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Polymer 47 (2006) 8173–8182

polymer
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Gelation and swelling behavior of end-linked hydrogels prepared from linear poly(ethylene glycol) and poly(amidoamine) dendrimers

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Received 3 August 2006; received in revised form 20 September 2006; accepted 24 September 2006
Available online 16 October 2006

Abstract

Linear α,ω di-epoxide-terminated poly(ethylene glycol) of molar mass 4000 g mol^{-1} was end-linked with amine-terminated poly(amidoamine) (PAMAM) dendrimers of generations 0, 2, and 4 in water to prepare architecturally well-defined copolymer hydrogels. The gelation and equilibrium swelling of the gels in water were characterized while systematically varying the polymer concentration at preparation, dendrimer generation, and mole ratio of dendrimer endgroups to PEG endgroups. The Ahmad–Rolfes–Stepto (ARS) theory of non-linear polymerization was applied to predict conditions favoring gelation, and to estimate the extent of reaction of amine and epoxide groups. Hydrogels having a large stoichiometric excess of amines over epoxides exhibited "superabsorbent" behavior upon extraction and equilibrium swelling in pure water. The mole ratio of amines to epoxides (equivalently, the mass fraction of dendrimers) was the most important factor governing superabsorbent behavior, although the polymer volume fraction at crosslinking and dendrimer generation also affected swelling to a lesser extent. The superabsorbency arises in part from protonation of the dendrimer amine endgroups at external pH = 7, which is supported by the drastic shrinkage of the most highly swelling gels in aqueous NH_4OH at pH = 11. Equilibrium swelling at pH = 7 was noticeably enhanced in gels having a high soluble fraction and high mass fraction of dendrimers. End-linking of linear polymer precursors to PAMAM dendrimers can potentially produce novel copolymer gels that combine attractive properties of the linear precursors with high swelling and pH-responsive behavior of PAMAM-containing networks.

Keywords: Dendrimer; End-linking; Hydrogels

1. Introduction

Hydrogels are water-swollen polymer networks that receive interest as biomedical materials [1], superabsorbent materials [2] and sensors [3]. Model hydrogels with well-defined molecular architecture can be synthesized by end-linking reactions [4,5] where end-functionalized linear polymer chains (precursors) are connected to multifunctional crosslinkers. End-linking is a preferred technique to prepare networks for fundamental studies, as it permits control of the molar mass of the elastic polymer chains between chemical crosslinks. End-linking has also been applied to prepare networks having controlled amounts of structural defects such as pendent (dangling) chains [6]. Numerous studies involving end-linked (dry) networks and (swollen) gels have been conducted since the late 1960s, and structure–property relationships have been established for networks of various polymers including polydimethylsiloxane [6–13], polyisoprene [14,15], polybutadiene [16,17], poly(ethylene oxide) [18–20], and others [5,21]. The effects of precursor molar mass [6,8,21,22], crosslink density [6], crosslinker functionality [23–25], initial preparation concentration [8,14,15,26,27], and defects [6,28] on the swelling and mechanical properties have been documented.

The present work explores physical properties of new hydrogels formed via end-linking of di-epoxide end-functionalized poly(ethylene glycol) (PEG) precursor chains with

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0032-3861/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.polymer.2006.09.048

amine-functionalized poly(amidoamine) (PAMAM) dendrimers, which act as multifunctional crosslinkers. Dendrimers are compact, symmetrical, highly branched polymers with a layered, tree-like structure that can terminate with reactive endgroups [29,30]. Hydrogels containing PAMAM dendrimers are especially interesting because the amine dendrimer endgroups are Lewis bases, acting as proton acceptors at pH = 7 in water. PAMAM–PEG gels are in that sense structurally well-defined ionomer gels (under appropriate conditions of pH), in which cationic blocks of well-defined size (dendrimers) are interconnected via neutral elastic chains (PEG). Previously, dendrimer-containing networks and gels were studied for various purposes including biomedical applications [31–33], constructing segmented polymer networks [34], and nanoparticle templating [35]. However, no systematic study concerning the gelation and swelling behavior of PAMAM dendrimer-containing hydrogels has been reported to date. PAMAM–PEG hydrogels offer control over many adjustable parameters including linear precursor chain molar mass, dendrimer generation (number of endgroups), end-linking reaction stoichiometry, and polymer concentration at end-linking. Manipulation of this suite of adjustable parameters permits tailoring the molecular structure and physical characteristics of hydrogels with essentially no change in polymer chemistry. This investigation represents the first systematic study of the gelation and swelling characteristics of dendrimer-containing gels prepared by end-linking in water. We examine how reaction conditions influence gelation and swelling behavior and discuss the physical basis for their interesting swelling behavior in aqueous solution.

2. Experimental section

2.1. Poly(ethylene glycol) di-epoxide synthesis

Linear α,ω dihydroxyl-terminated poly(ethylene glycol) of molar mass 4000 g mol^{-1} (Fluka) was used as received. Epichlorohydrin (Alfa Aesar, 54.0 g) was added dropwise to a 500 mL, 3-neck, round bottom flask containing PEG (75.0 g), NaOH (EMD Chemicals, 12.0 g) and distilled water (1162.5 μL) and stirred at 65 °C for 16 h. The resulting suspension was filtered and the liquid portion was retained and extracted three times with dichloromethane (Omnisolv). The dichloromethane phase was dried over anhydrous sodium sulfate (EMD Chemicals) and filtered. The polymer was concentrated by distillation and recovered by precipitation in diethyl ether (JT Baker Analytical) at −20 °C, then dried under vacuum at 20 °C.

2.2. PEG di-epoxide characterization by MALDI-TOF MS

PEG 4000 was characterized by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (*MALDI-TOF MS*) to confirm the –OH termination of the original PEG diol and to characterize replacement of the endgroups with epoxide groups. MALDI-TOF MS was performed on a Bruker Reflex TOF-MS in reflection mode at 25 kV acceleration and using delayed extraction. The analyte, 5 mg/mL PEG in tetrahydrofuran (THF), the matrix, 75 mg/mL all-trans-retinoic acid in THF, and the cationizing agent, 2.5 mg/mL sodium trifluoroacetate (NaTFA) in THF, were used to prepare a MALDI solution of 1:10:1 by volume PEG/matrix/NaTFA solutions. The MALDI samples were prepared by solution spotting 0.5 μL solution onto the MALDI target. Each spectrum equals 10 × 20 scans.

