Complexation Phenomena in pH-Responsive Copolymer Networks with Pendent Saccharides

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ABSTRACT: Sugar-containing copolymer networks of poly(methacrylic acid-*co*-methacryloxyethyl glucoside) were prepared by free-radical photopolymerization. Incorporation of the MAA in the polymer networks rendered the networks complex forming, in response to the environmental pH change. Using ATR−FTIR spectroscopy, the polymer complexes were investigated in their hydrated state. It was observed that in acidic media hydrogen bonds formed due to the protonation of the carboxylic acid groups of the PMAA while in basic or neutral conditions electrostatic repulsion occurred between the ionized carboxylic acid groups. This complexation affected the macroscopic swelling properties. The effect of copolymer compositions on the network structure was investigated. Both hydrogen-bonding and electrostatic interactions increased with MAA content in the networks.

Introduction

In three-dimensional polymer networks, polymer complexes can occur due to interactions between specific repeating units of the polymer chains. These polymer complexes are classified by their types of dominant interactions into stereocomplexes, polyelectrolyte complexes, and hydrogen-bonded complexes.[1] Complex formation is often sensitive to the surrounding environment and accompanied by a dramatic change in the swelling behavior, mechanical properties, and solute transport characteristics between complexed and uncomplexed networks. Thus, the complexing polymer networks have potential use as suitable materials for biomedical applications such as biosensors, membranes, molecular imprinting, and drug delivery devices.[2−12]

Typically, polymer networks containing poly(methacrylic acid) (PMAA) or poly(acrylic acid) (PAA) can form polyelectrolytic or hydrogen-bonded complexes that are strongly dependent on the environmental pH and ionic strength.[13−19] For example, Kono et al.[14] made use of the polyelectrolyte complexation between PAA and polyethyleneimine (PEI) to form pH-sensitive capsules that could release their contents in response to pH changes. Lowman et al.[15−17] studied the complexation of poly(methacrylic acid-*g*-ethylene glycol) (P(MAA-*g*-EG)) networks due to hydrogen bonding by investigating swelling/deswelling process and stress−strain behavior depending on the surrounding pH change.

In this work, we have developed sugar-containing polymer networks that exhibit pH-sensitive swelling behavior due to the formation of a ranged polymer complexes that respond to environmental pH changes. These polymer networks may be suitable candidates for carriers of oral protein delivery. In the acidic environment of the stomach the networks are collapsed, as a result of hydrogen bonding, thus protecting protein drugs incorporated in the networks. In the basic and neutral conditions of the intestine the networks are swollen to a high degree, due to electrostatic repulsion, thus releasing the protein.[20−23] In addition, the pendent sugars of the polymer networks can stabilize proteins by a preferential hydration mechanism that creates a thermodynamically favorable aqueous environment for native proteins.[24,25] In addition, sugars can interact with endogenous lectins on the walls of the gastrointestinal (GI) tract, resulting in increased protein absorption through the intestine or protein delivery to specific regions of the GI track, such as the colon.[26−28]

Attenuated total reflectance Fourier transform infrared (ATR−FTIR) spectroscopy was used to investigate the polymer complexes formed in hydrated networks. The macroscopic pH-sensitive swelling behavior of the polymer networks was also analyzed with appropriate studies.

Experimental Section

Polymer Network Synthesis. Random copolymers of methacrylic acid (MAA) and 2-methacryloxyethyl glucoside (MEG), henceforth designated as P(MAA-*co*-MEG), were prepared by free-radical UV polymerization. MAA (Polysciences, Warrington, PA) was distilled under vacuum (12 mmHg, 63 °C) prior to use in order to remove the inhibitor, while MEG (Polysciences, Warrington, PA) was used as received. Tetra(ethylene glycol) dimethacrylate (TEGDMA, Polysciences, Warrington, PA) was used as a cross−linking agent without further purification. 1-Hydroxycyclohexyl phenyl ketone (otherwise known as Irgacure 184, Ciba-Geigy, Hawthorne, NY) was used as a UV-light-sensitive initiator. Figure 1 summarizes the synthesis of the P(MAA-*co*-MEG).

