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pH-dependent swelling of hydrogels containing highly branched polyamine macromonomers

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ABSTRACT

We examine the pH-dependent swelling of end-linked hydrogels containing high concentrations of amine-functional macromonomers. Gels are formed by end-linking of epoxide-terminated, linear poly(ethylene glycol) (PEG) to either amine-terminated poly(amidoamine) (PAMAM) dendrimers or highly branched poly(ethyleneimine) (PEI). After extraction in neutral water, the hydrogels are swollen in aqueous solutions of HCl or NH_4OH to vary the external pH. Equilibrium volume swelling ratios (Q_s) pass through a maximum value (Q_{max}) at an external pH denoted as pH* which is approximately 4–5 for the gels studied. The swelling behavior is modeled using Donnan equilibrium theory to describe the ion swelling pressure, with the Flory–Rehner phantom network expression representing the elastic and mixing contributions to the free energy. The model accurately predicts the maximum in swelling near pH = 4–5, but overestimates Q_{max} for several of the gels due to neglecting the finite extensibility of the short linear PEG chains.

1. Introduction

Hydrogels, or water-swollen polymer networks, have recently received attention as biomedical materials [1], biomimetic materials [2], super-absorbent materials [3], and stimuli-responsive materials [4]. For certain applications where pH-responsive swelling is desirable, such as in drug delivery systems [5], weak acidic or basic functional groups are often engineered into the elastic network chains [6–8]. Dissociation or protonation of ionizable functional groups in solution occurs over a certain range of pH, causing a substantial volume increase in response to increased osmotic pressure. The simplest theory to describe the swelling behavior of weakly charged ionic gels is the Donnan equilibrium theory, in which the contribution of ionic groups to the free energy change of swelling is ascribed to differences in the concentration of charged groups between the gel and the outside solution [9,10]. Although Donnan equilibrium theory has been remarkably successful in describing equilibrium swelling of model ionomer gels [11], certain simplifying assumptions may not hold in other ionizable systems. For example, high concentrations of ionizable groups may significantly affect the pK_a of a weak acidic group, broadening or shifting the pH range over which dissociation occurs compared to dilute-solution behavior [12]. Ionizable groups may also experience a distribution of local bonding arrangements throughout the gel, leading to a range of effective pK_as.

An example of ionizable gels that may exhibit these non-idealities are those containing high concentrations of amine-functional groups. Amines are Lewis bases that become protonated to some extent in dilute aqueous solution generally below a pH of about 10–11, imparting cationic character to the network. However, in a gel containing high concentrations of amines, the pK_as of the conjugate acids may arguably decrease, as local accumulation of positive charges might ostensibly be discouraged by electrostatic repulsions. The pH dependence of equilibrium swelling might therefore be affected if the initial concentration of ionizable amine groups is high enough. Another factor affecting the pK_as of the amines is the fact that the basicity of primary (1°), secondary (2°), and tertiary (3°) amines generally differs depending on the degree and nature of substitution. Polyamine gels generally contain mixtures of 1°, 2°, and 3° amines, meaning protonation should occur over a broader range of pH compared to, say, a system only containing 3° amines. This broadening has been well documented in titrations of polyamines in aqueous solutions, including dendrimers [13,14].

The present study concerns swelling behavior of hydrogels that contain variable concentrations of ionizable polyamine macromonomers connected by short, neutral, linear chains. We examine how the pH dependence of equilibrium swelling is affected by the initial concentration of the ionizable amine groups. Gels are formed via end-linking of di-epoxide end-functionalized poly(ethylene glycol) precursor chains of molar mass 4000 g mol^{-1}

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(PEG di-epoxide) with multifunctional polyamines. Two types of polyamine macromonomers are examined: amine-terminated poly(amidoamine) (PAMAM) dendrimers (Generation 2), and highly branched poly(ethylene imine) (PEI) chains (nominal molar mass 10 kg mol^{-1}).

Poly(amidoamine) (PAMAM) dendrimers are layered, treelike polymers that contain ionizable 3° amines in their cores, but may also be functionalized with 1° amine endgroups. PAMAM dendrimers have been widely studied in aqueous systems as agents for gene delivery [15–17] and drug delivery [18–21]. PAMAM dendrimers are also known to serve as effective ligands for transition metal ions [22–25], leading to numerous studies regarding their use as templates for metal nanoparticle synthesis [26–29]. In aqueous solution, amine-terminated PAMAM dendrimers acquire cationic character by protonation of both 1° amine endgroups and the 3° amines in their interiors. Previous studies examined how the degree of ionization and the hydrodynamic size of PAMAM dendrimers vary with external pH in dilute solutions [14,30–32]. The dependence of the degree of ionization on pH is now known to vary with the dendrimer generation. In larger dendrimers (higher generation number), protonation of the primary and tertiary amines occurs almost concurrently, whereas for smaller dendrimers, the core tertiary amines become protonated at significantly lower pH compared to their endgroups [14]. Higher generation dendrimers contain large numbers of ionizable amine endgroups that presumably form a highly charged shell when fully protonated, though the most probable location of these endgroups (at the surface or within the interior) has been debated. In this study, we examine PAMAM dendrimers of G = 2 (theoretically having 16 –NH_2 endgroups and 14 internal 3° amine-functional groups) as one type of multifunctional macromonomers [33].

The second type of polyamine macromonomer examined here is a highly branched poly(ethylene imine) (PEI), a randomly branched polyamine that contains a mixture of 1°, 2°, and 3° amines prior to crosslinking. Several groups studied ionization of PEI in aqueous solutions [13,34–39], revealing a significant difference between the titration curves of branched PEI and linear PEI (which contains mostly 2° amines). Linear PEI shows two distinct protonation steps in the titration curve, whereas branched PEI shows a smooth titration curve, as its amines experience a wide distribution of local bonding arrangements due to the irregular branching scheme [36]. Highly branched PEI, such as that examined in the present study, is essentially unprotonated at pH > 10.5 and 65% protonated at pH = 4 in dilute aqueous solution [34,35].

