Novel pH-Sensitive Hydrogels of Segmented Poly(amine ureas) Having a Repetitive Array of Polar and Apolar Units in the Main Chain

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ABSTRACT: The pH-responsive swelling/deswelling of novel segmented poly(amine ureas) (SPAU) with a repetitive array of polar (*N,N*′-diethylethylenediamine) and apolar (diethylenephenylene) units in the main chain was examined as a function of ionic strength and temperature. An end-isocyanated polyamine was prepared by the 2:1 addition reaction of 4,4′-methylenediphenyldiisocyanate (MDI) to telechelic polyamine having secondary amino groups at both ends. The isocyanated polyamine was extended by the reaction with equimolar ethylenediamine to form a segmented poly(amine urea) (SPAU). The SPAU exhibited reproducible swelling/deswelling in response to pH changes. A discontinuous 270-fold change in the swelling degree was observed at a critical pH, indicating a phase transition. The shift of ethylenediamine units to the trans conformation on double protonation may play a role in the swelling transition through a stiffening of the polymer strands. The hysteresis observed in the swelling/deswelling cycle in water at 30 °C disappeared upon addition of 0.05 M NaCl or upon lowering of the temperature to 4 °C. The regulation of solute transport across the SPAU matrix responding to a change in external pH was demonstrated using vitamin B_{12} as a model solute, suggesting the formation of a barrier layer at the surface of the film that stopped solute diffusion at high pH. SPAUs can be cast on substrates of any shape, providing mechanically strong pH-responsive surface coatings.

Introduction

Recently, considerable attention has been directed to polymeric gels which undergo a volume change responding to external stimuli, including heat,[1] light,[2] an electric field,[3] pH,[4–6] and any particular chemical species.[7] More specifically, ionic gels have been intensively studied because of their close correlation with a variety of physiological phenomena[8–10] as well as of their wide applicability in the area of controlled drug delivery,[11–15] chemical valves,[16] and smart actuator systems.[17] Swelling of an ionic gel is mainly regulated by the balance between the osmotic pressure due to entrapped counterions and the rubber elasticity of the gel network.[18] A discontinuous change in the gel volume can be achieved by controlling the solvation of the gel network through proper selection of the comonomer composition and/or the variation in solvent composition.[4,5] Thus, a discrete volume change responding to pH has been demonstrated in an aqueous system for gels containing hydrophobic moieties.[19] In these systems, two stages are usually observed in the swelling with a pH change; a discrete volume change (phase transition) triggered by the solvation of the gel network and a subsequent continuous increase in the gel volume to compensate for the ion osmotic pressure. For numerous applications, it is desirable to maximize the volume change with a minute pH change near the phase transition point. As a promising candidate for such a system, we have been focusing on segmented poly(amine urea) (SPAU) with alternating polar and apolar units in the chain (see Figure 1).[20] This structure may cause a volume transition in the gel at the critical pH through a critical change in the protonation degree of the ethylenediamine units. In this SPAU gel, the ethylenediamine units in the main chain also drastically change their rotational freedom during protonation. This hindered rotation in the protonated form considerably increases the stiffness of the gel network, which may contribute to the volume change at the transition point through a shift in the equilibrium length of the polymer strands.

In addition to these unique features, this gel has the practical advantage that it can be prepared by casting from an *N,N*-dimethylacetamide (DMAc) solution because the gel structure is formed through the physical cross-linking of hard segments. This paper deals with the pH-dependent swelling/deswelling of these types of poly(amine ureas) with alternating *N,N*′-diethylethylenediamine (polar) and diethylenephenylene (apolar) units in the main chain as a function of ionic strength and temperature. The regulation of solute transport across the SPAU matrix responding to a pH jump in the external milieu was also demonstrated using vitamin B_{12} (VB_{12}) as a model solute.

Experimental Section

Materials. 1,4-Divinylbenzene (Asahi Chemical Industry Co.) was purified by fractional distillation over calcium hydride *in vacuo*. *N,N*′-Diethylethylenediamine (Tokyo Kasei Co.) was purified by two distillations over calcium hydride *in vacuo* (bp 60 °C at 60 mmHg). *n*-Butyllithium (Asahi Chemical Industry Co.) was used as a cyclohexane solution, and the concentration of the solution was determined using Gilman's double titration method.[21] *N,N*′-Diethyl-*N*-(4-vinylphenethyl)ethylenediamine was prepared by the anionic addition of 1,4-divinylbenzene to *N,N*′-diethylethylenediamine in the presence of lithium diisopropylamide.[22] Other reagents and solvents were purified by standard methods.