Comonomers with molar feed compositions of 1:0, 1:1, 1:2, 1:4, and 0:1 MEG:MAA were mixed, and the TEGDMA was added in the amount of 1.2 mol % of total monomers. The initiator was added in the amount of 0.1 wt % of the total monomers, and the ensuing mixtures were diluted to 60 wt % of the total monomers with a 1:1 mixture by weight of ethanol and water. Nitrogen was bubbled through the mixture for 15 min to remove dissolved oxygen that would otherwise act as an inhibitor for the reaction. The mixture was cast between glass slides and was exposed to UV light at an intensity of 15.0 ± 0.5 mW/cm^2 for 30 min in a nitrogen environment. The kinetics of such polymerizations have been discussed extensively.[29−33]

The ensuing polymer films were placed in deionized water for 7 days, and the water was changed every 12 h in order to

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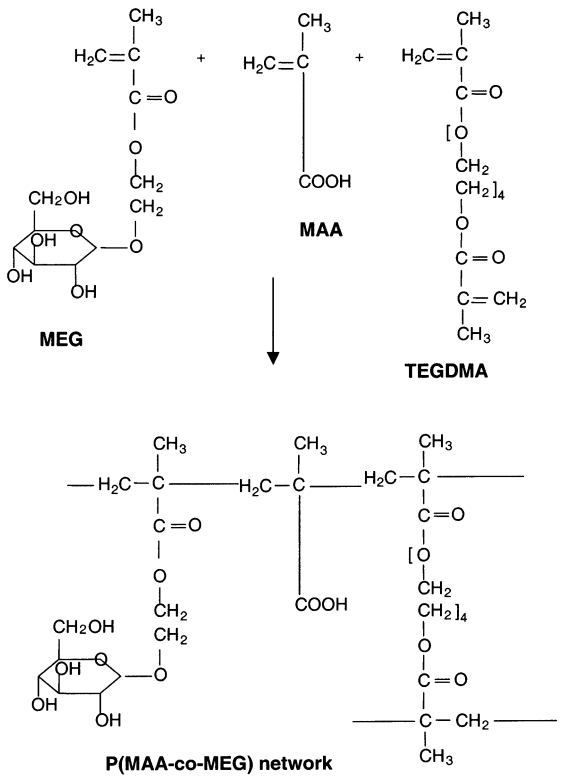

Figure 1. Synthesis of P(MAA-*co*-MEG) network by free-radical photopolymerization.

remove any unreacted monomers, cross-linking agents, and initiators. Then, the films were dried in air for 1 day and placed in a vacuum oven at 25 °C until their weight remained constant within 0.1 wt % over 24 h; subsequently, the polymer films were stored in a desiccator for future use.

Swelling Studies. To determine macroscopic swelling properties, the dried polymer samples were weighed and then placed in phosphate−citrate buffer solutions of pH values between 2.2 and 8.0 at 37 °C. The ionic strength of each buffer solution was adjusted to 0.5 M by the addition of KCl. After swelling, the samples were taken out of the buffer solutions and weighed.

The equilibrium weight swelling ratio, q, was determined as the ratio of the weight of the swollen polymer sample, W_s, over the weight of the initially dry polymer sample, W_d.

Spectroscopic Studies. The ATR−FTIR spectroscopy is a useful technique to study biomaterials in their biological conditions since the samples can be analyzed in their hydrated states.[34] To investigate the molecular structure of the polymer networks in the hydrated state, the polymer samples were swollen in phosphate−citrate buffer solutions with pH values of 2.2 and 8.0 for 24 h. The ionic strength of each buffer solution was adjusted to 0.5 M by the addition of KCl. These hydrated samples were place on the ZnSe crystal, and the spectra were obtained using a FTIR spectrometer (Nicolet Nexus 670, Madison, WI). The FTIR spectra were recorded in the wavenumbers range of 4000−650 cm^{-1} at a resolution of 4 cm^{-1}.