2.3. Hydrogel preparation

PEG–PAMAM hydrogels were prepared by reaction of PEG di-epoxide with poly(amidoamine) (PAMAM) dendrimers in aqueous solution. PAMAM Generation 0 (G0) dendrimers with theoretically 4 terminal amine groups (20 mass% in methanol, theoretical molar mass 516 g mol^{-1}), PAMAM Generation 2 (G2) dendrimers with theoretically 16 terminal amine groups (20 mass% in methanol, theoretical molar mass 3256 g mol^{-1}), and PAMAM Generation 4 (G4) dendrimers with theoretically 64 terminal amine groups (10 mass% in methanol, theoretical molar mass 14,215 g mol^{-1}) were obtained from Sigma Aldrich, Inc. and used as received.

PEG di-epoxide chains were attached to the dendrimer terminal $-NH_2$ groups via end-linking in aqueous solution. The solutions were cured in silicone rubber molds at 40 °C for 7 days. The hydrogels were prepared by varying polymer concentration in the system (ϕ_{PEG}) (0.1–0.35 volume fraction), dendrimer generation (G) (0, 2 or 4), number of endgroups of dendrimers (Z) (4, 16, or 64), and mole ratio of $-NH_2$ endgroups to PEG endgroups (r) (0.5–48).

2.4. Swelling experiments

Hydrogels were immersed in distilled water (pH = 7) after curing and swelled at 23 °C for at least 14 days or until the hydrogel reached an equilibrium mass. The gels were removed from their solution and placed into fresh distilled water daily to extract solubles. After the total mass at equilibrium swelling was recorded for each sample, the equilibrium swelling ratio, Q_s, was calculated according to

$$Q_s = \left(\frac{M_s - M_{ex}}{\rho_1}\right)\left(\frac{\rho_2}{M_{ex}}\right) + 1 \qquad (1)$$

where M_s is the total hydrogel mass at equilibrium swelling, M_{ex} is the dry mass of the extracted gel, and ρ_1 and ρ_2 are the densities of water and PEG in the solution state, respectively. For certain gels, the soluble fraction, w_{sol}, was determined as follows. After curing for 7 days at 40 °C, the gels were air-dried in a desiccator filled with anhydrous $CaCl_2$ (Drierite™) until their mass reached an equilibrium value (approximately 2 weeks). The mass of the dry, unextracted networks, M_{unex}, was recorded, and the dry networks were then extracted in distilled water at 23 °C for 2–3 weeks. After the equilibrium swelling was reached, the gels were dried by the same procedure and the final dry mass was recorded as the extracted mass, M_{ex}. The soluble fraction was calculated according to

$$w_{sol} = \frac{M_{unex} - M_{ex}}{M_{unex}} \tag{2}$$

For one series of samples, the swelling in aqueous ammonium hydroxide (0.06 M, pH = 11) was studied after extraction in water. These gels were immersed in a comparatively large volume of NH_4OH solution, which was changed daily until equilibrium swelling was reached. To obtain dry extracted masses (M_{ex}), samples were first dried by simple evaporation at ambient temperature and humidity for 2–3 days, and then subsequently dried in the desiccator as described above.

2.5. Model calculations: ARS theory

The Ahmad–Rolfes–Stepto (ARS) theory [36–38] was invoked to predict maximum and minimum values of r favoring gelation, or r_{min} and r_{max}, and to estimate the extent of reaction of the limiting reactant (epoxide or amine groups). The theory defines a ring forming parameter, λ_{a0}, which can be interpreted in terms of a competition between intermolecular and intramolecular reactions occurring throughout a polymerization. The resulting expression for the gel point, defining unit probability of growth between two statistically equivalent points, is given as:

$$\begin{aligned} rp_{ac}^2(f_a-1)(f_b-1) = {} & [1+(f_a-2)\varphi(1,3/2)\lambda_{a0}+(f_b-2) \\ & \times (f_a-1)r\varphi(1,3/2)\lambda_{a0}p_{ac}] \\ & \times [1+(f_b-2)r\varphi(1,3/2)\lambda_{a0}+(f_a-2) \\ & \times (f_b-1)r\varphi(1,3/2)\lambda_{a0}p_{ac}] \end{aligned} \tag{3}$$

where r is the initial mole ratio of A groups to B groups, p_{ac} is the extent of reaction of A groups at the gel point, f_a and f_b are the chemical functionalities of reactants bearing A groups and B groups, respectively. The numerical factor $\varphi(1,3/2) = \sum_{i=1}^{\infty} 1^i i^{-3/2} = 2.612$ is a Truesdell function [39] that sums over the opportunity for forming each size of ring structure, allowing the ring structures of all sizes to be accounted for, and $\lambda_{a0} = P_{ab}/c_{a0}$ is the ring forming parameter. P_{ab} is the probability density function of the end-to-end vector of a chain, it represents the mutual concentration of A and B groups at the ends of the shortest sub-chain that can react intramolecularly assuming that the end-to-end distance distribution can be represented by a Gaussian function, and c_{a0} is the initial concentration of A groups.

Theoretical gelation limits r_{min} and r_{max} were calculated by applying the ARS theory to the PAMAM–PEG system. "A" groups are defined as dendrimer endgroups (amines), and "B" groups are defined as PEG endgroups (epoxides). The chemical functionality for the dendrimers, f_a, was taken to be $(2 \times Z)$ considering the ability of each dendrimer amine endgroup to react with two epoxides. Because our "PEG di-epoxide" precursor samples actually contained both mono- and di-functional chains, the chemical functionality of the PEG chains, f_b, was calculated using the concept of weight-average functionality introduced by Stockmayer [40] that defines average functionality for any number of reactants bearing B groups, f_{bw} as follows:

