylate ion as a function of concentration of N^+ units of **5b** and **10b** in aqueous solutions at pH 11.4 and 25.0 °C. Estimated errors in rate constants are ±5%. The first-order rate constant in water was $k_w = 3.1 \times 10^{-6}$ s^{-1}.[16]

Conclusion

Poly(propyleneimine) dendrimers can be modified with one alkyl and one triethylenoxy methyl ether group at every chain end by common synthetic methods. We aim to expand this family of materials more extensively and to study their solution structures and their ability to solubilize organic compounds in water. The hydrophile/lipophile balance of both the amines and the quaternary ammonium ion derivatives can be varied systematically for nanoscopic transport agents and for catalysts.

Experimental Section

All starting materials were used as received from Aldrich unless otherwise stated. THF was freshly distilled from sodium. Triethylamine was dried over anhydrous 3 Å molecular sieves and freshly distilled. ^{1}H NMR spectra (400 or 300 MHz) and ^{13}C NMR spectra (100.6 or 75.4 MHz) were recorded with the solvent signal as the reference. Analytical TLC was performed on Kodak thin-layer chromatography plates with silica gel GF_{254}. Basic aluminum oxide (Baker, 50 mm) was used for flash chromatography. Amberlite IRA 402 anion-exchange resin in Cl^- form (Sigma) was used for the conversion of the polyammonium iodide dendrimers to chloride dendrimers. The resin was washed with aqueous NaOH, deionized water, aqueous HCl, deionized water, and MeOH. Analytical TLC was performed on Kodak thin-layer chromatography plates with silica gel GF_{254}, and the plates were pretreated with trimethylamine vapor and activated at 60 °C for 2 h. Dynamic light scattering (DLS) was studied using a Brookhaven Instruments BI-200SM goniometer and BI-9000AT multi-τ-digital correlator at a 90° scattering angle and 20 °C. The light source was a coherent INNOVA-90 argon laser (488 nm). The samples for DLS were prepared by dissolving 50−60 mg of the dendrimer in 2.50 mL of MeOH. UV−vis spectra and kinetic time traces were obtained in 1.00 cm polystyrene cells using a Hewlett-Packard model 8452A diode array spectrophotometer. ESI-MS spectra were obtained on a PE/Sciex API-III Quadra 950 triple quadrupole biomolecular mass analyzer at the University of Oklahoma Health Science Center. Injected solutions were prepared in either 50/50 (v/v) H_2O:acetonitrile or 50/50 (v/v) H_2O:MeOH acidified with 3% acetic acid. Calculated m/z values are for the lowest isotopomers.

G_4(Am32) (2). Octanoyl chloride (1.98 g, 12.2 mmol) was added to a solution of DAB-*dendr*-$(NH_2)_{32}$ **1** (940 mg, 0.268 mmol), DMF (3.0 mL), and triethylamine (1.51 g, 15.0 mmol) at 0 °C, and the solution was stirred under nitrogen at 70 °C for 24 h. Water (2.0 mL) was added, and the solution was stirred for 10 min and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed with 1% aqueous K_2CO_3 (2 × 15 mL) and brine, dried (K_2CO_3), and concentrated. The oily crude product was purified on an aluminum oxide column (MeOH/$CHCl_3$, 2:98) to give 1.64 g (82%) of **2** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3295, 3089, 1651 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.91 (t, $J = 6.57$, CH_3), 1.12−1.40 (m, CH_2), 1.42−1.80 (m, $NCH_2CH_2CH_2NCO$, $NCH_2CH_2CH_2N$ and $NHCOCH_2CH_2$), 2.20 (t, $NHCOCH_2$), 2.40 (m, $CH_2N(CH_2)_2$), 3.26 (q, CH_2NHCO), 7.18 (br, *NH*CO). ^{13}C NMR ($CDCl_3$, δ): 13.98 (alkyl C1), 22.52 (alkyl C2), 25.87 ($NCH_2CH_2CH_2NH$), 26.94 (alkyl C6), 29.05 (alkyl C5), 29.30 (alkyl C4), 31.69 (alkyl C3), 36.51 (alkyl C7), 37.57 ($NCH_2CH_2CH_2NH$), 51.29 ($NCH_2CH_2CH_2NH$), 52.05 ($NCH_2CH_2CH_2N$), 174.00 (C═O).