Results and Discussion

In a previous study,[35] we prepared copolymers with pendent glucose (P(MAA-*co*-MEG)) and showed that these polymer networks exhibited pH-responsive swelling behavior. These studies must be compared with our recent studies on glucose-free polymers.[36−40] The focus of the present study is to investigate the molecular and structural changes due to complexation in the P(MAA-*co*-MEG) networks using ATR−FTIR spectroscopy and to elucidate the macroscopic pH-responsive swelling behavior of the P(MAA-*co*-MEG) networks in the presence of complexation.

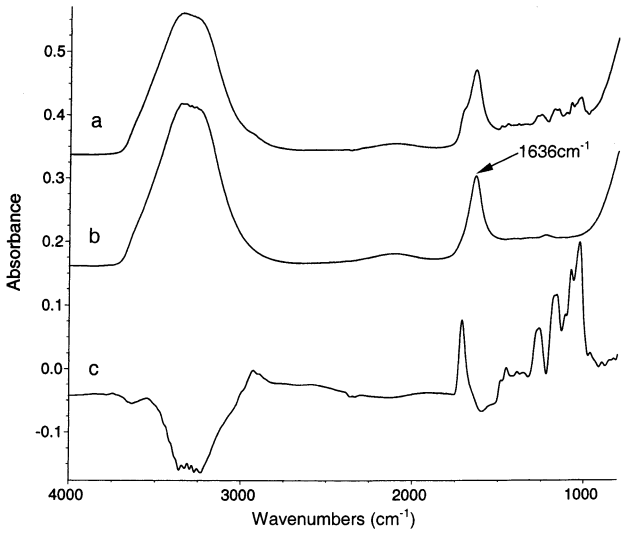

Figure 2. Spectral subtraction of water absorption for a hydrated polymer network: (a) spectrum of the hydrated sample, (b) spectrum of aqueous buffer solution, and (c) spectrum resulting from the subtraction spectrum b from spectrum a.

Effect of the pH on the Copolymer Networks. Figure 2 illustrates the spectral subtraction of water absorption used in this work in order to minimize the overwhelming water absorption peaks and improve the amount of information on the specific interactions of the P(MAA-*co*-MEG) networks in the hydrated state. Figure 2a shows the ATR spectrum of a P(MAA-*co*-MEG) network hydrated in a buffer solution with pH value of 2.2, while Figure 2b presents the ATR spectrum of the buffer solution used to hydrate the sample. By subtracting the spectrum of Figure 2b from the spectrum of Figure 2a, while minimizing the water absorption at 1636 cm^{-1}, we obtained the spectrum shown in Figure 2c. The spectral difference shown in the region of 3600−3000 cm^{-1} between parts a and c of Figure 2 indicates the existence of hydrogen bonds between water and the hydroxyl groups present in the hydrated polymer sample since that region contains information about the stretching frequency of the hydroxyl groups associating with hydrogen bond.[34]

The most distinct peak in the spectrum of the polymer networks of this work was the absorption band of the carbonyl group (C═O) observed in the region of 1850−1400 cm^{-1}; this peak contains information about the polymer complexes formed by hydrogen-bonding and electrostatic interactions.

ATR−FTIR spectra of PMEG networks swollen at pH values of 2.2 and 8.0 are shown in Figure 3. These spectra were obtained after the spectra of buffer solutions were subtracted. Despite the different pH conditions, the spectra were identical. The peak locations at 1713 cm^{-1}, representing the absorption of the carbonyl groups in the polymer network, indicate that the C═O groups on the polymer chains were not affected by the environmental pH change.