This work represents the first study of the pH dependence of swelling in hydrogels containing PAMAM dendrimers or PEI as branched macromonomers. We examine how external pH influences swelling behavior and identify an optimal value of the pH at which swelling is maximized, denoted as pH*. The concentration of amine units in the PAMAM–PEG gels is varied to probe the effects of concentrating the ionizable groups. Swelling vs. pH curves are modeled theoretically using Donnan equilibrium theory to describe the ion swelling pressure, using the Flory–Rehner phantom network expression to represent the elastic and mixing contributions to the free energy. By comparing experimental observations to simplified theoretical predictions, we deduce the extent to which the concentration of the polyamine macromonomers affects the pH range over which enhanced swelling is observed.

2. Experimental section

2.1. Hydrogel preparation

Hydrogels were prepared by reaction of PEG di-epoxide with ionizable PAMAM dendrimers or branched PEI in aqueous solution at a total PEG volume fraction of 0.25, where the solution phase density of PEG was taken to be 1.09 g cm^{-3}. The details of the PEG di-epoxide synthesis (molar mass 4000 g mol^{-1}; $M_w/M_n = 1.03$) and its end-group characterization are described elsewhere [33]. PAMAM Generation 2 (G2) dendrimers with theoretically 16 terminal 1° amine groups (20 mass% in methanol) were obtained from Sigma Aldrich, Inc. Branched PEI of nominal molar mass 10,000 g mol^{-1} was obtained from Alfa Aesar. PEG di-epoxide, water, and polyamine were homogenized by stirring briefly at 22 °C, and the resulting solutions were cured in silicone molds at 40 °C for 7 days. The compositions of four gels used for pH-dependent swelling studies are presented in Table 1. The stoichiometric parameter r is defined as 2 × [moles NH_2 endgroups]/[moles PEG endgroups], where the factor of 2 accounts for the fact that an amine group can react twice with epoxides. A value of $r = 1$ therefore corresponds to stoichiometric addition of amines and epoxides. The r parameter is quoted in the text only for the dendrimer-containing gels, as the PAMAM dendrimers contain well-defined numbers of primary amine endgroups, in contrast to the highly branched PEI.

2.2. Swelling experiments

Following crosslinking, hydrogels were immersed in distilled water and swollen at 23 °C until an equilibrium mass was reached. The gels were placed in fresh distilled water daily to extract solubles. Each extracted sample was cut into several pieces of identical composition, which were immersed in fresh distilled water (swollen gel mass:water mass = 1:40). Stock solutions of HCl or NH_4OH in water were added to the samples incrementally in order to vary the external solution pH. Following the addition of either HCl or NH_4OH, solution pH was monitored until a steady value was reached (24 h), by which time the swollen gel mass had stabilized. After the swollen masses and external pH were recorded, the samples were placed back into the solutions and the pH was adjusted to a new value. The equilibrium swelling ratio (Q_s) was calculated according to

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

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, assumed to be 1.00 g cm^{-3} and 1.09 g cm,$^{-3}$ respectively. The uncertainty in the reported Q_s values is approximately ±10%, based upon multiple tests with samples of the same composition. The soluble fraction of the network (w_{sol}) is defined as

$$w_{sol} = \frac{M_{unex} - M_{ex}}{M_{unex}} \quad (2)$$

where M_{unex} is the dry mass of the sample prior to extraction.

2.3. Dynamic mechanical analysis (DMA)

Dynamic shear tests were performed on swollen, extracted gels. Samples were tested at 30 °C and constant frequency of 1 Hz using

Table 1
Sample compositions and soluble fractions for gels used in pH-dependent swelling studies.

Gel	Polyamine	Mass fraction of PAMAM or PEI	r	w_{sol} (mass fraction)
G2-2	PAMAM G2	0.09	2	0.03
G2-6	PAMAM G2	0.24	6	0.07
G2-8	PAMAM G2	0.29	8	0.13
PEI-1	PEI	0.56	–	0.07

a dynamic mechanical analyzer (DMA Q800, TA Instruments) in the shear sandwich fixture. Under these conditions, the storage modulus $G'(\omega)$ was generally two orders of magnitude greater than the loss modulus $G''(\omega)$.

3. Results and discussion

3.1. Crosslinking reactions

All gels were formed by reaction of the endgroups of PEG di-epoxide with the amine groups of the chosen macromonomer in aqueous solution. The volume fraction of PEG was held constant at approximately 0.25, with the balance consisting of the polyamine and water combined. When PAMAM dendrimers are used as macromonomers, the epoxide endgroups react with the dendrimer terminal 1° amines to form a hydrolytically stable 2° amine linkage and a hydroxyl group. Reaction of an amine group with two epoxides to form a 3° amine is also possible. PAMAM dendrimers also contain internal 3° amines. Previously, we explored how the key adjustable parameters in this system (reaction stoichiometry, polymer volume fraction at crosslinking, PEG molar mass, and dendrimer generation) affect both gelation and swelling of the gels in neutral water [33]. Highly branched PEI is also examined as a macromonomer, as an example of a structurally less well-defined, low-cost alternative to dendrimers. When PEI is used as the crosslinker, di-epoxide groups can presumably bond to both the terminal 1° amine groups and the 2° amines in the backbone. For both types of macromonomers, the resulting gels therefore contain mixtures of 1°, 2°, and 3° amine groups, which are connected through an array of different bonding sequences. Hereafter, we will assume that these amine groups function as Lewis bases, the conjugate acids of which might have a distribution of pK_a values.

3.2. Extraction and swelling in water

All gels were exhaustively extracted in distilled water, during which solubles were leached from the networks into the surrounding water. The presence of a small amount of ionizable groups in the solubles can profoundly affect the equilibrium swelling of the gel by introducing ions into the external solution. To obtain true equilibrium swelling in neutral conditions, the external solution is therefore replaced with fresh water daily until equilibrium swelling is reached (as in this study), or the same can be accomplished by continuous Soxhlet extraction. The soluble fraction of the dry network (w_{sol}) is determined from the dry masses of the sample before and after extraction by Eq. (2). The w_{sol} is often taken as a qualitative indicator of the concentration of structural imperfections in the network structure. Table 1 lists w_{sol} values for four gels prepared from either PAMAM dendrimers or PEI. The soluble fraction is minimized for stoichiometric conditions ($r = 1 \pm 0.5$) in the PAMAM–PEG system [33] (where r is as defined in Section 2.1). For gels having $r \approx 1.0$, w_{sol} can be as low as 2 mass%, while w_{sol} increases as r deviates from 1.0.