Synthesis of Telechelic Polyamine (TA). Telechelic polyamine with secondary amino end groups was prepared as previously described[20,22,23] by the anionic self-addition reaction of *N,N*′-diethyl-*N*-(4-vinylphenethyl)ethylenediamine, followed

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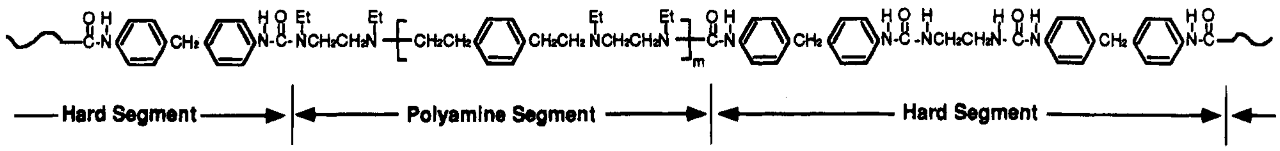
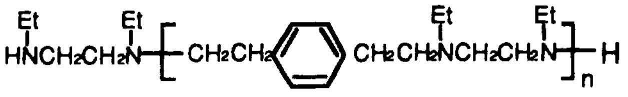


Figure 1. Structural formula of segmented poly(amine urea) (SPAU-EDA).



TA

by the end-capping reaction with an excess amount of *N,N'*-diethylethylenediamine. The molecular weight (M_n) of TA used in this study was determined to be 1500 using a dual-wavelength spectrophotometer.[20,23]

Synthesis of Poly(amine urea) without a Hard Segment (SPAU-0).[20] SPAU-0 was prepared by the addition reaction of TA with 4,4'-methylenediphenyldiisocyanate (MDI) in a *N,N*-dimethylacetamide (DMAc)/THF (4/1 (v/v)) solution at room temperature. The molar ratio of TA and MDI was 1:1. All experiments were carried out with a 5 wt % solution of TA. After 48 h, the polymer was precipitated into a water/methanol [3/7 (v/v), pH 8.5] mixture and dried *in vacuo* for 48 h. The number-average molecular weight (M_n) and the molecular weight distribution (M_w/M_n) of SPAU-0 were 2.1×10^4 and 2.9, respectively.

Synthesis of Segmented Poly(amine urea) with a Hard Segment (SPAU-EDA).[20] End-isocyanated polyamine was prepared by the 2:1 addition reaction of MDI to TA in DMAc/THF (4/1 (v/v)) at room temperature. The mixture was then cooled to approximately 4 °C, and a 5 wt % solution of ethylenediamine (EDA) was added from a dropping funnel. The molar ratio of MDI, TA, and diamine was 2:1:1. The obtained polymer was precipitated into the water/methanol [3/7 (v/v), pH 8.5] mixture and then dried *in vacuo* for 48 h.

Acid–Base Titration. A sample (0.1 mmol in terms of amino group) of TA or SPAU-0 was dissolved into 15 mL of a 0.01 N HCl standard solution. The solution was then titrated with 0.01 N NaOH using a Horiba F-12 pH meter. Turbidity of the solution was measured at 500 nm using a spectrophotometer (Hitachi U-3210) concurrently with the pH measurement.

Swelling Measurement. Transparent films were prepared by casting SPAU-EDA from a *N,N*-dimethylacetamide (DMAc) solution on a poly(ethylene terephthalate) plate. After drying *in vacuo* at 40 °C for 3 days, the films were removed and punched out into 9 mm diameter, 0.3 mm thick disks. The disks were immersed in solutions containing various HCl or NaOH concentrations until they reached a constant weight. The swelling degree was defined as $(W_{wet} - W_{dry})/W_{dry}$.