G_4(An32) (3). A solution of **2** (1.04 g, 0.138 mmol) in THF (6.0 mL) was added slowly to a suspension of $LiAlH_4$ (400 mg, 11.6 mmol) in THF (50 mL) under nitrogen with stirring at 0 °C. The suspension was stirred at reflux for 24 h and transferred slowly into saturated aqueous Na_2SO_4 solution (40 mL) at 5−10 °C. The THF layer was collected, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic phase was washed with 4% aqueous K_2CO_3 (3 × 20 mL), dried (K_2CO_3), and concentrated. The oily crude product was purified on an Al_2O_3 column (MeOH/$CHCl_3$, 2:98) to give 880 mg (90%) of **3** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3295, 1474, 1132 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.86 (t, $J = 6.62$, CH_3), 1.18−1.38 (m, CH_2), 1.38−1.70 (m, $NCH_2CH_2CH_2N$, $NCH_2CH_2CH_2$), 2.31−2.50 (m, $CH_2N(CH_2)_2$), 2.51−2.70 (m, CH_2NH). ^{13}C NMR ($CDCl_3$, δ): 13.99 (alkyl C1), 22.55 (alkyl C2), 24.23 ($NCH_2CH_2CH_2N$), 27.39 (alkyl C6 and $NCH_2CH_2CH_2NH$), 29.20 (alkyl C5), 29.49 (alkyl C4), 30.17 (alkyl C7), 31.75 (alkyl C3), 48.76 ($NCH_2CH_2CH_2NH$), 50.26 (alkyl C8), 52.22 ($NCH_2CH_2CH_2NH$), 53.20 ($NCH_2CH_2CH_2N$).

G_4(TAm32) (4). [2-(2-Methoxyethoxy)ethoxy]acetyl chloride (**16**) (1.28 g, 6.50 mmol) was added to a solution of **3** (920 mg, 0.130 mmol), DMF (3.0 mL), and triethylamine (445 mg, 4.4 mmol) at 0 °C, and the solution was stirred under nitrogen at 70 °C for 24 h. Water (2.0 mL) was added, and the solution was stirred for 10 min and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL), washed with 1% aqueous K_2CO_3 (3 × 10 mL), dried (K_2CO_3), and concentrated. The oily crude product was purified on an Al_2O_3 column (MeOH/$CHCl_3$, 2:98) to give 1.14 g (72%) of **4** as a yellow thick oil. IR (film on NaCl) ν_{max}: 1651, 1474, 1104 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.89 (m, CH_3), 1.18−1.42 (br, CH_2), 1.42−1.80 (m, CH_2CH_2NCO, $NCH_2CH_2CH_2N$), 2.39 (br, $NCH_2CH_2CH_2N$), 3.23−3.32 (m, CH_2NCO), 3.38 (s, CH_3O), 3.52−3.80 (m, OCH_2CH_2), 4.20 (s, $NCOCH_2O$). ^{13}C NMR ($CDCl_3$, δ): 13.99 (alkyl C1), 22.50 (alkyl C2), 24.98 ($NCH_2CH_2CH_2N$), 26.46 and 26.77 ($NCH_2CH_2CH_2NCO$), 26.92 (alkyl C6), 27.47 and 28.94 (alkyl C7), 29.17 (alkyl C5), 29.29 (alkyl C4), 31.67 (alkyl C3), 44.15, 44.74, and 45.45 ($NCH_2CH_2CH_2NCO$), 47.03 (alkyl C8), 51.00 and 52.16 ($NCH_2CH_2CH_2N$), 58.95 (CH_3O), 63.68, 70.00 ($COCH_2O$), 70.46 (CH_2O), 70.57 (CH_2O), 70.84 (CH_2O), 71.86 ($CH_3OCH_2CH_2O$).