Setting $r \neq 1$ has additional consequences besides raising w_{sol}. Fig. 1 illustrates the dependence of the equilibrium swelling ratio (Q_s) and swollen shear modulus (G') on r for PEG hydrogels containing G2 PAMAM dendrimers. Minimum swelling is observed for $r = 1$, and the increase in Q_s with increasing r is in part due to the higher concentration of ionizable amine endgroups. However, increasing the dendrimer mass fraction also lowers the mass fraction of linear PEG chains, and therefore lowers the concentration of elastically effective network chains (ν_e). Increasing r well beyond 1.0 also increases the probability of forming intramolecular loops and microgels due to non-stoichiometric reaction. The enhanced fraction of solubles that leaches from the network during extraction further decreases ν_e. Therefore, gels having $r \gg 1$ not only have higher mass fractions of ionizable groups, but also have higher concentrations of architectural imperfections, leading to higher Q_s and lower swollen G'. Compositions with r higher than a value r_{max} are unable to reach the gel point due to the highly non-stoichiometric reaction between amines and epoxides. The value of r_{max} depends strongly on the dendrimer generation and polymer volume fraction during crosslinking. A value of $r_{max} \approx 12$ was found for gels containing G2 PAMAM dendrimers and a PEG volume fraction of 0.25 during crosslinking [33]. Also note that setting $r < 1$ dramatically decreases the swollen modulus and increases the Q_s (Fig. 1), though these gels are of less concern in the present study, where high concentrations of amines are the point of interest.

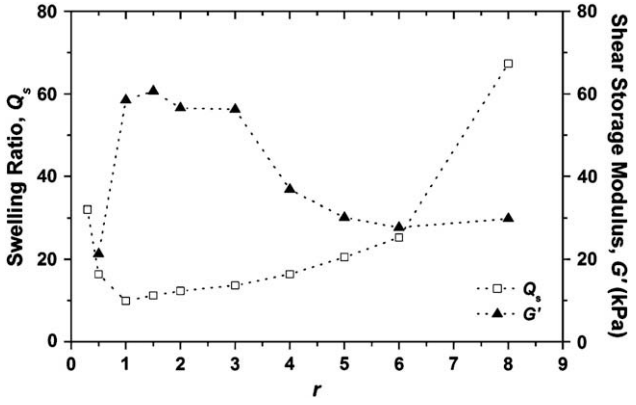

Fig. 1. Dependence of equilibrium swelling ratio (water, external pH = 7) and swollen shear modulus on r for PAMAM–PEG gels. The dashed lines are a guide to the eye.

3.3. pH dependence of equilibrium swelling

Fig. 2 summarizes the dependence of Q_s on pH for gels containing PAMAM G2 dendrimers. For all samples, Q_s passes through a maximum value (Q_{max}) at an external pH of approximately 4–5. Protonation of the amine groups has a more dramatic effect on the pH dependence of the equilibrium swelling for gels having $r \gg 1$. The swelling maximum is most pronounced for the gel G2-8, which has the lowest swollen modulus, lowest density of elastic PEG chains, and the highest concentration of ionizable amine groups (prior to swelling) among the PAMAM–PEG gels listed in Table 1. Gels having $r \gg 1$ also contain higher concentrations of unreacted 1° amines, due to the highly non-stoichiometric reaction between amines and epoxides. If we define Q_0 as the swelling ratio of the gel under conditions where the amines are essentially unprotonated (say, at pH = 11), then the ratio Q_{max}/Q_0 is an indicator of how dramatically the gel responds to changes in external pH. The ratio Q_{max}/Q_0 is equal to 1.6 for gel G2-2, 3.1 for gel G2-6, and 5.5 for gel G2-8.

Fig. 3 presents similar swelling data for a gel prepared with highly branched PEI as crosslinker instead of PAMAM dendrimers. The reaction between the epoxide endgroups of the PEG and the amines of PEI is complicated by the presence of 1°, 2°, and 3° amines, such that r does not have a clear definition as it did for the PAMAM–PEG gels. Thus, we present swelling behavior of a single gel having mass fractions of $w_{PEG} = 0.44$ and $w_{PEI} = 0.56$ in the dry state. The swelling data qualitatively resemble those for the gels G2-6 and G2-8, but with a broader maximum in the equilibrium swelling observed near (3 < pH < 6). These results confirm that the pronounced Q_{max} is not unique to gels containing PAMAM dendrimers, but applies more generally to randomly branched polyamine hydrogels. The pH dependence of swelling will, of course, be affected by the relative amounts of 1°, 2°, and 3° amines in the reacted macromonomers, so the dependence of Q_s on pH will