Release of Vitamin B_{12}. Vitamin B_{12} (0.1 g) was dissolved in 20 mL of 0.01 N HCl. A SPAU-EDA disk was immersed in this solution and was allowed to swell to equilibrium. The release of vitamin B_{12} from the disk was measured spectrophotometrically by immersing it alternately in 0.01 N HCl and 0.01 N NaOH solutions.

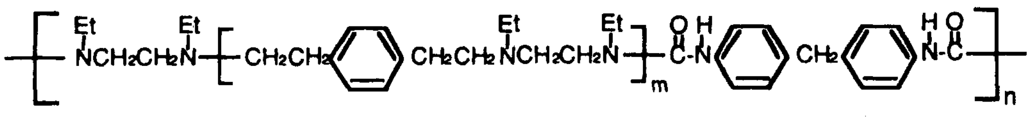
Measurement of the Glass Transition Temperature. Samples of TA with varying protonation degrees were prepared by freeze-drying the TA solution after adjusting the pH to an appropriate value by the addition of NaOH or HCl. DSC measurements were carried out using a Mettler TA 3000 equipped with a data station. All thermograms were baseline corrected, normalized to sample weight, and calibrated by using indium. All measurements were carried out under a dried argon purge. The samples were first heated to 120 °C at 10 °C/min and held at that temperature for 1 min. This was followed by quenching to −100 °C with liquid nitrogen as coolant at the maximum DSC programming rate. The quenched samples prepared in this fashion were heated to 100 °C at 20 °C/min. Glass transition temperatures were reported for the midpoint of the glass transition process.

Results and Discussion

Our gels with polyamine segments are formed by extending the telechelic polyamine (TA), which was prepared through the polyaddition reaction of *N,N'*-diethylethylenediamine to *p*-divinylbenzene in the presence of lithium alkylamide.[22,23] End-isocyanated polyamine was then prepared by the 2:1 addition reaction of 4,4'-methylenediphenyldiisocyanate (MDI) with TA, followed by reaction with equimolar amounts of ethylenediamine (EDA) as the chain extender to form SPAU-EDA.[20] To explore the protonation status as well as the water compatibility of the polyamine chain through acid–base titration, poly(amine urea) without a hard segment (SPAU-0) was prepared by the 1:1 addition reaction of MDI with TA. The absence of hard segments considerably alters the behavior of polymer samples versus solution pH; SPAU-0 became water-soluble below a critical solution pH, whereas SPAU-EDA, an SPAU with a hard segment, behaved as a hydrogel with a swelling/deswelling response to external pH. As in the case of segmented poly(urethane urea),[24] hard segments in the latter form hydrogen-bonded physical cross-links.

The solubility and protonation of SPAU-0 at various pHs were determined through pH titration, and the data thus obtained were utilized to explain the pH-responding swelling-deswelling behavior of the SPAU-EDA gel because of the structural analogy of SPAU-0 to SPAU-EDA except for the hard segments.

Acid-Base Titration of Telechelic Polyamine (TA) and SPAU-0. Both TA and SPAU-0 gave two-stage titration curves corresponding to the two-step protonation of the diamine moiety in the repeating units of the polyamine chain. The protonation degree of the amino groups at a given pH was calculated from the titration results and was plotted as a function of pH in Figure 2. The pH-dependent change in turbidity is also shown in the figure. There was observed a steep increase in turbidity in the region of pH 6.4–6.9, demonstrating phase separation due to the unfavorable interaction between polymer chain and water. The increased hydrophobicity through the deprotonation of the ethylenediamine units further facilitates the proton release to provoke phase transition from a water-soluble state to a water-insoluble state, as in the case with hydrophobic polyelectrolytes.[25,26] It should be noted that the polyamine changes the conformation from an extended rigid chain to a more entropically favorable flexible chain through the deprotonation process, which may also contribute to an easier proton release from the polyamine chain. Indeed, a discrete change in the chain flexibility by the release of a second proton from the ethylenediamine unit of TA is further supported by a change in the glass transition temperature (T_g) of TA with protonation as shown in Figure 3. Samples for T_g measurement were prepared by freeze-drying the TA solution after adjusting the pH to an appropriate value. T_g of TA with varying degrees of protonation revealed a steep change at around $\alpha = 0.4$, suggesting a transition in the flexibility of the polyamine chain. This increase in flexibility should facilitate the association of hydrophobic moieties in the polymer chain to result