$$f_{bw} = \frac{\sum_i N_{bi} f_{bi}^2}{\sum_i N_{bi} f_{bi}} \tag{4}$$

The calculation for f_b was done by taking MALDI-TOF results into account that showed our PEG 4000 sample contained approximately 90.3 mol% PEG di-epoxide chains and 9.7 mol% PEG mono-epoxide chains. Taking $N_{b1} = 0.097$, $f_{b1} = 1$ and $N_{b2} = 0.903$, $f_{b2} = 2$, the f_b value was calculated to be 1.946. P_{ab} was calculated as $P_{ab} = (3/2\pi\langle r^2\rangle C_\infty)^{3/2}/N_{Av}$, and assuming independent Gaussian chain statistics $\langle r^2\rangle = \upsilon b^2$ where $\langle r^2\rangle$ is the mean-square end-to-end distance of the linear sub-chain joining two groups that react, and b^2 (mean square bond length of the chain of υ bonds) is taken to be 2.1436 Å^2 for PEG. υ is the number of bonds in the chain forming the average smallest ring structure in a polymerization, and is taken to be one PEG precursor chain, giving $\upsilon = 3(M_n/44.05)$, where M_n is the molar mass of the PEG di-epoxide chains in g mol^{-1} and 44.05 g mol^{-1} is the theoretical molar mass of a ($-CH_2CH_2O-$) unit, which contains 3 backbone bonds. N_{Av} is Avogadro's number, 6.02×10^{23} mol^{-1}. C_∞, the characteristic ratio, is taken to be 4.0, its reported value for PEO [41].

Theoretical r_{min} values were calculated for hypothetical extents of reaction of A groups at the gel point, p_{ac}, which was taken as 1.0, 0.9, 0.8, or 0.7 for illustrative purposes. In order to calculate r_{max}, p_{ac} is set to p_{bc}/r. Values of p_{ac} of $1.0/r$, $0.9/r$, $0.8/r$, and $0.7/r$ were considered. Substituting $r = r_{min}$ or r_{max} and the chosen value of p_{ac} for the desired extent of reaction into Eq. (3), one finds polynomial equations which can be solved for their roots to find either r_{min} or r_{max}. Mathematica® software (Wolfram Research, Inc.) was used to find the two roots of these equations numerically. In most cases, the negative roots were discarded and the positive roots were reported as r_{min} or r_{max}. In cases where two positive real roots were found, the value of the greatest root was typically unrealistically high, being on the order of 10^5, and was discarded. For a few cases, no positive real root was found, and calculated gelation limits are not reported.

3. Results and discussion

3.1. Poly(ethylene glycol) di-epoxide synthesis and characterization

Treatment of PEG 4000 diol with excess epichlorohydrin in the presence of sodium hydroxide and a trace of water yielded α,ω diglycidyl ether-terminated poly(ethylene glycol), hereafter called PEG di-epoxide. PEG 4000 diol and PEG 4000 di-epoxide were characterized by MALDI-TOF MS (Fig. 1) to quantify endgroup functionalization. Both MALDI-TOF

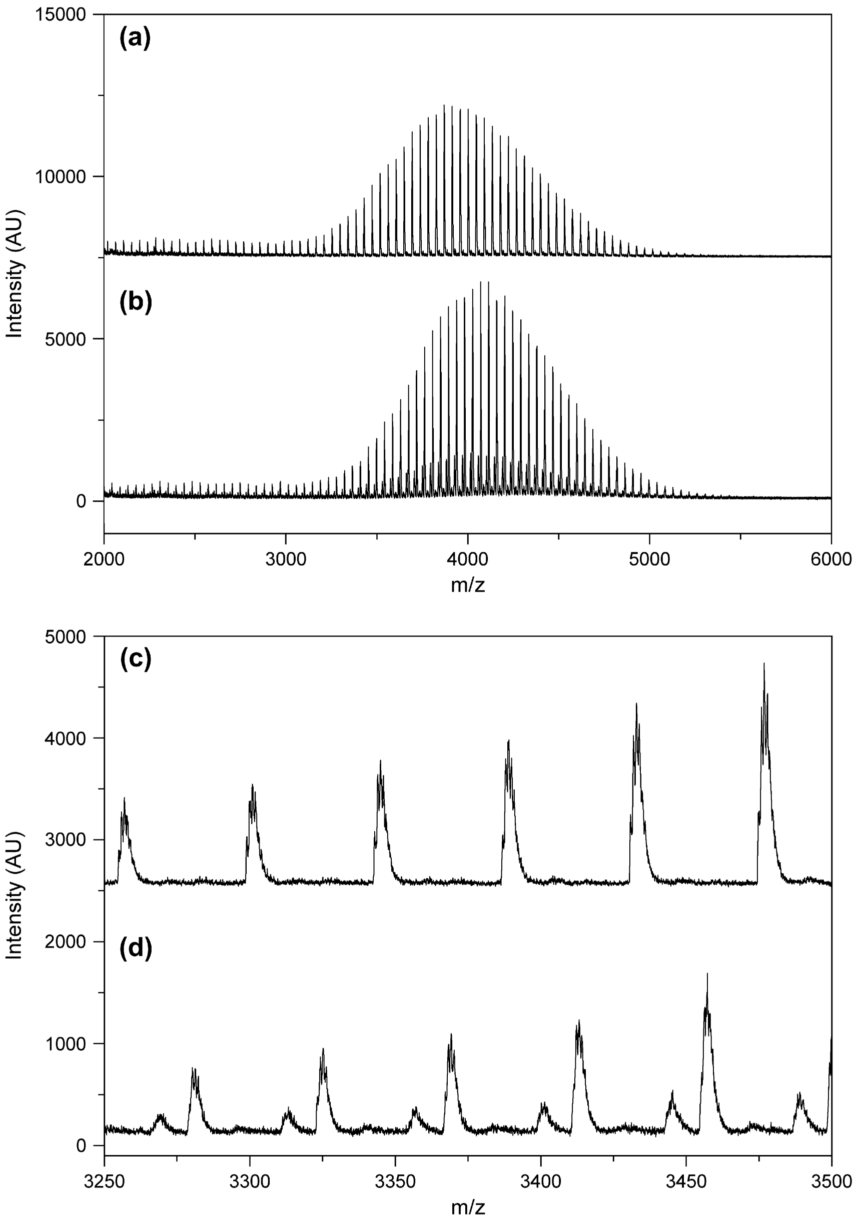

Fig. 1. MALDI-TOF MS results for commercial PEG 4000 (a, c) and synthesized PEG 4000 di-epoxide (b, d).