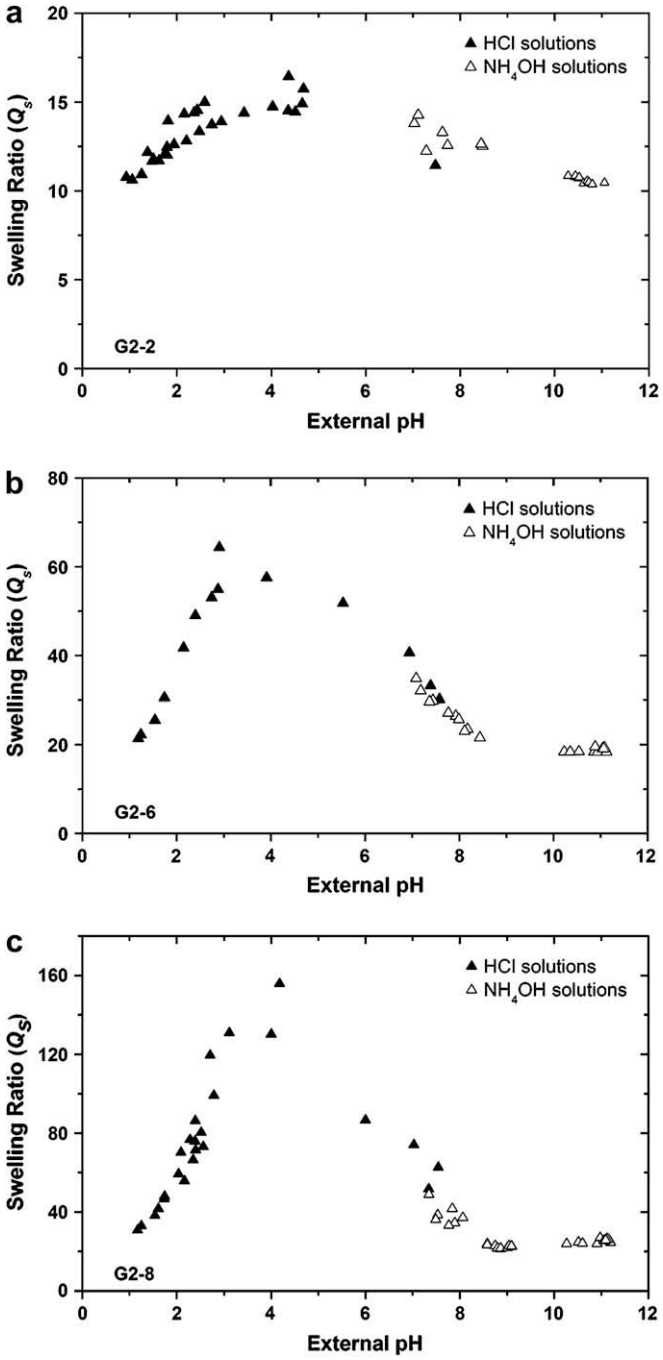

Fig. 2. Dependence of Q_s on pH for gels containing PAMAM G2 dendrimers. a) $r = 2$; b) $r = 6$; and c) $r = 8$.

generally not be the same for gels based upon different polyamine macromonomers.

For gels that exhibit a clear maximum in the Q_s vs. pH curve, the swelling behavior can be rationalized in terms of the relative concentrations of charged groups inside and outside the gel. Above pH ≈ 11, few of the amine-functional groups are protonated, so there is little ionic contribution to the driving force for water to swell the network. The elastic free energy penalty for swelling is essentially balanced by the free energy of mixing of the polymer segments with the solvent, as in a neutral polymer network. As the external pH is lowered to 7.0, some fraction of the dendrimer amines become protonated, and the concentration of mobile ions inside the gel (notably OH^-) increasingly exceeds that in the external solution, increasing the driving force for water to enter the gel. Q_{max} is observed at an external pH of approximately 4–5, under which conditions the concentration of mobile ions within the gel greatly exceeds that in the outside solution. Supposing that nearly all of the amine groups are protonated by HCl when $Q_s = Q_{max}$, further addition of HCl to lower the pH produces a significant increase in the concentration of free ions in the external solution, while there is little or no increase in the concentration of protonated amines inside the gel, reducing the ionic contribution to the driving force for swelling and therefore decreasing Q_s. Shrinkage of the gel is observed as the external pH is lowered and the difference between the concentration of free ions inside and outside the gel becomes less significant. We verify the preceding ideas in a more quantitative fashion in Section 3.4, where the concentrations of all ions inside and outside the gel are calculated numerically by applying the Donnan equilibrium theory.

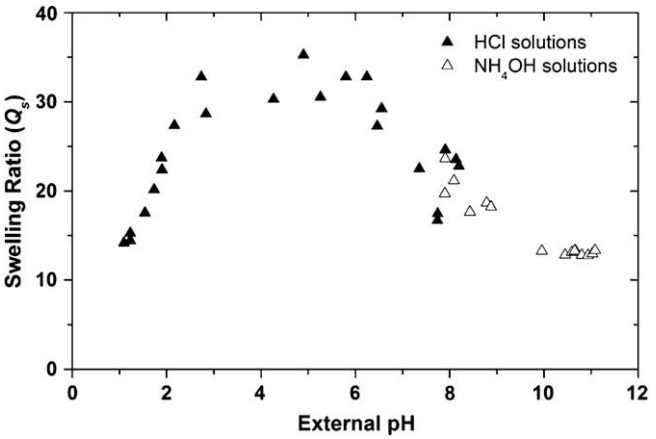

Fig. 3. Dependence of Q_s on external solution pH for gel PEI-1, which contained 56 mass% branched PEI macromonomers.

3.4. Theoretical swelling predictions: Donnan equilibrium

In this section, we invoke the Donnan equilibrium theory to predict the pH-dependence of equilibrium swelling for gels containing amine-functional groups. Our intent is not to exactly duplicate the observed swelling behavior for the PAMAM–PEG and PEI–PEG gels, which is complicated by non-idealities such as local variations in pK_a, variations in the degree of substitution of the amines, and possibly electrostatic repulsion effects. Instead, we choose to model a simplified scenario in which all protonated amine groups have a single value of pK_a, and the effects of electrostatic repulsions on pK_a are assumed to be insignificant. Other structural and thermodynamic parameters are kept identical to the four gel samples characterized experimentally. Comparison of experiments to simplified model predictions allows one to deduce the influence of various non-idealities on the pH-dependence of equilibrium swelling.

The amine-functional groups are Lewis bases that are anchored to the polymer network, increasing the driving force for swelling under conditions where protonation is favored. The acid–base equilibrium inside the gel follows Eq. (3):

$$NR_xH_{3-x} + H^+ \leftrightarrow NR_xH_{4-x}^+ \tag{3}$$

where $x = 1$, 2, or 3 for primary, secondary, or tertiary amines, respectively. The –R groups vary depending on the local bonding arrangement, but all N atoms are considered to form only C–N or C–H single bonds. The internal amides of the dendrimers are not considered to participate in the acid–base equilibrium. We consider

a simplified situation in which all protonated amines have $pK_a = 10.5$, a typical value for a protonated aliphatic amine. The acidity constant of the protonated amines is therefore given by:

$$K_a = \frac{[B][H^+]}{[BH^+]} = 10^{-10.5} \tag{4}$$

where "B" represents a Lewis base site (amine). In addition, for an aqueous solution,

$$K_w = [H^+][OH^-] = 10^{-14} \tag{5}$$

where all concentrations are expressed in mol L^{-1}.