SPAU-O

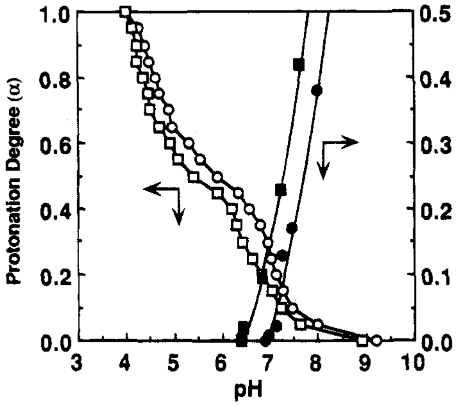


Figure 2. Dependence of protonation degree (open symbols) and turbidity (closed symbols) on pH for telechelic polyamine (TA) (○,●) and SPAU-0 (□,■) at 30 °C.

Table 1. Apparent pK Values and Solubility of Telechelic Polyamine and SPAU-0

sample	temp (°C)	NaCl (mol/L)	pK_1[a]	pK_2[a]	$pH_{\alpha=0.5}$[b]	pH at turbidity point[c]
telechelic polyamine	30		4.7	7.0	5.9	6.9 (0.3)
SPAU-0	30		4.4	6.6	5.4	6.4 (0.3)
	30	0.05	4.9	7.0	5.9	6.7 (0.4)
	30	0.10	4.9	7.1	6.1	6.8 (0.4)
	30	0.15	5.1	7.4	6.3	6.9 (0.4)
	4		4.8	7.1	6.0	7.0 (0.3)

[a] pK_1 and pK_2 are the pHs of the system at $\alpha = 0.75$ and 0.25, respectively. [b] Half equivalent point ($\alpha = 0.5$). [c] The number in parentheses is the protonation degree at the turbidity point.

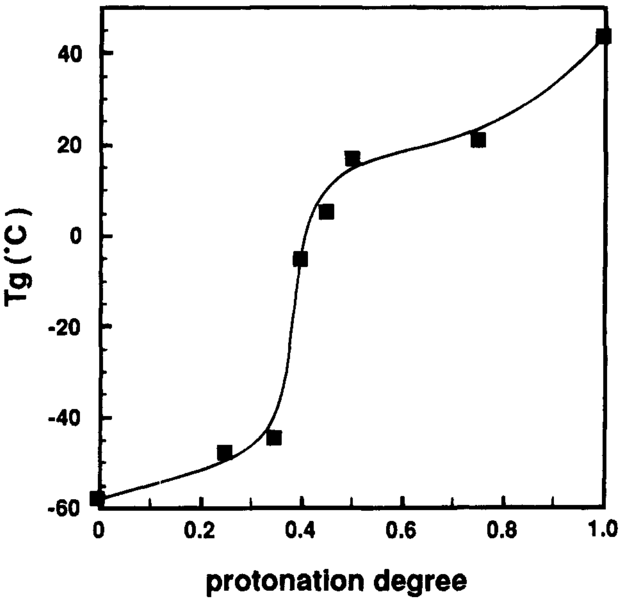


Figure 3. Change in T_g of telechelic polyamine (TA) based on protonation degree.

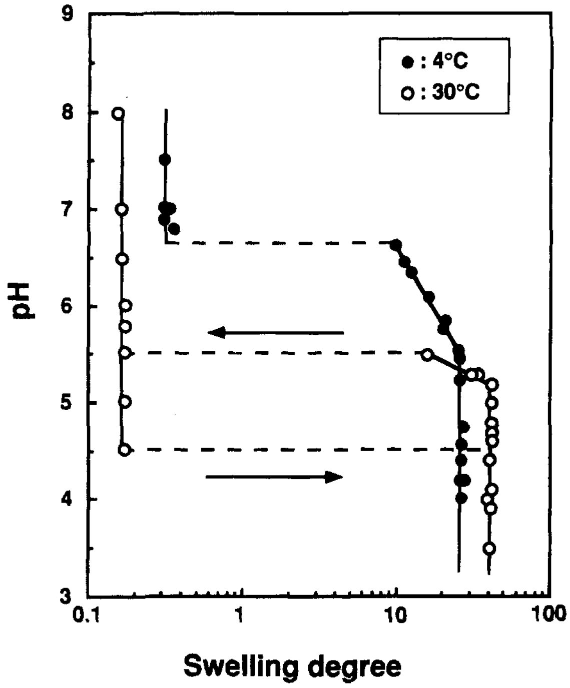


Figure 4. pH vs swelling curves for SPAU-EDA at different temperatures: (○) 30 °C; (●) 4 °C.

in a phase separation of the polymer from the water phase to form a precipitate.