spectra showed a relatively narrow, unimodal molar mass distribution and a comparatively weak tail of lower molar mass material. Fig. 1 (bottom) expands the spectral features in the range of *m*/*z* from 3250 to 3500 g mol^{-1}. Analysis of the PEG 4000 diol spectral data gave a repeat mass of 44.03 ± 0.49 g mol^{-1} corresponding to $-CH_2CH_2O-$ (theoretical 44.053 g mol^{-1}) and an endgroup mass of 18.087 ± 0.23 g mol^{-1} corresponding to $-OH$ and $-H$ (theoretical 18.010 g mol^{-1}). MALDI-TOF spectra of the PEG 4000 di-epoxide sample showed two series. The predominant series corresponded to PEG terminated by two epoxide groups at the α,ω sites (130.64 ± 0.30 g mol^{-1}; theoretical monoisotopic 130.063 g mol^{-1}), while the minor series corresponded to only one epoxide replacement (74.47 ± 0.45 g mol^{-1}; theoretical monoisotopic 74.038 g mol^{-1}). The remaining amount of PEG diol was too small to be reliably quantified and was thereafter taken to be zero. Molar mass moments were also determined from the MALDI-TOF MS data. The PEG diol spectrum yielded a number average molar mass, M_n, of 3820 g mol^{-1} and a polydispersity index, PDI $\equiv M_w/M_n$, of 1.03; the PEG di-epoxide gave an M_n of 4070 g mol^{-1} and a PDI of 1.02. Simple integration of the mono-epoxide and di-epoxide spectral peaks over the entire molar mass range indicated that the sample contained approximately 90.3 mol% PEG di-epoxide chains and 9.7 mol% PEG mono-epoxide chains. The conversion of the alcohol endgroups to epoxide endgroups was calculated to be 95.2 mol% overall.

3.2. End-linking reaction

PEG di-epoxide chains were reacted with the dendrimer terminal primary amine groups via end-linking in aqueous solution Fig. 2. Reaction of a single epoxide group with

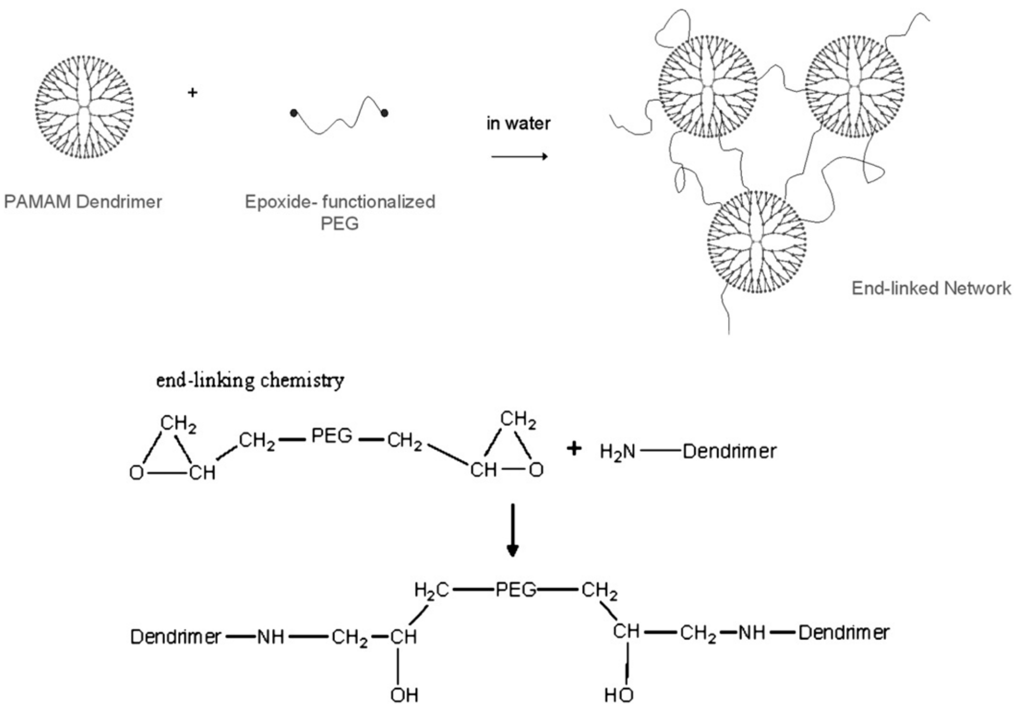

Fig. 2. End-linking reaction between PEG di-epoxide linear precursors and PAMAM dendrimers.

a primary amine produces a secondary amine and a pendent primary alcohol group. This secondary amine can then undergo reaction with another epoxide group to form a tertiary amine [42]. Therefore, a dendrimer with Z terminal primary amine groups is assumed to function as a crosslink junction with a maximum of $f_{\max} = 2Z$ reactive sites, meaning G0 dendrimers have $Z = 4$ and $f_{\max} = 8$, G2 dendrimers have $Z = 16$ and $f_{\max} = 32$, and G4 dendrimers have $Z = 64$ and $f_{\max} = 128$. This definition does not necessarily imply that complete reaction of endgroups can occur, as steric crowding at the dendrimer surface may conceivably limit the maximum number of PEG chains that can be grafted to a single dendrimer. In an earlier work, Hedden and Bauer examined grafting of monofunctional PEG-vinyl sulfone chains ($M_w = 5000\ \mathrm{g\,mol^{-1}}$) to the endgroups of PAMAM dendrimers to form dendrimer-star polymers [30]. Steric crowding did not significantly limit the grafting reaction for PAMAM dendrimers of Generation 4 or lower under the conditions employed in Ref. [30], although it may have played a significant role for dendrimers of Generation 5 and higher.

A parameter describing the reaction stoichiometry, designated r, was defined as $r = 2 \times (\text{moles } {-NH_2} \text{ endgroups})/(\text{moles epoxide endgroups})$, where the factor of 2 accounts for the ability of the amine endgroups to react twice. It is important to note that increasing the value of r also increases the mass fraction of PAMAM dendrimers in the network. Mass ratios of the reactants ranged from 0.3% PAMAM:99.7% PEG to 70.0% PAMAM:30.0% PEG, excluding water. The parameter ϕ_{PEG} is defined as the total volume fraction of PEG precursor chains in water prior to adding the PAMAM dendrimers. For simplicity, the density of PEG in the water/dendrimer solutions was assumed to have an approximate value of $1.09\ \mathrm{g\,cm^{-3}}$ herein regardless of the molar mass and concentration of PEG used. Any uncertainties involved in the approximation of densities would introduce only a small systematic error in the calculation of ϕ_{PEG}, which would not impact the conclusions of this study.

