Highly pH and Temperature Responsive Microgels Functionalized with Vinylacetic Acid

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ABSTRACT: Temperature-responsive microgels based on poly(*N*-isopropylacrylamide) (PNIPAM) and functionalized with vinylacetic acid (VAA) are observed to exhibit a host of novel swelling responses compared with equally functionalized microgels prepared using the conventional acrylic acid (AA) and methacrylic acid (MAA) comonomers. VAA−NIPAM microgels are ionized over a narrow pH range and show functional group pK_a values which are independent of the degree of ionization. Ionization induces a much larger swelling response in VAA−NIPAM microgels than in the conventional microgels; upon ionization at physiological temperature, VAA−NIPAM swells 3 times more than either AA−NIPAM or MAA−NIPAM. VAA−NIPAM microgels also display sharp, PNIPAM-like thermal deswelling profiles when protonated but, upon ionization, undergo no volume phase transition up to at least 70 °C. The highly responsive and tunable ionization and swelling profiles observed for VAA−NIPAM are consistent with the tendency of VAA to behave as a chain transfer agent, resulting in the incorporation of a large number of well-separated VAA units on highly mobile chain ends at or near the microgel surface. VAA−NIPAM microgels may thus be ideal for use in biomolecule separation, medical diagnostics, and biodelivery applications in which sharp responses to multiple environmental stimuli are required.

Introduction

Thermosensitive microgels based on poly(*N*-isopropylacrylamide) (PNIPAM) undergo a reversible volume phase transition (VPT) at near-physiological temperature. First synthesized in our research group,[1] PNIPAM-based microgels exhibit dramatic changes in particle size, surface charge density, and water content over a small (5−10 °C) temperature range. This thermal sensitivity makes PNIPAM-based microgels attractive in applications which demand "smart" material responses to environmental stimuli, including drug delivery,[2] optical filtering,[3] and controlled biomolecule recovery.[4]

More recent work has attempted to broaden the applicability of such "smart" gels by incorporating functional groups within the microgel matrix. Of particular interest are carboxylic acid groups, generally incorporated into PNIPAM-based gels via the free radical copolymerization of acrylic acid (AA)[5] or methacrylic acid (MAA).[6] Carboxylic acid groups are pH-ionizable, provide an electrophilic site for functional group chemistry, and, when ionized, increase the volume phase transition temperature of the microgel.

However, both copolymerization kinetics[7] and experimental observations[8] indicate that AA and MAA tend to form blocks within the NIPAM-rich polymer chains comprising the microgel. This is generally undesirable since the ionization of one carboxylic acid residue increases the pK_a of a directly adjacent acid group (the commonly described polyelectrolyte effect[9]), significantly decreasing the sensitivity of a "blocky" gel to subtle changes in the solution pH. Furthermore, for applications such as medical diagnostics which require microgel postmodification, the conjugation of ligands to functional group blocks is sterically hindered as the conjugation reaction proceeds. A higher molar ratio of functional monomer must therefore be added to the gel to provide sufficient reactive sites to support a desired degree of conjugation. This mandates a decrease in the NIPAM fraction and (correspondingly) the temperature sensitivity of the microgel.

On the basis of these considerations, the "ideal" microstructure for a functionalized microgel would consist of a NIPAM-rich core and a near-surface "shell" consisting of low cross-link density NIPAM chains which are carboxy-terminated. Such a microstructure should provide both the sharp thermal sensitivity (NIPAM-rich core) and sharp pH sensitivity (well-separated carboxylic acid groups in similar chemical environments on the microgel surface) desirable for triggering and bioconjugation-related applications. Furthermore, this "ideal" microgel contains a high local polyanion concentration within a relatively lightly cross-linked, near-surface polymer domain, a morphology previously shown to undergo very large volume changes in response to changes in pH.[5b,10]

To achieve such a morphology using conventional microgel synthesis techniques, one would have to carry out a costly and time-consuming three-step reaction: synthesizing a carboxylic acid-containing microgel, activating the carboxylic acid groups for nucleophilic attack, and grafting an expensive end-functionalized PNIPAM oligomer to the microgel surface. In this paper, we discuss a novel synthetic method which appears to produce a similar morphology in a single reaction step, exploiting the tendency of allylic monomers such as vinylacetic acid (VAA) to behave as chain transfer agents instead of propagating monomers in free radical environments.[11]

Experimental Section

Materials. *N*-Isopropylacrylamide (NIPAM, 99%, Acros Organics) was purified by recrystallization from a 60:40

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Table 1. Microgel Polymerization Recipes and Carboxylic Acid Content of the Purified Microgel Products As Measured by Conductometric Titration

sample	NIPAM (mol)	VAA (mol)	MAA (mol)	AA (mol)	MBA (mol)	SDS (mol)	APS (mol)	−COOH in product (mmol/g)
NIPAM	1.24×10^{-2}	0	0	0	6.5×10^{-4}	1.7×10^{-4}	4.4×10^{-4}	0.01 ± 0.02
MAA−NIPAM	1.24×10^{-2}	0	7.9×10^{-4}	0	6.5×10^{-4}	1.7×10^{-4}	4.4×10^{-4}	0.52 ± 0.03
AA−NIPAM	1.24×10^{-2}	0	0	7.9×10^{-4}	6.5×10^{-4}	1.7×10^{-4}	4.4×10^{-4}	0.53 ± 0.03
VAA−NIPAM-3.3	1.24×10^{-2}	1.2×10^{-3}	0	0	6.5×10^{-4}	1.7×10^{-4}	4.4×10^{-4}	0.26 ± 0.02
VAA−NIPAM-6.5	1.24×10^{-2}	3.5×10^{-3}	0	0	6.5×10^{-4}	1.7×10^{-4}	4.4×10^{-4}	0.50 ± 0.02

toluene:hexane mixture. Methacrylic acid (MAA, 99%, Aldrich) and acrylic acid (AA, 99%, Aldrich) were both purified by vacuum distillation. *N*,*N*-Methylenebisacrylamide (MBA, 99+%, Aldrich), vinylacetic acid (VAA, 97%, Aldrich), sodium dodecyl sulfate (SDS, 98%, Aldrich), and ammonium persulfate (APS, 99%, BDH) were all used as received. All water used in the synthesis and characterization was of Millipore Milli-Q grade.