G_4(TAn32) (5). A solution of **4** (1.66 g, 0.136 mmol) in THF (4.0 mL) was added slowly to a suspension of $LiAlH_4$ (300 mg, 7.89 mmol) in THF (30 mL) under nitrogen with stirring at 0 °C. The suspension was stirred at reflux for 24 h, cooled, and quenched by transferring into saturated aqueous Na_2SO_4 solution (30 mL) at 5−10 °C. The THF layer was collected, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic phase was washed with 4% aqueous K_2CO_3 (3 × 10 mL), dried (K_2CO_3), and concentrated. The oily crude product was purified on an Al_2O_3 column (MeOH/$CHCl_3$, 2:98) to give 1.21 g (75%) of **5** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 1473, 1118 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.84 (t, $J = 6.18$, CH_3CH_2), 1.16−1.36 (m, CH_2), 1.36−1.70 (m, $NCH_2CH_2CH_2N$), 2.30−2.50 (m, $NCH_2CH_2CH_2N$), 2.61 (t, NCH_2CH_2O), 3.34 (s, CH_3O), 3.50 (m, OCH_2CH_2O), 3.62 (m, NCH_2CH_2O and OCH_2CH_2O). ^{13}C NMR ($CDCl_3$, δ): 14.02 (alkyl C1), 22.55 (alkyl C2), 24.52 ($NCH_2CH_2CH_2N$), 27.03 (alkyl C6), 27.47 (alkyl C7), 29.26 (alkyl C5), 29.52 (alkyl C4), 31.78 (alkyl C3), 51.90 (alkyl C8), 53.11 (NCH_2), 53.31 (CH_2N), 54.78 (NCH_2CH_2O), 58.96 (CH_3O), 69.87 (NCH_2CH_2O), 70.40 (OCH_2CH_2O), 70.50 (OCH_2CH_2O), 70.60 (OCH_2CH_2O), 71.90 (CH_2OCH_3).

G_4(PMI32) (5a). Methyl iodide (10.0 g, 70.0 mmol) was added slowly to a solution of **5** (680 mg, 0.0577 mmol) in CH_2Cl_2 (3.0 mL) in a thick-walled ampule at 0 °C. The ampule was sealed at −110 °C under vacuum and heated at 100 °C for 48 h. The excess methyl iodide and the solvent were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed with aqueous $Na_2S_2O_3$ and NaI, dried (Na_2SO_4), concentrated under reduced pressure, and dried under vacuum at 60 °C for 24 h to give 986 mg (83%) of **5a** as a yellow powder. ^1H NMR ($CDCl_3$, δ): 0.84 (t, $J = 6.46$, CH_3CH_2), 1.16−1.58 (m, CH_2), 1.82 (m, $NCH_2CH_2CH_2N$), 2.62−2.92 (m, $NCH_2CH_2CH_2N$, NCH_2CH_2 and NCH_3), 3.38 (s, CH_3O), 3.42−4.32 (m, NCH_2CH_2O, CH_2O). ^{13}C NMR ($CDCl_3$, δ): 13.94, 18.76, 22.46, 22.75, 26.22, 29.06, 31.56, 49.76, 59.01, 64.65, 70.16, 70.29, 71.75.

G_4(PMCl32) (5b). A solution of dendrimer **5a** (600 mg, 0.0291 mmol) in MeOH (1.0 mL) and water (0.5 mL) was placed on a column packed with Amberlite IRA 402 in Cl^- form and eluted using 1.2:1 MeOH/H_2O. The eluate was evaporated under reduced pressure. The residue was dissolved in a mixture of MeOH (2.0 mL) and aqueous saturated NaCl (10 mL) and stirred for 24 h. The MeOH was removed under reduced pressure, and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The extracts were washed with brine and water, concentrated under reduced pressure, and dried under vacuum at 60 °C for 24 h to give 308 mg (71%) of **5b** as a light yellow powder. ^1H NMR ($CDCl_3$, δ): 0.84 (t, $J = 5.91$, CH_3CH_2), 1.21−1.42 (m, CH_2), 1.60−1.78 (br, $N^+CH_2CH_2CH_2N^+$), 2.58, 3.32 (s, CH_3O), 3.34−4.18 (m, OCH_2CH_2O, N^+CH_2 and N^+CH_3), 4.22−4.42 (br, $OCH_2CH_2N^+$). ^{13}C NMR ($CDCl_3$, δ): 13.99 (alkyl C1), 17.0−18.0, 22.53 (alkyl C2), 26.36 (alkyl C6 and C7), 29.11 (alkyl C4), 29.20 (alkyl C5), 31.67 (alkyl C3), 48.0−50.0 (m, N^+CH_3), 58.90 (CH_3O), 57−62 (m, N^+CH_2), 64.78 ($N^+CH_2CH_2O$), 70.23 (OCH_2CH_2O), 71.73 (CH_2OCH_3). Anal. Calcd for $C_{726}H_{1542}Cl_{62}N_{62}O_{96}$: C, 58.5; H, 10.6; Cl, 14.7; N, 5.8; O, 10.3. Found: C, 49.47; H, 11.10; Cl, 12.27; N, 4.85; I, <0.10. Found after further drying under vacuum: C, 54.65; H, 11.11; N, 5.33. Calcd C/N mol ratio: 11.7. Found: 11.91 before drying; 11.96 after drying. Calcd Cl/N mol ratio: 1.00. Found: 1.00.