A constant reaction time of 7 days was selected for all gels after studying the equilibrium swelling of gels crosslinked for different amounts of time at 40 °C. The hydrogels showed a constant equilibrium swelling ratio after 4–5 days of reaction. For highly swelling samples (those having Q greater than about 50), a gradual increase in equilibrium swelling was sometimes observed after more than 10 days reaction time, possibly indicating a degradation of the dendrimers at 40 °C. The choice of 7 day's reaction time does not guarantee that the extent of reaction had reached a maximum value, but represented a compromise between allowing enough time for reaction and minimizing possible degradation of the dendrimers. No evidence of degradation was noted in swelling experiments at 23 °C in water.

3.3. Gelation

The polymer concentration at crosslinking strongly affects gelation and swelling behavior, as diluting the reaction mixture with water increases the average separation between dendrimers, forming many intramolecular loops at the expense of elastically effective network chains. Under conditions of infinite dilution, only loops are formed, and the system will not reach the gel point. For the hydrogels in this report, all of the gels we studied reached the gel point for at least some values of r, however. For any series of samples at a constant value of ϕ_{PEG}, there is a minimum value of r (denoted as $r_{\min}$) below

Table 1
Experimental gelation data for hydrogels prepared with PEG precursors of $M_n = 4000$ g mol^{-1}

G0

	r															
ϕ_{PEG}	0.1	0.2	0.3	0.5	1.0	1.5	1.8	2.0	2.2	2.4	2.6	2.8	3.0	3.4	4.0	5.0
0.10	○	○	○	○	●	●	●	●	●	●	●	○	○	○	○	○
0.15	○	○	○	●	●	●	●	●	●	●	●	●	○	○	○	○
0.20	○	○	○	●	●	●	●	●	●	●	●	●	●	○	○	○
0.25	○	○	○	●	●	●	●	●	●	●	●	●	●	●	○	○
0.30	○	○	●	●	●	●	●	●	●	●	●	●	●	●	○	○
0.35	○	○	●	●	●	●	●	●	●	●	●	●	●	●	○	○

G2

	r															
ϕ_{PEG}	0.1	0.2	0.3	0.2	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0	16.0
0.10	○	○	○	○	●	●	●	●	●	●	●	●	●	●	○	○
0.15	○	○	○	●	●	●	●	●	●	●	●	●	●	●	○	○
0.20	○	○	○	●	●	●	●	●	●	●	●	●	●	●	○	○
0.25	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	○
0.30	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	○
0.35	○	●	●	●;	●	●	●	●	●	●	●	●	●	●	●	○

G4

	r															
ϕ_{PEG}	0.1	0.2	0.3	0.5	0.9	1.5	4.0	6.0	8.0	12.0	16.0	24.0	32.0	40.0	44.0	48.0
0.10	○	○	○	○	●	●	●	●	●	●	●	●	●	●	○	○
0.15	○	○	○	●	●	●	●	●	●	●	●	●	●	●	○	○
0.20	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	○
0.25	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	○
0.30	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	○
0.35	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	○

(○) Indicates the compositions for which gelation was not observed; (●) indicates compositions for which gelation was observed.

which the gel point is not reached and a maximum value of r (denoted as r_{max}) above which the gel point is not reached. Table 1 presents the experimental gelation data for all samples studied. The parameters r_{min} and r_{max} depend on both ϕ_{PEG}, G, and the extent of reaction of both epoxide and amine endgroups in a complex way, and it was not straightforward to estimate the extent of reaction by standard spectroscopic techniques. Therefore, a theoretical framework is helpful for understanding experimental observations, and for estimation of the extent of reaction. The Ahmad–Rolfes–Stepto (ARS) theory predicts gel points for $\sum_i RA_{\mathrm{fai}} + \sum R'B_{\mathrm{fbj}}$ non-linear polymerizations by evaluating the probability of growth between two statistically equivalent groups, A or B [36–38]. ARS theory was applied to predict gelation limits as described in Section 2, and Table 2 presents calculated values of r_{min} and r_{max} assuming various extents of reaction for epoxide (B) and amine (A) groups. The r_{max} values for G0 and G2 gels are in close agreement with the experimental results (Table 1) for $p_{\mathrm{bc}} = 0.8$, while for G4 gels, the experimental data lie between the model predictions for $p_{\mathrm{bc}} = 0.8$ and $p_{\mathrm{bc}} = 0.9$. An extent of reaction of 80–90% for epoxide groups is quite reasonable, although we are presently unable to verify these results spectroscopically. On the other hand, calculated r_{min} values are predicted to be close to or higher than the experimental values for all cases, even assuming complete reaction of amines. The calculated values agree well with the experimentally determined values for G0 gels, but deviations from the predictions increase as dendrimer size increases. This deviation may arise from the finite size of the dendrimers, which could possibly exclude PEG chains, whereas dendrimers are treated as point junctions of functionality f in the model calculations. Given the complexity of the dendrimer-containing networks, the ARS theory does capture the dependence of the gelation limits on the concentration of precursor chains (ϕ_{PEG}) remarkably well. The expected narrowing of the gelation limits as precursor concentration decreases physically corresponds to the expected increase in the proportion of intramolecular loops as the system is diluted with solvent during crosslinking. The ARS theory suggests that the extent of reaction is higher for the case where epoxides outnumber amines (r_{min}), compared to the case where amines outnumber epoxides (r_{max}). Finally, the model calculations suggest that the extent of reaction of the limiting reactant (epoxide or amine) is quite high, exceeding 80% for all situations examined.