The protonation behavior and solubility of SPAU-0 are a function of temperature as well as of ionic strength. In Table 1, the values of pK_1, pK_2, the half-equivalent point ($pH_{\alpha=0.5}$), and turbidity point of SPAU-0 at different conditions are summarized. pK_1 and pK_2 increased with decreasing temperature from 30 to 4 °C, reflecting the increased basicity of the amine as the temperature is reduced.[27] The release of protons from the diamine unit was also suppressed by the addition of NaCl due to electrostatic shielding, leading to an increase in the pK_a and turbidity point as summarized in Table 1.

Swelling Behavior of SPAU-EDA Gel Responding to pH. Poly(amine urea) without a hard segment (SPAU-0) is soluble in an acidic aqueous solution as well as in several organic solvents including benzene, THF, methanol, and *N*,*N*-dimethylacetamide (DMAc). On the other hand, segmented poly(amine urea) with a hard segment (SPAU-EDA) has a strong cohesive force between the hard segments and is insoluble in all solvents except DMAc. A SPAU-EDA slab (thickness: 0.3 mm) was then prepared from a DMAc solution by casting on a poly(ethylene terephthalate) boat, and disks were punched out from the slab for use as samples in order to explore the pH-responsive change in swelling.

The pH-responsive change in the swelling degree of SPAU-EDA is demonstrated in Figure 4. In this experiment, a dried disk was first immersed in a pH 3 aqueous solution and allowed to reach equilibrium swelling, followed by successive bathing in a series of solutions with increasing pH up to 8. The disk was bathed at each pH solution until it reached a constant weight. The disk was then successively bathed in a series of solutions with decreasing pH from 8 to 3.5 in a similar manner. This swelling/deswelling cycle was repeated several times to determine the reproducibility.

At 30 °C, the gel maintained a high swelling degree of 40 (water content: 97.6%) below pH 5.2, whereas drastic shrinking in a discontinuous manner took place in the pH 5.2–5.5 region. At pH 5.5, the swelling degree was as low as 0.15 (water content: 13.0%), which is $^1/_{270}$ of the initial value at pH 5.2. Taking into account the considerably high weight fraction (~27 dry wt %) of the hard segment (cross-linking region), the 270-fold change in the swelling degree is unprecedented. Compared to the other hydrophobic polyelectrolytes gels so far reported, the SPAU gel achieves an extremely higher swelling degree. Siegel *et al.* reported the pH-dependent equilibrium swelling of a series of poly(alkyl methacrylate) gels with tertiary amino groups in the network.[19] The maximal change in the swelling degree at the transition is approximately 20 in this case. Worth noting is that the pH of the contraction point (pH 5.2) corresponds to $pH_{\alpha=0.5}$ (pH 5.4) of the polyamine segment in SPAU-0, indicating that release of the second proton from the ethylenediamine unit is coupled with the gel contraction and is also in line with a discrete change in the T_g of the polyamine chain with protonation (Figure 3).

It is to be noted that no increase in swelling in the pH range below 5.2, the region where $\alpha > 0.5$, took place, indicating that this gel is in maximum swelling at $\alpha = 0.5$. A further increase in the counterion due to the second protonation of the ethylenediamine unit has a negligible effect when the gel is in such a highly swollen state.

In a general theory applicable to the swelling of ionic gels, stiffness of the constituent polymer chains of the gel network is taken as a constant throughout the swelling process.[18] Obviously, ionic gels based on vinyl polymers with side-chain dissociative groups satisfy this condition at least in the region of moderate charge density where the freedom of internal rotation of the main chain can be assumed to be constant.[5,6,19,28] On the other hand, Tanaka has pointed out in his theory for volume phase transition of ionic gels the importance of the chain stiffness as well as the ionization degree to induce the discontinuous phase transition.[5,6] One plausible explanation for the sharp and large volume transition observed for the SPAU gel is that the chain stiffness as well as hydrophobicity discretely change with protonation to induce a large transition.