G_2(Am8) (7). By the procedure for **2,** DAB-*dendr*-$(NH_2)_8$ (**6**) (773 mg, 1.00 mmol), octanoyl chloride (1.60 g, 9.80 mmol), triethylamine (1.51 g, 15.0 mmol), and DMF (2.0 mL) gave **7** (1.60 g, 90%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3296, 3089, 1650, 1553 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.93 (t, $J = 6.60$, CH_3), 1.20−1.42 (m, CH_2), 1.43−1.81 (m, $NCH_2CH_2CH_2NCO$, $NCH_2CH_2CH_2N$ and $NHCOCH_2CH_2$), 2.20 (t, $NHCOCH_2$), 2.40 (m, $CH_2N(CH_2)_2$), 3.24 (q, CH_2NHCO), 6.92 (br, *NH*CO). ^{13}C NMR ($CDCl_3$, δ): 13.92 (alkyl C1), 22.47 (alkyl C2), 25.78 ($NCH_2CH_2CH_2NH$), 26.83 (alkyl C6), 28.94 (alkyl C5), 29.24 (alkyl C4), 31.62 (alkyl C3), 36.57 (alkyl C7), 37.68 ($NCH_2CH_2CH_2NH$), 51.40 ($NCH_2CH_2CH_2NH$), 52.92 ($NCH_2CH_2CH_2N$), 173.81 (C═O). MS (ESI) calcd for $C_{104}H_{208}N_{14}O_8$: 1781.63. Found: 1783.6 $(M + H)^+$, 892.4 $(M + 2H)^{2+}$, 595.2 $(M + 3H)^{3+}$.

G_2(An8) (8). By the procedure for **3**, amide **7** (800 mg, 0.448 mmol), THF (40 mL), and $LiAlH_4$ (380 mg, 10.0 mmol) gave **8** (680 mg, 91%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3298, 1475, 1133 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.86 (t, $J = 6.73$, CH_3), 1.18−1.39 (m, CH_2), 1.38−1.72 (m, $NCH_2CH_2CH_2N$, $NCH_2CH_2CH_2$), 2.30−2.51 (m, $CH_2N(CH_2)_2$), 2.52−2.72 (m, CH_2NH). ^{13}C NMR ($CDCl_3$, δ): 13.96 (alkyl C1), 22.54 (alkyl C2), 24.39 ($NCH_2CH_2CH_2N$), 24.99 ($NCH_2CH_2CH_2CH_2N$), 27.36 (alkyl C6 and $NCH_2CH_2CH_2NH$), 29.18 (alkyl C5), 29.47 (alkyl C4), 30.12 (alkyl C7), 31.73 (alkyl C3), 48.74 ($NCH_2CH_2CH_2NH$), 50.23 (alkyl C8), 52.24 ($NCH_2CH_2CH_2NH$), 54.22

($NCH_2CH_2CH_2N$). MS (ESI) calcd for $C_{104}H_{224}N_{14}$: 1669.80. Found: 1672.0 $(M + H)^+$, 836.4 $(M + 2H)^{2+}$, 557.6 $(M + 3H)^{3+}$.