However, incorporation of MAA in the PMEG network caused pH sensitivity in the networks, as shown in Figure 4. Figure 4 presents a comparison of the spectra of a P(MAA-*co*-MEG) network with 1:4 MEG:MAA hydrated in pH 2.2 and 8.0 buffer solutions. At pH 8.0 the spectrum contains the C(═O)−O^- peaks of sym-

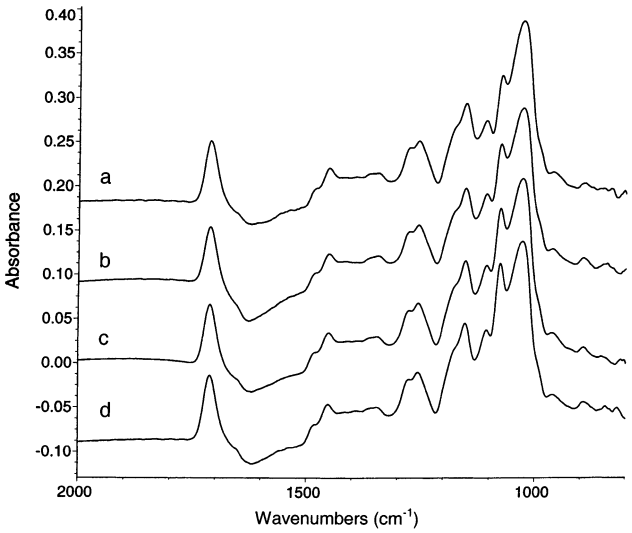

Figure 3. ATR−FTIR spectra of PMEG hydrated with different pH buffer solutions (after water subtraction): (a) pH 8.0, (b) pH 6.0, (c) pH 4.0, and (d) pH 2.2.

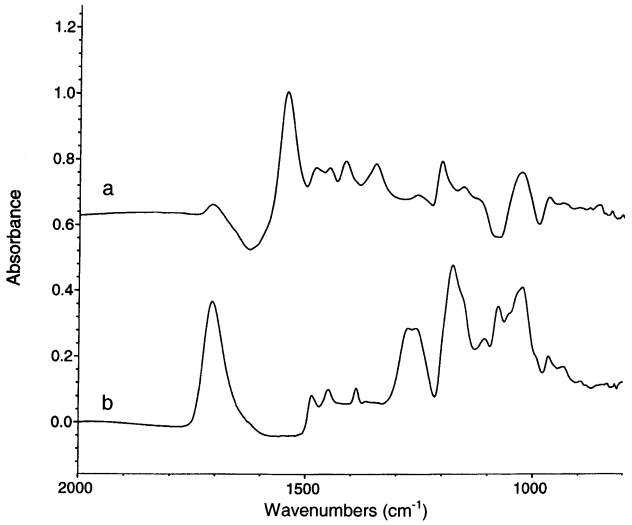

Figure 4. ATR−FTIR spectra comparison of 1:4 MEG:MAA of P(MAA-*co*-MEG) network hydrated in pH 2.2 and 8.0 buffer solutions (after water subtraction): (a) pH 8.0 and (b) pH 2.2.

Table 1. Assignment of FTIR Spectra of P(MAA-*co*-MEG) Polymer Networks Tested in Their Hydrate States after Equilibrated in Buffered Solutions of pH Values of 2.2 and 8.0

	absorption wavenumber (cm^{-1})	
functional group	pH 2.2	pH 8.0
C═O stretching	1708	1708
C(═O)−O⁻ symmetric stretching	−	1543
CH_2 deformation	1450	1450
C(═O)−O⁻ asymmetric stretching	−	1414
C−C(═O)−O⁻ stretching	−	1202
C−O−C symmetric C−O stretching	1024	1026

metric stretching vibrations at 1543 cm^{-1} and asymmetric stretching vibrations at 1414 cm^{-1}. The spectrum at pH 2.2 no longer exhibits the C(═O)−O⁻ symmetric and asymmetric stretching vibration peaks but contains the strong peaks of the C═O stretching at 1708 cm^{-1}. The peak locations and corresponding groups are listed in Table 1. These results clearly show that there was a structural change of the copolymer networks depending