As the SPAU structure has alternating arrays of polyamines with a definite molecular weight (in this case, $M_n = 1500$) and a hard segment, cross-linking should have a rather uniform nature. This is also an advantage of this system over conventional gels prepared by radical polymerization of vinyl compounds where the monomer reactivity ratio significantly affects the uniformity of the cross-links. Further, it should be noted that physical cross-linking of hard segments is strong enough to tolerate an increase in ion osmotic pressure due to protonation. Indeed, a reproducible swelling/deswelling cycle was confirmed for the SPAU-EDA gel system. SPAU-EDA in a film form has the stretching vibrational band of urea NH (ν_{NH}) at 3400 cm^{-1} in the IR spectrum. Also, an additional band was clearly observed at 3320 cm^{-1}, which was assigned to the ν_{NH} band of urea that forms hydrogen bonding.[29] This indicates that hydrogen bonding between urea linkages effectively formed in SPAU-EDA to increase the cohesive force in the hard segments, which contributes to good mechanical tolerance against osmotic pressure.

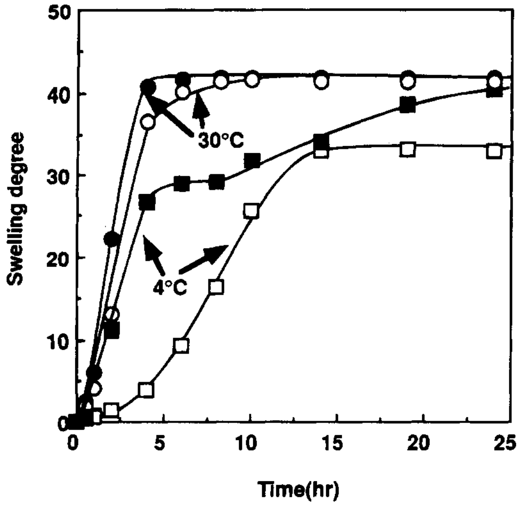


Figure 5. Effect of urea addition on the swelling kinetics of SPAU-EDA at 4 °C (□,■) and 30 °C (○,●). Open symbols: without urea. Closed symbols: with urea (0.15 mol/L).

Effect of Temperature and Salt on the Swelling Behavior of the SPAU-EDA Gel. Hysteresis was observed in the swelling/deswelling cycle of SPAU-EDA at 30 °C. The pH should be decreased below 4.5 to induce the collapsed gel to swell. This stabilization of the collapsed state might be due to the interaction of polymer chains through a short-range force. An alternating-arrayed structure of the diethylenephenylene units along the polymer chain may contribute to the interaction of the polyamine chains in the deprotonated state. On the other hand, as also shown in Figure 4, hysteresis is not apparent at 4 °C. This indicates that a short-range force to associate the polymer chain in the collapsed gel is temperature-sensitive and should be weakened by lowering the temperature. Presumably, hydrophobic interaction plays a role in polymer association in the collapsed state. Indeed, there was observed an approximately 2-fold increase in the swelling degree in the collapsed state (>pH 6.6) by lowering the temperature to 4 °C from 30 °C, which is consistent with a decreased hydrophobic interaction.

In the swollen state, there was a decrease in the maximum degree of swelling at 4 °C (swelling degree: 33) compared with that at 30 °C (swelling degree: 42). One possibility to explain this decrease in the swelling is an increased contribution of hydrogen bonding that restricts gel swelling. Figure 5 shows the swelling kinetics of SPAU-EDA at different temperatures (4 and 30 °C) in an aqueous solution with pH 2.3. In sharp contrast with smooth swelling at 30 °C (open circles), there was observed a considerable retardation in swelling at 4 °C (open squares). However, a dramatic acceleration in the swelling took place at 4 °C with urea addition (closed squares), suggesting the breakage of hydrogen bonding. The equilibrium degree of swelling was also increased by urea addition, reaching to almost the same value at 30 °C. The bimodal nature of the swelling curve at 4 °C suggests the presence of at least two different types of hydrogen bonding that are breakable by urea, although the detailed characteristics of these urea- and temperature-sensitive hydrogen bonds are still unclear.