3.4. Equilibrium swelling and extraction

The soluble fraction of a polymer network w_{sol} is defined as the mass fraction of the network that is removable by exhaustive extraction in a good solvent. The soluble fraction is often taken as an indicator of the degree of perfection of the network structure. Two sets of gels ($\phi_{\mathrm{PEG}} = 0.25$, G2, $r = 2$–10 and

Table 2
Theoretical gelation limits of gels with PEG precursors of $M_n = 4000\ \mathrm{g\ mol^{-1}}$ calculated by the ARS theory for extents of reactions of 100%, 90%, 80%, and 70% of the limiting reactant (epoxides or amines)

	100%		90%		80%		70%	
ϕ_{PEG}	r_{min}	r_{max}	r_{min}	r_{max}	r_{min}	r_{max}	r_{min}	r_{max}
G0								
0.10	0.87	3.54	0.96	2.18	1.07	*	1.22	*
0.15	0.66	4.71	0.73	3.50	0.83	2.41	0.96	1.35
0.20	0.55	5.21	0.62	4.01	0.70	2.93	0.82	1.96
0.25	0.49	5.50	0.55	4.29	0.62	3.21	0.73	2.25
0.30	0.44	5.68	0.50	4.47	0.57	3.38	0.67	2.43
0.35	0.41	5.81	0.46	4.59	0.53	3.51	0.63	2.55
G2								
0.10	1.43	11.06	1.53	*	1.65	*	1.80	*
0.15	1.00	17.79	1.07	12.83	1.16	8.12	1.27	*
0.20	0.78	20.35	0.84	15.46	0.91	11.04	1.00	7.00
0.25	0.64	21.77	0.70	16.88	0.76	12.48	0.84	8.55
0.30	0.55	22.69	0.60	17.78	0.66	13.38	0.73	9.47
0.35	0.49	23.33	0.53	18.41	0.58	13.99	0.65	10.08
G4								
0.10	2.60	*	2.77	*	2.97	*	3.21	*
0.15	1.79	48.66	1.91	33.28	2.04	*	2.21	*
0.20	1.37	58.85	1.46	44.34	1.57	30.79	1.70	17.36
0.25	1.12	64.33	1.19	49.89	1.28	36.64	1.38	24.46
0.30	0.94	67.81	1.00	53.35	1.08	40.13	1.17	28.15
0.35	0.82	70.23	0.87	55.73	0.94	42.50	1.02	30.55

(*) Denotes cases for which no real positive root exists for Eq. (3).

$\phi_{PEG} = 0.25$, G0, $r = 1–3$) were prepared expressly for the calculation of w_{sol} by Eq. (2). The soluble fraction results obtained are shown in Table 3 along with the corresponding equilibrium swelling ratios Q_s. For the gels prepared with lower r values, the soluble fraction is around 3 mass%, while it increases dramatically as r approaches r_{max}. Increasing the dendrimer concentration well beyond the stoichiometric concentration is expected to encourage formation of comparatively small dendrimer–PEG clusters or "microgels" that are not attached to the parent network, which leach from the network during extraction along with unreacted dendrimers and PEG precursors. Gels having $r \gg 1$ may possibly become porous or inhomogeneous as microgels are lost as solubles during extraction, leaving behind voids that essentially fill with water.

Table 3
Soluble fractions for two series of gels with PEG precursors of $M_n = 4000\ \mathrm{g\ mol^{-1}}$ with varying values of r (defined in text)

r	w_{sol} (mass fraction)	Q_s
Series 1: $\phi_{PEG} = 0.25$, G2		
2.0	0.03	12.4
4.0	0.05	16.4
6.0	0.07	25.3
8.0	0.13	67.3
10.0	0.26	480
Series 2: $\phi_{PEG} = 0.25$, G0		
1.0	0.03	13.4
1.5	0.05	18.7
1.8	0.07	23.1
2.0	0.08	27.5
2.2	0.09	31.5
2.4	0.12	47.8
2.6	0.16	73.7
2.8	0.33	137
3.0	0.38	320

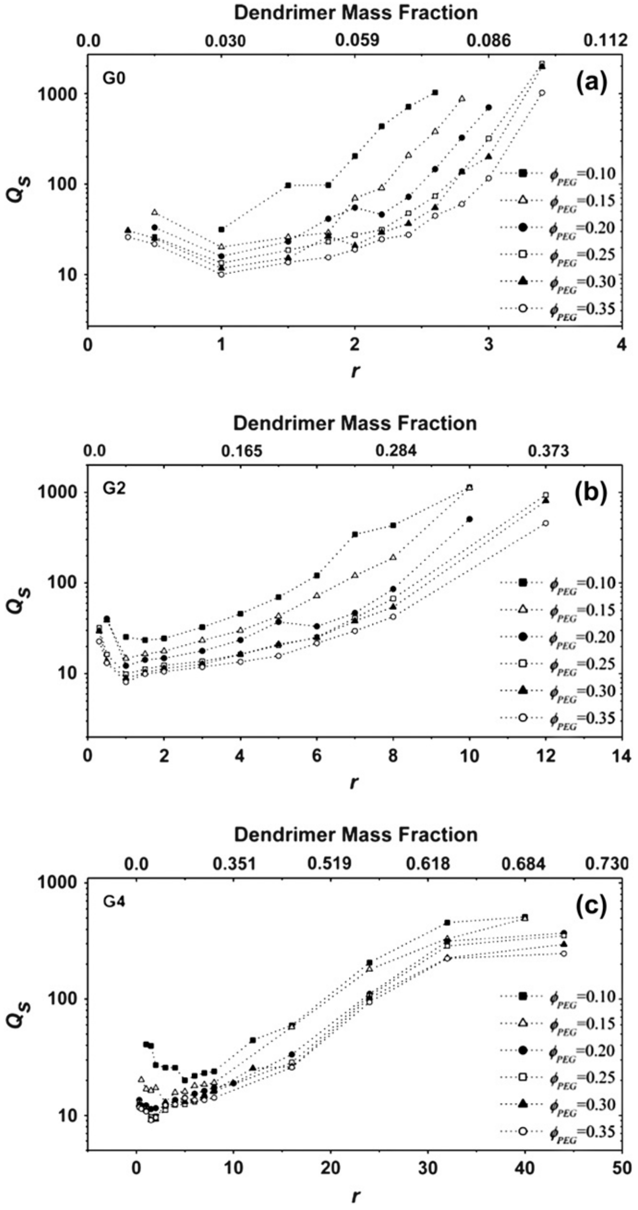

Fig. 3. Dependence of the equilibrium swelling ratio Q_s on the mole ratio of dendrimer endgroups to precursor endgroups, r, for gels prepared from G0 (a), G2 (b), and G4 (c) PAMAM dendrimers. Initial PEG concentrations in water are ϕ_{PEG}. The dashed lines are a guide to the eye.