G_2(TAm8) (9). By the procedure for **4**, amine **8** (600 mg, 0.36 mmol), acid chloride **16** (845 mg, 4.30 mmol), DMF (3.0 mL), and triethylamine (445 mg, 4.40 mmol) gave **9** (806 mg, 76%) as a yellow thick oil. IR (film on NaCl) ν_{max}: 1652, 1475, 1106 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.94 (m, CH_3), 1.25 (br, CH_2), 1.42−1.78 (m, CH_2CH_2NCO, $NCH_2CH_2CH_2N$), 2.40 (br, $NCH_2CH_2CH_2N$), 3.23−3.32 (m, CH_2NCO), 3.39 (s, CH_3O), 3.50−3.81 (m, OCH_2CH_2), 4.22 (s, $NCOCH_2O$). ^{13}C NMR ($CDCl_3$, δ): 13.96 (alkyl C1), 22.50 (alkyl C2), 24.22 and 24.93 ($NCH_2CH_2CH_2N$), 26.45 and 26.80 ($NCH_2CH_2CH_2NCO$), 26.92 (alkyl C6), 27.45 and 28.91 (alkyl C7), 29.15 (alkyl C5), 29.27 (alkyl C4), 31.66 (alkyl C3), 44.18, 44.74, and 45.48 ($NCH_2CH_2CH_2NCO$), 47.06 (alkyl C8), 51.12 and 52.16 ($NCH_2CH_2CH_2N$), 58.97 (CH_3O), 69.97 ($COCH_2O$), 70.47 (CH_2O), 70.58 (CH_2O), 70.84 (CH_2O), 71.86 ($CH_3OCH_2CH_2O$). MS (ESI) calcd for $C_{160}H_{320}N_{14}O_{32}$: 2950.38. Found: 1476.8 $(M + 2H)^{2+}$, 985.2 $(M + 3H)^{3+}$, 738.8 $(M + 4H)^{4+}$.

G_2(TAn8) (10). By the procedure for **5**, amide **9** (660 mg, 0.224 mmol), THF (20 mL), and $LiAlH_4$ (102 mg, 2.68 mmol) gave **10** (584 mg, 92%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 1473, 1118 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.86 (t, J = 6.66, CH_3CH_2), 1.2 (br, CH_2), 1.32−1.52 (m, $NCH_2CH_2CH_2N$), 2.30−2.51 (m, $NCH_2CH_2CH_2N$), 2.62 (t, NCH_2CH_2O), 3.36 (s, CH_3O), 3.52 (m, OCH_2CH_2O), 3.62 (m, NCH_2CH_2O and OCH_2CH_2O). ^{13}C NMR ($CDCl_3$, δ): 14.06 (alkyl C1), 22.55 (alkyl C2), 24.40 ($NCH_2CH_2CH_2N$), 24.93 ($NCH_2CH_2CH_2N$), 26.95 (alkyl C6), 27.47 (alkyl C7), 29.24 (alkyl C5), 29.52 (alkyl C4), 31.76 (alkyl C3), 51.93 (alkyl C8), 52.40, 53.12 (NCH_2), 53.25 (CH_2N), 54.77 (NCH_2CH_2O), 58.97 (CH_3O), 69.81 (NCH_2CH_2O), 70.38 (OCH_2CH_2O), 70.51 (OCH_2CH_2O), 70.60 (OCH_2CH_2O), 71.89 (CH_2OCH_3). MS (ESI) calcd for $C_{160}H_{336}N_{14}O_{24}$: 2838.55. Found: 1420.8 $(M + 2H)^{2+}$, 947.6 $(M + 3H)^{3+}$, 710.8 $(M + 4H)^{4+}$, 568.8 $(M + 5H)^{5+}$.

G_2(PMI8) (10a). By the procedure for **5a**, **10a** was obtained as brown powder. ^1H NMR ($CDCl_3$, δ): 0.84 (t, J = 6.73, CH_3CH_2), 1.16−1.50 (m, CH_2), 1.78 (br, $NCH_2CH_2CH_2N$), 2.52 (br, NCH_3, $NCH_2CH_2CH_2N$ and NCH_2CH_2), 3.38 (s, CH_3O), 3.42−4.32 (m, NCH_2CH_2O, CH_2O). ^{13}C NMR ($CDCl_3$, δ): 13.98, 18.29, 22.47, 22.70, 26.21, 29.03, 31.56, 49.59, 52.20, 59.02, 60.76, 63.22, 64.62, 66.03, 70.17, 70.32, 71.76, 72.49.