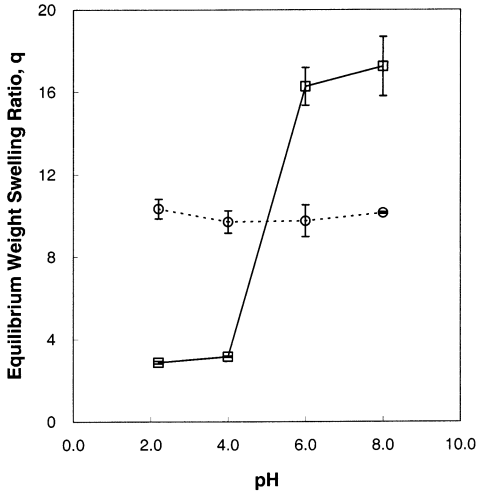

Figure 5. Equilibrium weight swelling ratio of PMEG (○) and 1:4 MEG:MAA of P(MAA-*co*-MEG) (□) networks as a function of the pH.

on environmental pH due to the incorporation of the MAA in the PMEG networks. In turn, this structural change affected the macroscopic swelling properties.

It is possible to elucidate the macroscopic swelling behavior responding to the environmental pH change with this FTIR spectroscopic analysis since the equilibrium swelling ratio of the polymer is affected significantly by the network structure resulting from the interactions in the networks. Figure 5 shows the equilibrium weight swelling ratios of PMEG and of P(MAA-*co*-MEG) with 1:4 MEG:MAA networks as a function of pH in the range of 2.2−8.0. As the PMEGs contained no ionizable functional groups, their swelling behavior was essentially independent of pH. However, incorporation of MAA in the PMEG resulted in a swelling behavior of typical pH-sensitive anionic hydrogel, i.e., low swelling ratios at low pH and high swelling ratios at high pH.

There was a drastic change in the equilibrium swelling ratio of P(MAA-*co*-MEG) networks at pH of about 5, which is approximately the pK_a of PMAA. Above pH 5, the networks swelled to 16−17 times of the initial dry weight. The reason for this was that, at pH higher than the pK_a of PMAA, the carboxylic acid groups of the PMAA chains became ionized, leading to hydrogel swelling to a high degree due to the electrostatic repulsion between these charged groups.

This sharp transition between the swollen and collapsed states indicates that this system can swell and collapse fast in response to the environmental pH changes. Thus, if the pH of the microenvironment of the network is very close to the transition, a very small increase of the pH can induce the networks to swell completely, leading to release drug through the network.

Copolymer Complexation at High pH. Figures 6 and 7 show spectral comparisons of P(MAA-*co*-MEG) with different composition of MEG and MAA at pH 8.0. Figure 6 shows the spectra before the water subtraction and contains a strong water peak at 1636 cm^{-1} and C(═O)−O⁻ peaks of symmetric stretching vibrations at around 1550 cm^{-1}. With increasing MAA fraction in the polymer network the intensity of the C(═O)−O⁻ peaks at around 1550 cm^{-1} increased. The C(═O)−O⁻ peaks are clearly defined after the water subtraction procedure (Figure 7), and their locations can be assigned more precisely. For example, the C(═O)−O⁻ peaks of the