The swelling behavior of SPAU-EDA was also examined under different NaCl concentrations in the range between 0.05 and 0.15 mol/L at 30 °C. The results are shown in Figure 6. The swelling/deswelling cycle was completely reversible without any hysteresis, although

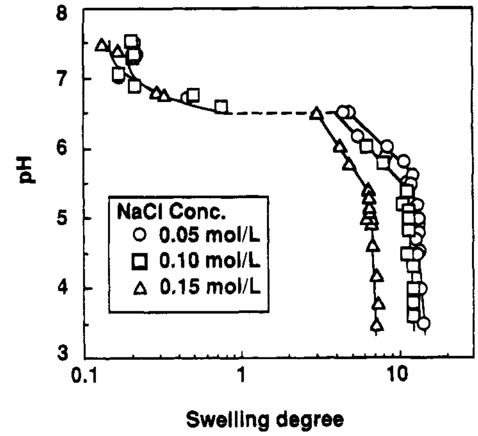


Figure 6. pH-dependent swelling/deswelling of SPAU-EDA at 30 °C with different NaCl concentrations: (○) 0.05 mol/L; (□) 0.10 mol/L; (△) 0.15 mol/L.

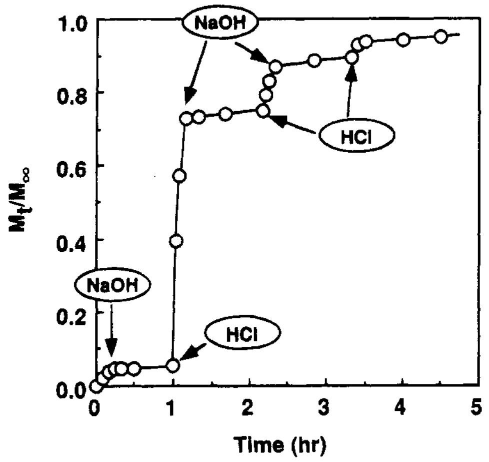


Figure 7. pH-responsive release of vitamin B_{12} from SPAU-EDA in a 0.15 mol/L NaCl solution at 30 °C. Samples were alternately immersed in 0.01 N HCl and 0.01 N NaOH.

a progressive decrease in maximum swelling was observed by increasing the salt concentration, as is generally the case for ionic gels (shielding effect). However, a 45-fold increase in the swelling degree was still achieved even in the presence of 0.15 mol/L of NaCl (physiological concentration).

On-Off Regulation of Solute (Vitamin B_{12}) Release from SPAU-EDA by pH Jump. A polymer gel undergoing rapid dehydration during the deswelling process may have a potential utility in on-off regulation of solute permeation due to the formation of a barrier (skin) layer at the surface of the gel matrix.[30] In this context, the SPAU-EDA gel may be applicable as a chemical valve responding to pH.

The on-off regulation of solute transport across the SPAU-EDA matrix responding to a pH jump in external milieu was demonstrated using vitamin B_{12} (VB_{12}) as a model solute in Figure 7. Rapid release of VB_{12} from the SPAU-EDA matrix in acidic milieu was effectively shut off by transferring the matrix from acidic to alkali milieu, suggesting the formation of a surface barrier layer. Further, VB_{12} release was immediately recovered by returning the matrix to the acidic milieu again. Thus, SPAU-EDA may be applied in a thin-film form as the command-layer coating on an appropriate membrane to regulate the solute transport responding to pH. As previously mentioned, the availability to form a stable thin film by solvent casting is one of the advantages of these novel pH-responsive materials.

Conclusions

Segmented poly(amine urea) with a repetitive array of diamine units in the main chain showed remarkable swelling at a critical pH. This seems to be due to the significant change in the main-chain stiffness through the protonation of diamine units along the main chain as well as to an abrupt increase in ion-osmotic pressure. This particular example of a gel network introduces a new concept in the design of intelligent gels showing a volume transition responding to external stimuli through a critical change in the stiffness of the gel network, which, in general, had been regarded as constant throughout the transition.

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