Consider the acid–base equilibrium under conditions where a strong base M^+OH^- has been added to the external solution to adjust the external pH. (Although NH_4OH, a weak base, was used to adjust the external pH above 7.0 in the experiments, here we consider the simpler case for which M^+ and OH^- are fully dissociated in solution). Under basic conditions, the charge balance inside the gel is written:

$$[M^+] + [BH^+] + [H^+] = [OH^-] \tag{6}$$

and the charge balance in the external solution (basic conditions) is:

$$[M^+] + [H^+] = [OH^-] \tag{7}$$

Similarly, consider conditions where a strong acid such as HCl has been added to the external solution, such that the charge balance inside the gel is written:

$$[BH^+] + [H^+] = [OH^-] + [Cl^-] \tag{8}$$

The charge balance in the external solution (acidic conditions) is given by:

$$[H^+] = [OH^-] + [Cl^-] \tag{9}$$

Next, we predict the pH dependence of equilibrium swelling by invoking the Donnan equilibrium theory [10]. Following the discussion of Rička and Tanaka [11], at equilibrium, the distribution of mobile ions between the gel and the solution can be expressed as:

$$\frac{[i]}{[i]'} = K^{z_i} \tag{10}$$

where the subscript i refers to mobile ions of type i, [i] and [i]′ are the concentrations thereof in the gel and in the external solution, respectively, K is the Donnan ratio, and z_i is the valency of species i. The ionic contribution, Π_{ion} to the swelling pressure is caused by the concentration differential of mobile ions between the gel and the outer solution:

$$\Pi_{ion} = RT\sum_i \left([i] - [i]'\right) \tag{11}$$

The restoring force exerted by the network, which opposes Π_{ion} at equilibrium, is defined as

$$\Pi_{net} = -\frac{1}{\nu_s}\left.\frac{\partial G_{net}}{\partial n_s}\right|_{P,T,n_i} \tag{12}$$

Here, n_s is the number and ν_s is the volume of the solvent molecules, and n_i is the number of mobile ions of type i.

Applying Eq. (10) to Eq. (6) for basic conditions,

$$K[M^+]' + K[BH^+]' + K[H^+]' = \frac{[OH^-]'}{K} \tag{13}$$

The concentrations of protonated amines ($[BH^+]$) and non-protonated amines ([B]) in the gel are related to the initial concentration of amines in the *dry* gel, $[B]_0$, by:

$$[BH^+] + [B] = [B]_0/Q_s \tag{14}$$

Using Eq. (4), it is possible to show that

$$[BH^+] = \frac{[B]_0/Q_s}{(K_a/K[H^+]') + 1} \tag{15}$$

Combining Eqs. (5) and (7), the charge balance in the external solution becomes:

$$[M^+]' = \frac{10^{-14}}{[H^+]'} - [H^+]' = 10^{pH-14} - 10^{-pH} \tag{16}$$

Inserting Eqs. (15) and (16) into Eq. (13), the charge balance becomes

$$10^{pH-14}(K - K^{-1}) + \frac{[B]_0/Q_s}{\frac{K_a}{K\cdot 10^{-pH}} + 1} = 0 \tag{17}$$

Solving for the solution pH, the charge balance equations for basic conditions yield:

$$pH = \log_{10}\left\{ -1 + \left[1 - \frac{4\times 10^{14} K_a [B]_0/K}{Q_s(K - K^{-1})}\right]^{1/2} \right\} - \log_{10}\left(\frac{2K_a}{K}\right) \tag{18}$$

We next relate the solution pH to (Π_{ion}/RT). Combining Eqs. (10) and (11) yields

$$\frac{\Pi_{ion}}{RT} = [H^+]'(K-1) + [M^+]'(K-1) + [OH^-]'(K^{-1} - 1) \tag{19}$$

Substituting Eqs. (5) and (16) for $[M^+]'$ and $[OH^-]'$ and simplifying,

$$\frac{\Pi_{ion}}{RT} = 10^{pH-14}(K + K^{-1} - 2) \tag{20}$$

Substituting Eq. (18) for the pH,

$$\frac{\Pi_{ion}}{RT} = \frac{10^{-14}K}{K_a}(K + K^{-1} - 2) \times \left(-\frac{1}{2} + \frac{1}{2}\left[1 - \frac{4\times 10^{14} K_a [B]_0}{Q_s(K^2 - 1)}\right]^{1/2} \right) \tag{21}$$

Eq. (21) relates the ion swelling pressure to the equilibrium swelling ratio and the Donnan ratio, K for *basic* conditions.

Starting from the charge balances for acidic conditions (Eqs. (8) and (9)) and following a similar approach yield Eqs. (22) and (23). Intermediate results are presented in Appendix 1.

$$pH = -\log_{10}\left(\frac{\frac{-[B]_0}{Q_s} - K_a + \frac{K_a}{K^2}}{K - K^{-1}}\right) \tag{22}$$

$$\frac{\Pi_{ion}}{RT} = \left(K + K^{-1} - 2\right)\left(\frac{\frac{-[B]_0}{Q_s} - K_a + \frac{K_a}{K^2}}{K - K^{-1}}\right) \tag{23}$$

To predict the dependence of Q_s on external solution pH, an expression relating Π_{ion}/RT (or $-\Pi_{net}/RT$) to Q_s is needed. We choose to relate the elastic restoring force of the network to Q_s

using the Flory–Rehner "phantom" network expression [40], which is more appropriate than the affine model for networks undergoing large deformations. A similar approach has been used by Brannon–Peppas and Peppas to model the equilibrium swelling behavior of ionizable hydrogels containing carboxylic acid functional groups, though the affine network approximation was chosen instead [41]. The elastic restoring force exerted by the swollen phantom network is taken as:

$$-V_1\left(\frac{\Pi_{\text{net}}}{RT}\right) = \ln(1-\phi_{2s}) + \phi_{2s} + \chi\phi_{2s}^2 + \left(\frac{V_1}{\bar{v}M_c}\right) \times\left(1-\frac{2M_c}{M_n}\right)\phi_{2r}^{2/3}\phi_{2s}^{1/3} \quad (24)$$