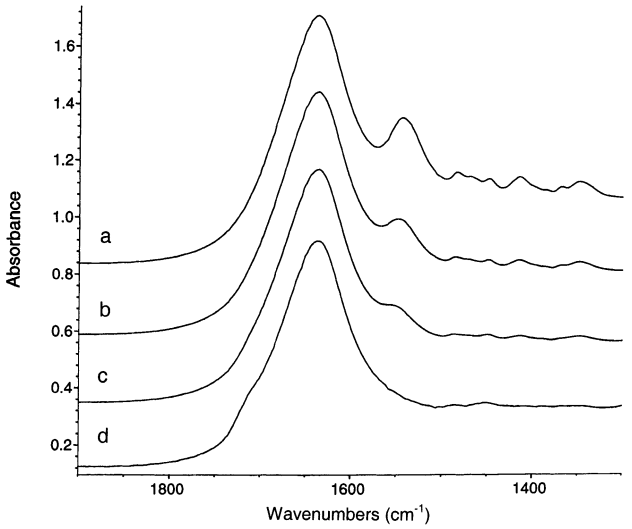

Figure 6. ATR−FTIR spectra of P(MAA-*co*-MEG) with different composition of MEG and MAA in pH 8.0 (before water subtraction): (a) 0:1, (b) 1:4, (c) 1:1, and (d) 1:0 MEG:MAA.

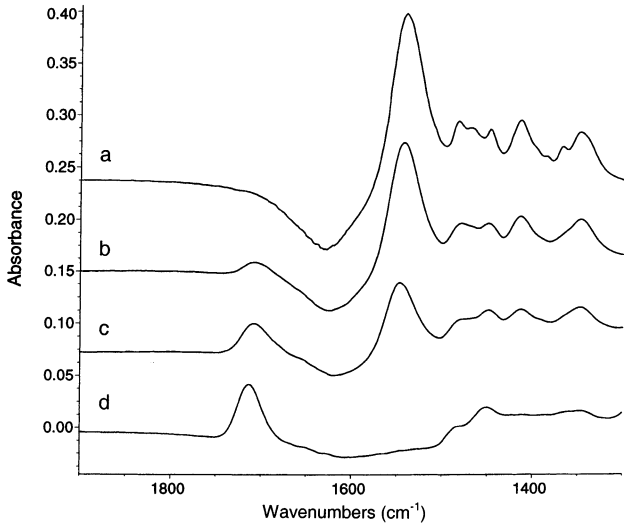

Figure 7. ATR−FTIR spectra of P(MAA-*co*-MEG) with different composition of MEG and MAA in pH 8.0 (after water subtraction): (a) 0:1, (b) 1:4, (c) 1:1, and (d) 1:0 MEG:MAA.

symmetric stretching vibrations of P(MAA-*co*-MEG) network with 1:4 MEG:MAA before and after the water subtraction are 1548 and 1543 cm^{-1}, respectively. The C(═O)−O$^-$ peaks of asymmetric stretching vibrations at 1414 cm^{-1} were clearly observed, and their intensity increased with the MAA fraction in the network. The C(═O)−O$^-$ peak locations before and after the water subtraction are listed in Table 2. Additionally, it was observed in Figure 7 that the intensity of the carbonyl (C═O) peaks between 1713 and 1708 cm^{-1} increased with the fraction of glucose moiety in the networks. This was because that the monomer MEG contained carbonyl groups that were not ionized at high pH.

The effect of the MAA content of the copolymer on the macroscopic swelling behavior at high pH is shown in Figure 8. The equilibrium weight swelling ratios of the networks increased with the MAA fraction in the polymer networks. This was because a higher MAA content in the polymer networks led to higher carboxylate anion concentration at high pH. This, in turn, produced more electrostatic repulsions between the charged groups, leading to higher swelling.

Table 2. FTIR Peak Location Summary of C(═O)−O$^-$ Group of Samples of P(MAA-*co*-MEG) Polymer Networks in Their Hydrate States with Buffered Solution of pH 8.0 before and after Water Subtraction[a]

	before water subtraction		after water subtraction	
MEG:MAA (molar ratio)	sym (cm^{-1})	asym (cm^{-1})	sym (cm^{-1})	asym (cm^{-1})
0:1	1544	1414	1541	1414
1:4	1548	1414	1543	1414
1:1	1559	1414	1547	1414
1:0	–	–	–	–

[a] Sym: absorption wavenumber for symmetric stretching vibrations. Asym: absorption wavenumber for asymmetric stretching vibrations.