G_2(PMCl8) (10b). By the procedure for **5b, 10b** was obtained as a light yellow powder.^1H NMR ($CDCl_3$, δ): 0.84 (t, J = 6.58, CH_3CH_2), 1.21−1.42 (m, CH_2CH_2), 1.60−1.78 (br, $N^+CH_2CH_2CH_2N^+$), 2.58, 3.32 (s, CH_3O), 3.34−4.18 (m, OCH_2CH_2O, N^+CH_2 and N^+CH_3), 4.22−4.42 (br, $OCH_2CH_2N^+$). ^{13}C NMR ($CDCl_3$, δ): 13.99 (alkyl C1), 17.57 (m), 22.53 (alkyl C2), 26.36 (alkyl C6 and C7), 29.11 (alkyl C4), 29.20 (alkyl C5), 31.67 (alkyl C3), 49.00−51.00 (m, N^+CH_3), 58.90 (CH_3O), 57.10−61.69 (m, N^+CH_2), 64.78 ($N^+CH_2CH_2O$), 70.23 (OCH_2CH_2O), 71.73 (CH_2OCH_3).

G_5(Am64) (12). By the procedure for **2**, octanoyl chloride (2.30 g, 14.0 mmol), DAB-*dendr*-$(NH_2)_{64}$ **11** (1.00 g, 0.140 mmol), DMF (3.0 mL), and triethylamine (1.60 g, 15.8 mmol) gave 1.98 g (93%) of **12** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3294, 3090, 1650, 1550 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.91 (t, J = 6.60, CH_3), 1.12−1.40 (m, CH_2), 1.42−1.80 (m, $NCH_2CH_2CH_2NCO$, $NCH_2CH_2CH_2N$ and $NHCOCH2CH_2$), 2.18 (br, $NHCOCH_2$), 2.40 (br, $CH_2N(CH_2)_2$), 3.26 (q, CH_2NHCO), 7.58 (br, $NHCO$). ^{13}C NMR ($CDCl_3$, δ): 14.37 (alkyl C1), 22.90 (alkyl C2), 25.30 ($NCH_2CH_2CH_2NH$), 26.29 and 27.41 (alkyl C6), 28.94 (alkyl C5), 29.44 (alkyl C4), 29.72, 31.99 (alkyl C3), 32.07, 36.84 (alkyl C7), 37.93 and 38.25 ($NCH_2CH_2CH_2NH$), 51.56 ($NCH_2CH_2CH_2NH$), 52.47 ($NCH_2CH_2CH_2N$), 174.06 (C=O).

G_5(An64) (13). By the procedure for **3**, amide **12** (1.95 g, 0.128 mmol), THF (38 mL), and $LiAlH_4$ (660 mg, 17.3 mmol) gave **13** (1.68 g, 91%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3300, 1476, 1135 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.86 (t, J = 6.61, CH_3), 1.18−1.38 (m, CH_2), 1.38−1.70 (m, $NCH_2CH_2CH_2N$, $NCH_2CH_2CH_2$), 2.31−2.50 (m, $CH_2N(CH_2)_2$), 2.51−2.70 (m, CH_2NH). ^{13}C NMR ($CDCl_3$, δ): 13.97 (alkyl C1), 22.56 (alkyl C2), 27.41 (alkyl C6 and $NCH_2CH_2CH_2NH$), 29.21 (alkyl C5), 29.49 (alkyl C4), 30.15 (alkyl C7), 31.74 (alkyl C3), 48.75 ($NCH_2CH_2CH_2NH$), 50.24 (alkyl C8), 52.24 ($NCH_2CH_2CH_2N$).

G_5(TAm64) (14). By the procedure for **4**, amine **13** (1.00 g, 0.070 mmol), acid chloride **16** (1.38 g, 7.00 mmol), Et_3N (0.76 g, 7.5 mmol), and DMF (2.0 mL) gave **14** (1.18 g, 69%) as a yellow thick oil. IR (film on NaCl) ν_{max}: 1653, 1476, 1102 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.89 (m, CH_3), 1.18−1.42 (br, CH_2), 1.42−1.80 (m, CH_2CH_2NCO, $NCH_2CH_2CH_2N$), 2.39 (br, $NCH_2CH_2CH_2N$), 3.23−3.32 (m, CH_2NCO), 3.38 (s, CH_3O), 3.52−3.80 (m, OCH_2CH_2), 4.20 (s, $NCOCH_2O$). ^{13}C NMR ($CDCl_3$, δ): 14.02 (alkyl C1), 22.55 (alkyl C2), 25.05 ($NCH_2CH_2CH_2N$), 26.50 and 26.84 ($NCH_2CH_2CH_2NCO$), 26.96 (alkyl C6), 27.51 and 28.98 (alkyl C7), 29.30 (alkyl C5), 29.38 (alkyl C4), 31.66 (alkyl C3), 44.18, 44.75, and 45.49 ($NCH_2CH_2CH_2NCO$), 47.06 (alkyl C8), 51.11 and 52.15 ($NCH_2CH_2CH_2N$), 58.97 (CH_3O), 70.01 ($COCH_2O$), 70.47 (CH_2O), 70.58 (CH_2O), 70.85 (CH_2O), 71.86 ($CH_3OCH_2CH_2O$).