where M_c is the average molecular weight between crosslink junctions, $\bar{v}$ is the specific volume of the polymer, V_1 is the molar volume of the swelling agent, ϕ_{2s} *is* the polymer volume fraction in the swollen system, equal to $1/Q_s$, ϕ_{2r} is the polymer volume fraction in the relaxed state (after crosslinking but before swelling), χ is the Flory–Huggins polymer–solvent interaction parameter, and M_n is the number-average molar mass of the polymer prior to crosslinking. In the present study, since the network is formed from short, linear PEG chains, we neglect trapped entanglements and take $M_c = 4000\ \text{g mol}^{-1}$ for simplicity. In addition, we assume $M_n \to \infty$, which is equivalent to assuming that the gels contain only elastically effective chains. This approximation is justified for "model" networks by the high degree of epoxide end-functionalization found in the linear PEG di-epoxide precursor chains, but may fail for networks having $r \gg 1$, which have high soluble fractions and numerous architectural defects [33]. Values of $1.802\times10^{-5}\ \text{m}^3\ \text{mol}^{-1}$ and $1.0\times10^{-3}\ \text{m}^3\ \text{kg}^{-1}$ were assumed for V_1 of water and $\bar{v}$ of the polymer, respectively.

To use Eq. (24) effectively, a value for χ is necessary, which presents a complication in the present study, where the gels consist of PEG–polyamine copolymers, and the mass fraction of the polyamine varies between samples. Thus, we estimate a value of χ experimentally for each gel according to the following procedure. We note that the equilibrium swelling of the gels reaches a nearly constant value near an external pH of 10–12, under which conditions the gels are assumed to behave essentially as neutral polymer networks, such that $\Pi_{\text{ion}}/RT \approx 0$. For each gel, a value of the swelling ratio Q_0 was estimated from the experimental data at high pH. The χ parameter is then calculated from Eq. (24) by setting $\phi_{2s} = 1/Q_0$ and setting $\Pi_{\text{ion}}/RT = 0$. Assumed values of Q_0 and calculated values of χ are listed in Table 2, along with assumed values of $[B]_0$ for each gel, which are referenced to the dry state. The value of χ decreases with increasing mass fraction of PAMAM dendrimers (decreasing mass fraction of PEG), and the values found for χ lie within the ordinary range expected for polymers in thermodynamically "good" solvents.

Using the calculated values of χ, it is then possible to plot the function $\Pi_{\text{ion}}/RT(=-\Pi_{\text{net}}/RT)$ vs. Q_s $(=1/\phi_{2s})$ for each gel. Fig. 4 shows such a plot for a gel having $Q_0 = 24$ and $\chi = 0.08$, similar to gel G2-8. The ion swelling pressure is set to 0 under neutral conditions ($Q_s = Q_0$), but increases steeply with increasing Q_s, at least initially. After passing through a maximum, $-\Pi_{\text{net}}/RT$ actually decreases slightly with increasing Q_s, as the phantom network model does not account for the finite extensibility of the network chains. Tanaka and Rička experimentally determined the function $-\Pi_{\text{net}}/RT$ (Fig. 1 in Ref. [11]) for their ionizable poly(acrylate) gels [11], by following a procedure which is not directly applicable to the polyamine gels studied here. However, it is interesting to note that a similar dependence of $-\Pi_{\text{net}}/RT$ on Q_s was obtained experimentally for low Q_s, though a steep upturn is observed at high Q_s resulting from finite extensibility effects that are not captured by the phantom network model.

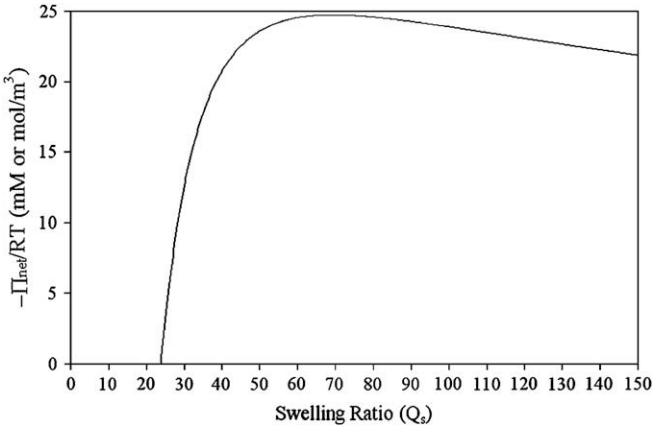

Fig. 4. The function $-\Pi_{\text{net}}/RT(=\Pi_{\text{ion}}/RT)$ calculated from the Flory–Rehner expression for a phantom network having $Q_0 = 24$ and $\chi = 0.08$, similar to gel G2-8.

Using the phantom network expression in Eq. (24), Eqs. (20) and (23) were solved numerically to obtain values for the Donnan ratio, K. For acidic conditions, two real roots were found for K in Eq. (23) for any arbitrarily selected value of Q_s. The gel can thus exhibit the same equilibrium swelling ratio at two different values of the external pH under acidic conditions, leading to a maximum in Q_s at pH < 7. The calculated values for K were substituted into Eq. (22) to calculate the respective values of the external pH corresponding to the chosen Q_s value. For basic conditions, only one real root was found for K in Eq. (21), which was substituted into Eq. (18) to obtain the external pH at which the gel swells to Q_s at equilibrium.

Fig. 5 shows the theoretical dependence of Q_s on external pH calculated for all gels, using the values of $[B]_0$, Q_0, and χ listed in Table 2. The theory predicts that a maximum in Q_s is observed near pH = 4–5, in reasonable agreement with experimental observations. The maximum is predicted to occur under acidic conditions at a critical external solution pH (denoted as pH*) at which the two roots of Eq. (23) converge. Fig. 6 shows a plot of

Table 2
Assumed values of $[B]_0$, Q_0, and χ used in swelling model calculations.