Fig. 3 summarizes the dependence of Q_s on structural parameters: the PEG volume fraction at crosslinking, ϕ_{PEG} (0.1–0.35), the mole ratio of $-NH_2$ endgroups to epoxide endgroups, r (0.5–48), and dendrimer generation G (0, 2 or 4). In Fig. 3, "dendrimer mass fraction" is defined as (total mass of dendrimers in the network)/(total polymer mass in the network), and ignores water. For any given series at constant ϕ_{PEG}, the observed swelling ratio, Q_s, depends strongly on r, passing through an "optimum" point (r_{opt}) at which swelling is minimized. From Fig. 3, the observed values of

r_{opt} for the G0 and G2 series are close to stoichiometric conditions ($r_{opt} = 1 \pm 0.5$). We did not attempt to find a more accurate value for r_{opt} because Q_s depends rather weakly on r in this regime. For the G4 series, the observed r_{opt} is greater than 1 and increases as ϕ_{PEG} decreases. For values of r above r_{opt}, Q_s increases with increasing r up to a limiting value r_{max}, above which the gel point was not reached during the 7 days allowed for the end-linking reaction to proceed. Similarly, below r_{opt}, Q_s increases with decreasing r down to a limiting value r_{min}, below which the gel point was not reached.

An optimum value of r is a common feature of end-linked polymer network and gel systems, and it is expected that $r_{opt} \neq 1$ for some of our data series. Patel et al. [6] examined model end-linked poly(dimethylsiloxane) networks prepared by Pt-catalyzed hydrosilylation using a tetrafunctional crosslinker ($f = 4$), and found values of r_{opt} ranging from 1.44 to 2.05 depending on the molar mass of the precursor chains (shorter precursor chains generally resulted in lower values of r_{opt}). Sivasailam and Cohen [8] examined an end-linked PDMS system diluted with PDMS chains having unreactive (trimethylsilyl) endgroups and found $r_{opt} \approx 1.5$. Gilra et al. [43] used computer simulations to show that $r_{opt} \neq 1$ for end-linked networks with $f = 4$, but the deviations from $r = 1$ predicted by the simulations (1–1.2) were not as large as those observed in experiments. Takahashi et al. [28] examined end-linked poly(tetrahydrofuran) (PTHF) networks prepared by a reaction of allyl-terminated PTHF with tetrafunctional crosslinkers having thiol (–SH) endgroups. They found values of r_{opt} ranging from 1.25 to 2.25 depending on the molar mass of the precursor chains. In each of the preceding studies, the observed deviations from $r = 1$ may have more than one physical origin. Factors that may influence r_{opt} include incomplete reaction of precursor chain endgroups, incomplete precursor chain end-functionalization, intramolecular loop formation, and incomplete reaction of crosslinkers and precursor chain endgroups.

The swelling data reveal a weak dependence of Q_s on r in the vicinity of r_{opt} (Fig. 3), which is most prominent for the G4 series and is related to the functionality (2 × number of endgroups) of the dendrimers. For large polyfunctional crosslinkers like G4 PAMAM dendrimers, only a few elastically effective chains need to be connected to the dendrimer to allow it to function as an effective network junction, so a small percentage conversion of dendrimer endgroups is sufficient to produce macroscopic gelation. By similar logic, when the extent of reaction of dendrimer endgroups is high, most dendrimers are already connected by elastic chains, so further reaction would have only a minimal effect on the network modulus and equilibrium swelling. Systems with fairly substantial fractions of unreacted dendrimer endgroups ($r \gg 1$) can still produce a network in which dendrimers function as elastically effective junctions. Conversely, for the case where epoxide groups outnumber amine groups ($r < 1$), the multifunctional nature of the G4 dendrimers would obscure the effects of incomplete epoxide reaction. This situation could also mask the effects of incomplete reaction under conditions where steric crowding at the dendrimer surface limits the grafting reaction. In contrast, for G0 dendrimers (or any other crosslinker with comparatively small functionality), a comparatively higher extent of crosslinker reaction is needed to produce elastically effective junctions. From Fig. 3, as dendrimer generation increases (f increases), the observed r_{max} for gelation also increases, which supports the preceding arguments.

From Fig. 3, the magnitude of the equilibrium swelling ratio is very high, especially in the case of highly imperfect networks having $r \gg r_{opt}$, considering that the networks are prepared from relatively short precursor chains (~90 monomers). Several of the samples from each series (*G0*, *G2*, and *G4*) exhibit equilibrium swelling ratios in excess of $Q_s = 1000$. This "superabsorbent" behavior is only noted in samples with $r \gg r_{opt}$, which also have higher mass fractions of dendrimers. It is somewhat remarkable to observe superabsorbent behavior in a gel prepared from neutral PEG precursors, as superabsorbency is more frequently associated with ionomer hydrogels and networks [44–46]. However, the PAMAM–PEG gels are not "neutral," as the dendrimers do have some cationic character in water at pH = 7 due to protonation of amine endgroups and internal amines. In dilute solution, the tertiary amines in the core of PAMAM dendrimers are protonated below pH = 7.53, and the primary amine endgroups are protonated below pH = 10.5 [47]. At pH = 7, at least some of the dendrimer amines are protonated, and the driving force for water to swell the network is enhanced by its reduction in chemical potential upon mixing with the charged constituents. The charged species are unable to diffuse out of the gel (provided solubles have been extracted), so the swelling force of the water is greatly enhanced by the charging (Donnan equilibrium effect) [48]. The effects of amine protonation on equilibrium swelling are illustrated by comparing swelling in neutral water to swelling under basic conditions. Fig. 4 compares equilibrium swelling for some hydrogels (PAMAM G2, $\phi_{PEG} = 0.15$) in neutral water (pH = 7) and in 0.06 M NH_4OH (pH = 11.0). At pH = 11, dendrimer endgroups are no longer protonated, resulting in a large decrease in Q_s. This shrinkage is most pronounced for the gels

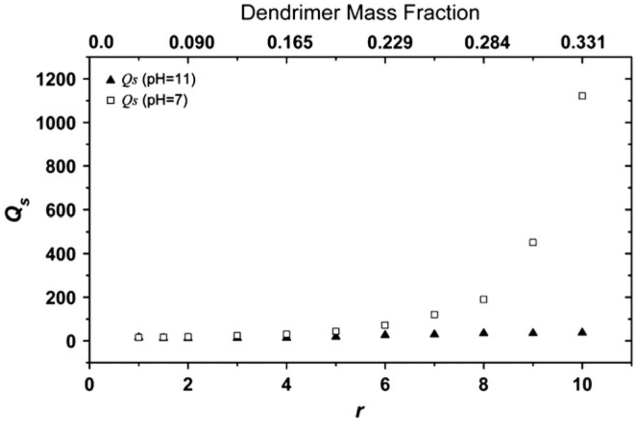

Fig. 4. Equilibrium swelling ratios of G2 gels ($\phi_{PEG} = 0.15$) in water (pH = 7) and 0.06 M NH_4OH (pH = 11).

with high dendrimer mass fraction (high r). Deprotonation of the endgroups at pH = 11 decreases the osmotic driving force for water to swell the network.