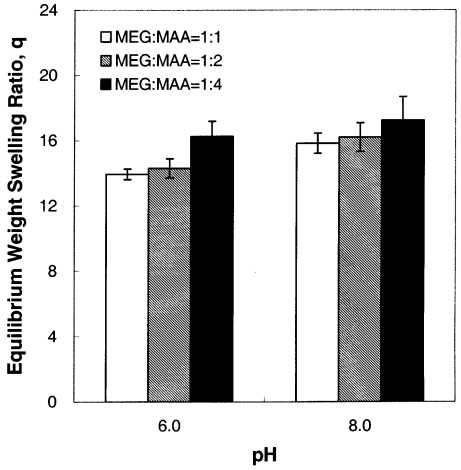

Figure 8. Equilibrium weight swelling ratio of P(MAA-*co*-MEG) networks at pH 6.0 and 8.0 with different monomer compositions.

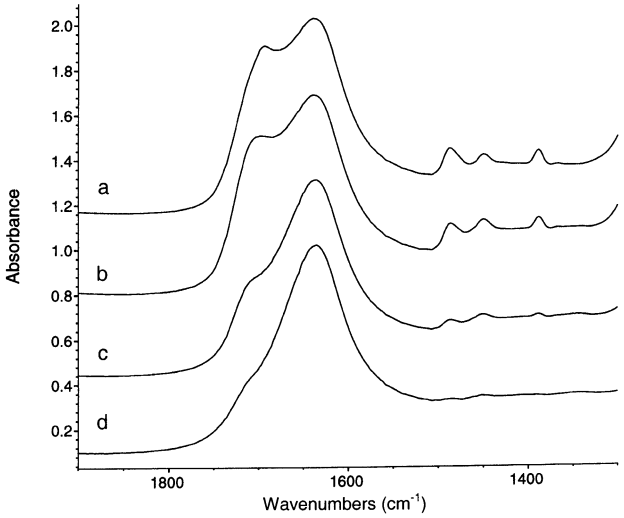

Figure 9. ATR−FTIR spectra of P(MAA-*co*-MEG) with different composition of MEG and MAA in pH 2.2 (before water subtraction): (a) 0:1, (b) 1:4, (c) 1:1, and (d) 1:0 MEG:MAA.

Copolymer Complexation at Low pH. Figures 9 and 10 show spectral comparisons of P(MAA-*co*-MEG) samples with different copolymer compositions of MEG and MAA in pH 2.2. Figure 9 shows the spectra before the water subtraction; it contains the water peak at 1636 cm^{-1} and the peaks of the C═O stretching at around 1695 cm^{-1}. The intensity of the C═O peaks at around 1695 cm^{-1} increased with MAA fraction in the polymer networks. After the water subtraction

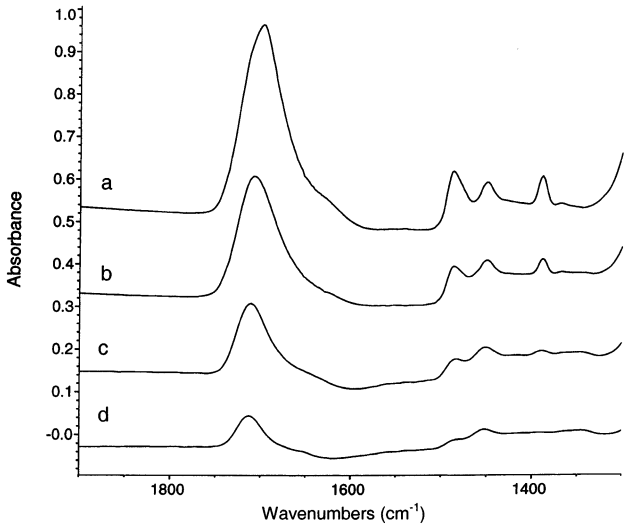

Figure 10. ATR−FTIR spectra of P(MAA-*co*-MEG) with different composition of MEG and MAA in pH 2.2 (after water subtraction): (a) 0:1, (b) 1:4, (c) 1:1, and (d) 1:0 MEG:MAA.