Gel	$[B]_0$ (mol L^{-1})	Q_0	χ
G2-2	0.87	10.3	0.44
G2-6	2.18	18.4	0.25
G2-8	2.71	24.0	0.08
PEI-1	5.84	12.8	0.34

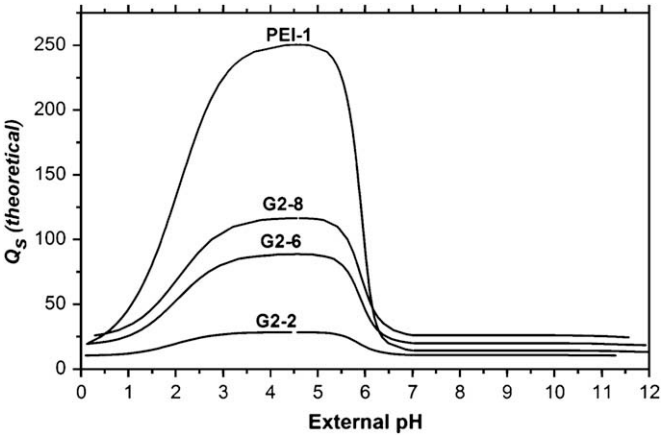

Fig. 5. Theoretical dependence of Q_s on external solution pH from Eq. (21) (basic conditions) and Eq. (23) (acidic conditions).

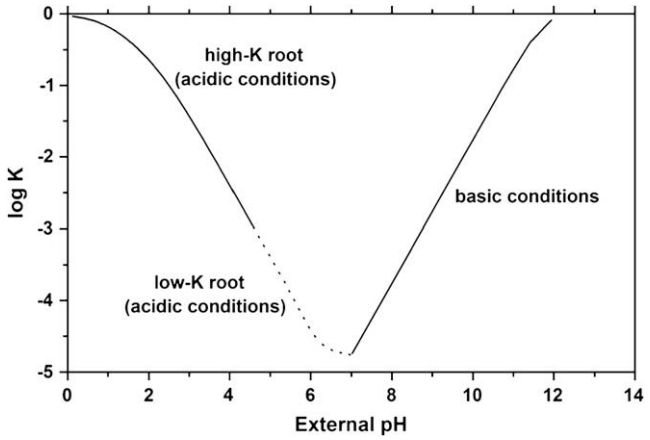

Fig. 6. Theoretical dependence of Donnan ratio (K) on external pH for gel G2-6.

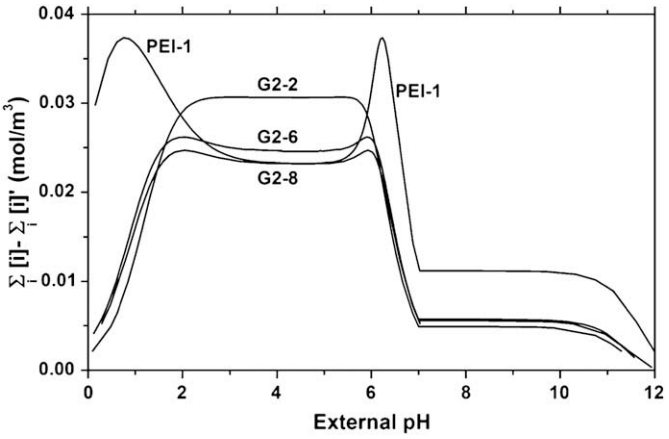

Fig. 7. Relationship between external pH and the difference between total concentrations of mobile ions inside $\sum_i[\mathrm{i}]$ and outside $\sum_i[\mathrm{i}]'$ of the gels, which is equivalent to the function Π_{ion}/RT by Eq. (11).

the calculated Donnan ratio for a gel G2-6, illustrating the convergence of the "high K" and "low K" roots of Eq. (23) near $\mathrm{pH} = 4.57 = \mathrm{pH}^*$. Table 3 lists calculated values of pH^* and compares the theoretical ($Q_{\mathrm{max\_theo}}$) and experimental ($Q_{\mathrm{max\_exp}}$) maximum swelling ratios for all gels. When the external pH is close to pH^*, the total concentration of mobile ions inside the gel ($\sum_i[\mathrm{i}]$) greatly exceeds that in the external solution ($\sum_i[\mathrm{i}]'$), meaning there is a significant ionic contribution to the driving force for swelling. Fig. 7 shows a plot of the concentration differential ($\sum_i[\mathrm{i}] - \sum_i[\mathrm{i}]'$) vs. external pH for all gels based upon the model calculations, which is equal to Π_{ion}/RT by Eq. (11).

A local minimum in the concentration differential is observed near pH^*, which becomes more pronounced as $Q_{\mathrm{max\_theo}}$ increases. This minimum is observed because the quantity $\sum_i[\mathrm{i}]$ is reduced in the highly swollen state. Thus, the maximum value of ($\sum_i[\mathrm{i}] - \sum_i[\mathrm{i}]'$) is not actually observed at pH^*. Rather, two maxima are noted at values of the external pH somewhat higher and lower than pH^*.

The model calculations also predict the collapse of the gel at high and low external pH. The model predicts a steep decrease in swelling as the pH increases to ≈6.5, and the weak dependence of Q_s on external pH is captured at pH above 11. Here we note a difference between theory and experiment in that the observed maximum in swelling occurs over a broader pH range in the experiments, and the upturn in swelling begins as the pH drops below about 9.0 (for gels G2-6 and G2-8) or below 10.0 (for gels G2-2 and PEI-1). This discrepancy is related to the fact that the amine-functional groups in the gels exhibit a distribution of $\mathrm{p}K_a$s, with some fraction of the amines becoming protonated at higher values of the external pH than expected for a system with uniform $\mathrm{p}K_a = 10.5$. This result is consistent with the broad titration curves observed for PAMAM dendrimers in aqueous solutions, which result from the protonation of 1° and 3° amines at widely different values of solution pH [14]. A steep drop in Q_s at very low pH is observed in both theory and experiments, resulting from the decrease in the concentration differential ($\sum_i[\mathrm{i}] - \sum_i[\mathrm{i}]'$), which decreases the driving force for water to swell the network.