G_5(TAn64) (15). By the procedure for **5**, amide **14** (1.07 g, 0.044 mmol), THF (32 mL), and $LiAlH_4$ (420 mg, 10.6 mmol) gave **15** (0.82 g, 78%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 1474, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.84 (t, J = 6.66, CH_3CH_2), 1.16−1.36 (m, CH_2), 1.36−1.70 (m, $NCH_2CH_2CH_2N$), 2.30−2.50 (m, $NCH_2CH_2CH_2N$), 2.61 (t, NCH_2CH_2O), 3.34 (s, CH_3O), 3.50 (m, OCH_2CH_2O), 3.62 (m, NCH_2CH_2O and OCH_2CH_2O). ^{13}C NMR ($CDCl_3$, δ): 14.12 (alkyl C1), 22.61 (alkyl C2), 24.58 ($CH_2CH_2CH_2$), 27.09 (alkyl C6), 27.51 (alkyl C7), 29.32 (alkyl C5), 29.58 (alkyl C4), 31.82 (alkyl C3), 51.85 (alkyl C8), 53.30 (CH_2N), 54.75 (NCH_2CH_2O), 58.92 (CH_3O), 69.85 (OCH_2CH_2N), 70.35 (OCH_2CH_2O), 70.46 (OCH_2CH_2O), 70.55 (OCH_2CH_2O), 71.86 (CH_2OCH_3).

2-[2-(2-Methoxyethoxy)ethoxy]acetyl chloride (**16**) was prepared by heating 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (5.34 g, 30.0 mmol) and thionyl chloride (5.95 g, 50.0 mmol) in toluene (3.0 mL) for 4 h at 65 °C. The solvent and excess reagent were removed under reduced pressure, and the residue was dried at 60 °C under vacuum to give a light yellow oil which was used for the next step without further purification. ^1H NMR ($CDCl_3$, δ): 3.40 (s, CH_3O, 3H), 3.57 (m, OCH_2CH_2O, 2H), 3.63 (m, OCH_2CH_2O, 2H), 3.70 (m, OCH_2CH_2O, 2H), 3.80 (m, OCH_2CH_2O, 2H), 4.52 (s, CH_2OCO, 2H). ^{13}C NMR ($CDCl_3$, δ): 58.91, 70.44, 70.64, 71.17, 71.70, 76.55, 171.97.

Kinetic Experiments and Calculations. The pH of the dendrimer solution was adjusted to 11.4 using aqueous NaOH, and the sample was placed into a polystyrene cuvette and diluted with aqueous NaOH (pH 11.4) to give 3.0 mL of a solution with a certain concentration of N^+ units. The solution was allowed to equilibrate to 25.0 °C for 10 min. 6-Nitrobenzisoxazole-3-carboxylic acid in ethanol solution (22 μL, 1.06 × 10^{-2} M) was added to produce a substrate concentration of 7.82 × 10^{-5} M. Formation of 2-cyano-5-nitrophenoxide ion was followed with a Hewlett-Packard diode array spectrophotometer by the increase of the average absorbance at 400−430 nm. The λ_{max} in the dendrimer solution was 418 nm. The rate constants were calculated from data over the first 25% conversion using the first-order kinetic equation $k_{obsd} = \ln[(A_{inf} - A_0)/(A_{inf} - A_t)]/t$, where t is the time of reaction, and A_0, A_t, and A_{inf} are the absorbance at time 0, t, and infinity.

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References and Notes

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