Table 3. FTIR Peak Location Summary of C═O Group of Samples of P(MAA-*co*-MEG) Polymer Networks in Their Hydrate States with Buffered Solution of pH 2.2 before and after Water Subtraction

	absorption wavenumber (cm^{-1})	
MEG:MAA (molar ratio)	before water subtraction	after water subtraction
0:1	1693	1699
1:4	1697	1708
1:1	1708	1711
1:0	–	1713

procedure (Figure 10), the C═O peaks were clearly defined, and their locations could be assigned more precisely.

For instance, the C═O peaks of P(MAA-*co*-MEG) networks with 1:4 MEG:MAA before and after the water subtraction are 1697 and 1708 cm^{-1}, respectively (see also Table 3). The maxima of the C═O peaks shifted from 1713 to 1699 cm^{-1} as the MAA fraction increased. This indicates as the MAA fraction increased, hydrogen bonding became stronger at low pH values, since the frequency of the carbonyl stretching vibration was dependent on hydrogen bonding, resulting in a shift of the absorption band to lower frequencies.[41,42]

It is clear that a C═O peak shift due to hydrogen bonding is independent of whether the bonding is inter- or intramolecular. Therefore, it is difficult to identify which molecules formed the hydrogen bonds with the carboxylic groups of the PMAA. In other words, we can simply guess that three different types of hydrogen bonds can occur: hydrogen bonds between carboxylic groups and water, hydrogen bonds between carboxylic groups, and hydrogen bonds between carboxylic groups and oxygen in MEG units.

The effect of the MAA content in the polymer networks on the equilibrium swelling ratio at low pH is shown in Figure 11. The equilibrium weight swelling ratios of the networks decreased below pH 5 with increasing incorporation of MAA. The reason for this was that increasing MAA content in the polymer networks caused increased hydrogen bonding at low pH values. Therefore, the networks with high MAA content could shrink more.

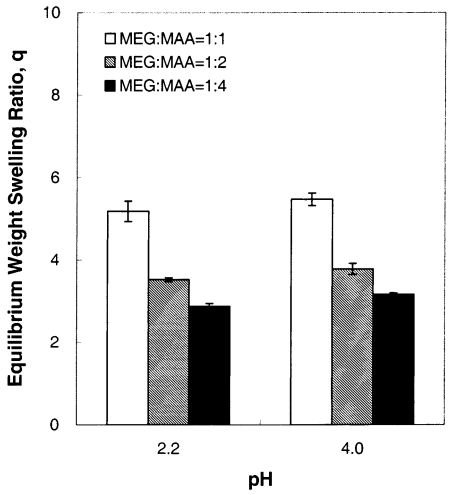

Figure 11. Equilibrium weight swelling ratio of P(MAA-*co*-MEG) networks at pH 2.2 and 4.0 with different monomer compositions.

Conclusions

Complex formation by molecular interactions in polymer networks has a significant effect on the structure and properties of the ensuing materials. The effect of complexation on the network structure and macroscopic swelling properties was observed with P(MAA-*co*-MEG). Incorporation of the MAA groups in the polymer networks could render these polymer networks more complex forming in response to the environmental pH change. Using ATR−FTIR spectroscopic analysis, we showed that these networks could form hydrogen bond at low pH values (below 5) by protonation of the carboxylic acid groups of the PMAA, whereas electrostatic interaction prevailed at high pH values (above 5) by ionization of the carboxylic acid groups of the PMAA.

In acidic media, hydrogen bonds forming in the networks rendered the networks more hydrophobic, resulting in a collapsed state. However, in neutral or basic conditions, electrostatic repulsion occurred, leading to high swelling. The hydrogen-bonding and electrostatic interactions increased with MAA content in the copolymer networks.

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