The theoretical maximum value of the swelling ratio, $Q_{\mathrm{max\_theo}}$, was generally not in quantitative agreement with the experimentally determined value $Q_{\mathrm{max\_exp}}$, though $Q_{\mathrm{max\_theo}}$ differs from $Q_{\mathrm{max\_exp}}$ by no more than a factor of 2 for all gels studied. The theoretical prediction is expected to overestimate Q_{max} due to neglecting the finite extensibility of the short linear PEG chains. In three of the four gels studied, $Q_{\mathrm{max\_exp}}$ is in fact less than $Q_{\mathrm{max\_theo}}$. An exception is gel G2-8, which swells slightly more than predicted, perhaps because it contains a highest concentration of architectural defects, judging by its comparatively high value of w_{sol}. In assuming that all PEG chains act as elastic chains (by taking $M_n \to \infty$ in Eq. (24)), we neglect the fact that the equilibrium swelling is influenced by the perfection of the network structure. In addition, we have assumed that only PEG chains contribute to the elastic modulus of the network by taking $M_c = 4000\ \mathrm{g\ mol^{-1}}$, an approximation that is not valid for networks having a high mass fraction of branched polyamine macromonomers.

Table 3
Experimental maximum swelling ratios ($Q_{\mathrm{max\_exp}}$) for all gels studied. ($Q_{\mathrm{max\_theo}}$) is the calculated maximum swelling ratio by Eq. (23), with the simplifying assumption that all protonated amines have $\mathrm{p}K_a = 10.5$. ($Q_{\mathrm{max\_theo}}$) is observed at an external solution pH of pH^*.

Gel	$Q_{\mathrm{max\_exp}}$	$Q_{\mathrm{max\_theo}}$	pH^*
G2-2	16.4	28.4	4.50
G2-6	57.5	88.6	4.57
G2-8	131	116.5	4.59
PEI-1	32.8	250.5	4.59

4. Summary and conclusions

End-linked PEG hydrogels containing high mass fractions of polyamine macromonomers, either PAMAM dendrimers or highly branched PEI, exhibit strongly pH-dependent swelling in aqueous solutions. Equilibrium volume swelling ratios reach a value Q_{max} at an external pH^* of about 4–5, but these gels behave essentially as neutral polymer networks at pH greater than $\mathrm{p}K_a$. At pH^*, the majority of amine-functional groups is protonated, and there is a large differential in the concentration of mobile ions inside and outside the gel. This behavior is not unique to gels having dendritic crosslink junctions, similar swelling behavior was found in the gel PEI-1, which contains a randomly branched polyamine macromonomer instead. The swelling maximum is most pronounced for gels having high concentrations of ionizable amine groups (in the dry state), with the gel G2-8 exhibiting $Q_{\mathrm{max}}/Q_0 \approx 5.5$. However, no evidence was found to support the supposition that the initial concentration of amine groups might affect the value of pH^* due to electrostatic repulsions between charged groups. The experimentally determined swelling curves did not reveal a significant shift in pH^* as the value of $[\mathrm{B}]_0$ increased, within the limits of experimental uncertainty. These observations are reasonable given that the amine groups are highly diluted when $Q_s \approx Q_{\mathrm{max}}$, under which conditions electrostatic repulsions between neighboring macromonomers may not play a large role in establishing the swelling

equilibrium, even though the concentration of amines was as high as 5.8 M in the dry state.

The Donnan equilibrium theory captures the key feature of the pH-dependent swelling in that the maximum in swelling is predicted near $pH^* = 4–5$, with the simplifying assumption that all protonated amine groups have $pK_a = 10.5$, a typical dilute-solution value for an aliphatic amine group. It might be possible to more accurately capture the pH dependence of swelling by assuming a more realistic mixture of 1°, 2°, and 3° amines with separate pK_a values assigned to their conjugate acids. The accuracy of the theoretical swelling predictions is also limited by the need to assume a functional form for the elastic restoring force exerted by the network, which balances the swelling forces arising from mixing and ionic effects. In using the Flory–Rehner phantom network expression representing the elastic and mixing contributions to the free energy, Q_{max} is usually overestimated due to neglecting the finite extensibility of the network chains. More quantitative agreement between theory and experiment might be obtained (though at the expense of simplicity) by choosing an expression relating Π_{net}/RT to Q_s that better accounts for non-idealities such as varying junction functionality, architectural defects, and finite chain extensibility.

Acknowledgements

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Appendix 1. Derivation of Eqs. (22) and (23)

Applying Eq. (10) to Eq. (8) for acidic conditions,

$$K[BH^+]' + K[H^+]' = \frac{[OH^-]'}{K} + \frac{[Cl^-]'}{K} \tag{25}$$

The concentration of protonated amines in the gel, $[BH^+]$, is related to the initial concentration of amines in the *dry* gel, $[B]_0$, by:

$$[BH^+] + [B] = [B]_0/Q_s \tag{26}$$

where [B] is the concentration of non-protonated amines in the swollen state, and Q_s is the equilibrium swelling ratio. Using Eq. (4), it is possible to show that

$$\left[BH^+\right] = \frac{[B]_0/Q_s}{\left(K_a/K[H^+]'\right) + 1} \tag{27}$$

Combining Eqs. (5) and (9), the charge balance in the external solution becomes:

$$[Cl^-]' = [H^+]' - \frac{10^{-14}}{[H^+]'} = 10^{-pH} - 10^{pH-14} \tag{28}$$

Inserting Eqs. (27) and (28) into Eq. (25), the charge balance becomes

$$10^{-pH}(K - K^{-1}) + \frac{[B]_0/Q_s}{\frac{K_a}{K \cdot 10^{-pH}} + 1} = 0 \tag{29}$$

Solving for the external solution pH, the charge balance equations for acidic conditions yield:

$$pH = -\log_{10}\left(\frac{\frac{-[B]_0}{Q_s} - K_a + \frac{K_a}{K^2}}{K - K^{-1}}\right) \tag{22}$$

Combining Eqs. (10) and (11) yields

$$\frac{\Pi_{ion}}{RT} = [H^+]'(K-1) + [Cl^-]'(K^{-1}-1) + [OH^-]'(K^{-1}-1) \tag{30}$$

Substituting Eqs. (5) and (28) for $[Cl^-]'$ and $[OH^-]'$ and simplifying,

$$\frac{\Pi_{ion}}{RT} = 10^{-pH}\left(K + K^{-1} - 2\right) \tag{31}$$

Substituting Eq. (22) for the pH,

$$\frac{\Pi_{ion}}{RT} = (K + K^{-1} - 2)\left(\frac{\frac{-[B]_0}{Q_s} - K_a + \frac{K_a}{K^2}}{K - K^{-1}}\right) \tag{23}$$

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