Protonation of the dendrimer amines is a necessary but not sufficient condition for superabsorbency, however. The samples having $r \approx r_{opt}$ exhibit much lower swelling (Q_s on the order of 10–20), despite containing charged dendrimers. The rather sharp upturn in swelling at high r is not merely a consequence of increasing the mass fraction of dendrimers in the network. For example, from Fig. 3, the swelling upturn occurs at a comparatively low mass fraction of dendrimers in the G0 series compared to the G2 and G4 series, suggesting that the large swelling also depends on other architectural factors. Another factor that contributes to the anomalously high swelling ratios at $r \gg r_{opt}$ is formation of a significant proportion of elastically ineffective chains, such as loops and pendent chains. Gels having $r \gg r_{opt}$ are more likely to contain defects because they were crosslinked in solution under conditions of non-optimal stoichiometry. This idea is supported by their significantly higher soluble fractions compared to gels prepared near $r \approx r_{opt}$. The soluble fraction is often taken as an indicator of the perfection of the network structure. In addition, removal of the solubles by extraction may produce pores or voids in the networks as unreacted precursors and microgels diffuse out of the parent network. The increase in architectural defects and the loss of solubles both serve to reduce the density of elastically effective network chains, decreasing the elastic contribution to the network free energy and increasing the capacity of the network to accommodate solvent. Summarizing, the gels with the highest values of r are superabsorbent at pH = 7 due to a combination of factors: they contain high concentrations of charged dendrimer amines, and they also have the lowest density of elastically effective chains.

In contrast to the superabsorbent behavior of highly defective gels having ($r \gg r_{opt}$), the equilibrium swelling of the optimal networks ($r = r_{opt}$) is more typical of conventional polymer hydrogels. Fig. 5 illustrates how the PEG concentration at preparation (ϕ_{PEG}) affects equilibrium swelling of optimal networks. For each series at constant ϕ_{PEG}, the least highly swelling gel was chosen to represent $r = r_{opt}$. The swelling of all gels increased steadily with decreasing ϕ_{PEG}, as expected, but no "superabsorbent" samples were noted. The optimal networks are the most tightly crosslinked samples based upon the minimal loss of solubles, and they also contain a relatively low mass fraction of dendrimers, both of which factors would work against high equilibrium swelling. Q_s exhibited an apparent linear dependence on log(ϕ_{PEG}), and least-squares fits to the data were performed, yielding best-fit slopes given in Fig. 5. The values of the slopes differ from the predictions of Obukhov et al. [49] and Bastide et al. [50] for swelling of *neutral* polymer networks prepared in good solvents, which give $Q_s \sim \phi_0^{-0.25}$ and $Q_s \sim \phi_0^{-0.40}$, respectively. (We note that the definitions of ϕ_{PEG} and ϕ_0 differ slightly, but they are nearly equal for the optimal networks, which contain very low mass fractions of dendrimers.) The stronger dependence of swelling on dilution at crosslinking observed in our system is another manifestation of the charging of the dendrimer endgroups in water. Beyond dendrimer-containing networks, these ideas are broadly applicable to the swelling of any polymer hydrogel containing amine crosslinkers or amine functionality.

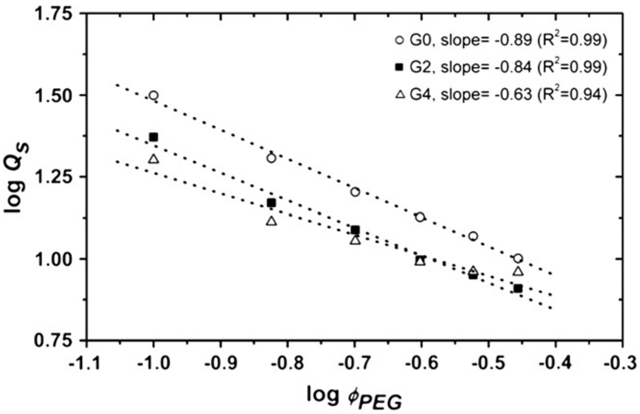

Fig. 5. Equilibrium swelling of "optimal" networks as a function of PEG concentration during crosslinking.

4. Summary and conclusions

The PAMAM–PEG hydrogels discussed herein are interesting for their remarkable dependence of swelling behavior on both composition and pH. The ratio of dendrimer endgroups to linear precursor endgroups, r, or equivalently the mass fraction of dendrimers in the network, is the most significant parameter governing the equilibrium swelling in water. Off-stoichiometric reaction between amine and epoxide groups can produce hydrogels with exceptional swelling capacity, even when linear precursor chains are quite short. At $r \gg r_{opt}$, the protonation of dendrimer endgroups, coupled with a low density of elastically effective network chains, permits a tremendous uptake of water during equilibrium swelling, even for gels containing G0 dendrimers. The ARS theory calculations suggest that the superabsorbent behavior probably did not arise from a low extent of reaction of the epoxides. Superabsorbent behavior was noted in all hydrogels at $r \gg r_{opt}$, irrespective of dendrimer generation, suggesting that large, multifunctional (G4) dendrimers did not present any unique advantages from a practical standpoint. In fact, G0 hydrogels became superabsorbent at a significantly lower dendrimer mass fraction. PAMAM–PEG gels differ from most conventional polymer gels in that their swelling behavior can be tailored to cover an unprecedented range of equilibrium swelling ratios (from ~15 to more than 1000) simply by changing the gel composition through the r parameter. The ideas presented here are applicable to further design of end-linked hydrogel systems with unique swelling behavior. For example, interesting new gels could be designed by end-linking of temperature-responsive or pH-responsive linear precursors with PAMAM dendrimers, providing hybrid materials that exhibit anomalously large changes in swelling with temperature or pH.

Acknowledgements

The authors thank Michelle Byrd and Barry J. Bauer from the Polymers Division of the National Institute of Standards and Technology for the MALDI-TOF measurements. This work was supported by the American Chemical Society-Petroleum Research Fund grant ACS PRF# 41322-G 7.

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