Microgel Preparation. Polymerizations were conducted in a 250 mL three-necked flask fitted with a condenser and a glass stirring rod with a Teflon paddle according to the recipes in Table 1. The amount of functional monomer used was determined such that the same total carboxylic acid content was achieved in each of the functionalized microgels (i.e., each gel contains the same number of moles of −COOH groups per gram of dried microgel). Thus, the ionization and swelling profiles of the novel VAA−NIPAM microgel can be compared directly to those of the conventional AA−NIPAM and MAA−NIPAM microgels without correcting for differences in the bulk functional group content. NIPAM, MBA, SDS, and the functional monomer were all dissolved in 150 mL of water and heated to the polymerization temperature of 70 °C under a nitrogen purge. After 30 min, APS was dissolved in 10 mL of water and injected to initiate the polymerization. Polymerizations were carried out for 6 h under 200 rpm mixing. After cooling, all microgels were purified by at least five cycles of ultracentrifugation (Beckman model L7-55, 45 min at 12000*g*), decantation, and redispersion in water until the supernatant conductivity was less than 5 μS/cm. Microgels were lyophilized and stored at 4 °C.

Particle Sizing. Particle sizing was performed by dynamic light scattering using a detector angle of 90°. A Lexel 95 ion laser operating at a wavelength of 514 nm and a power of 100 mW was used as the light source. Correlation data were analyzed using a BI-9000AT digital autocorrelator, version 6.1 (Brookhaven Instruments Corp.), and the CONTIN statistical method was used to calculate the particle size distributions. All microgels synthesized in this study were highly monodisperse. Samples were prepared in thoroughly cleaned vials by suspending a small quantity of lyophilized microgel in filtered 10^{-3} M KCl such that the scattering intensity was between 100 and 250 kilocounts/s. Sample pH values were adjusted using 0.1 M HCl and NaOH. At least five replicates were conducted for each sample; the experimental uncertainties represent the standard deviation of the replicate measurements.

Electrophoretic Mobility. Electrophoretic mobility values were measured using a ZetaPlus analyzer (Brookhaven Instruments Corp.) operating in phase analysis light scattering mode. Samples were prepared as described earlier for dynamic light scattering. A total of 10 runs (each comprised of 15 cycles) were conducted; the experimental uncertainties represent the standard error of the mean of the replicate runs.

Titration. Simultaneous conductometric and potentiometric titrations were performed using a Burivar-I2 automatic buret (ManTech Associates) as described previously.[10] Briefly, 0.050 g of lyophilized microgel was suspended in 50 mL of filtered 10^{-3} M KCl. Quantitative data were acquired using slow base-into-acid titrations (67 min/unit pH) to ensure complete equilibration between the aqueous and gel phases. The potentiometric titration data are analyzed using the method of Kawaguchi et al.[12] The degree of ionization α_d is calculated as a function of pH by subtracting the experimental microgel and blank titration curves. Equation 1 can subsequently be used to calculate the apparent pK_a of the carboxylic acid functional groups as a function of the degree of ionization.

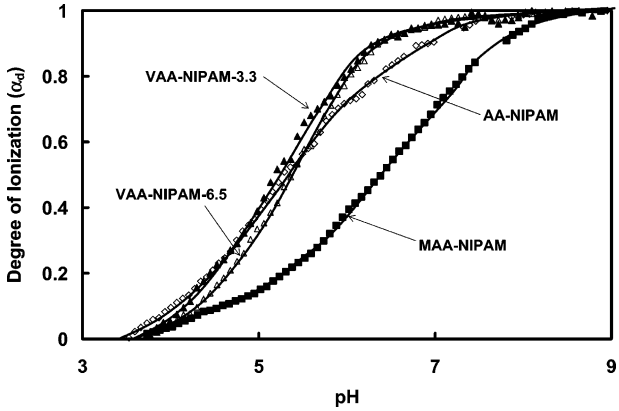

Figure 1. Degree of ionization of acrylic acid, methacrylic acid, and vinylacetic acid-functionalized microgels as a function of pH.

$$pK_a = pH - \log\left(\frac{\alpha_d}{1-\alpha_d}\right) \quad (1)$$

Transmission Electron Microscopy (TEM). Lyophilized microgels were resuspended in distilled, deionized water at a concentration of 0.5 wt %. The anionic (sulfate and carboxylic acid) functional groups in the microgel were selectively stained by mixing a 0.05 mL aliquot of the microgel suspension with 0.5 mL of a 1 mM uranyl acetate solution and agitating the mixture for 1 h. A single drop of the stained suspension was dropped on a Formvar-coated copper TEM grid and dried overnight. TEM micrographs are acquired using a JEOL 1200EX TEMSCAN microscope operating at 80 kV.

Results

Titration. Potentiometric titrations of polyelectrolyte microgels or macrogels tend to require long equilibration times (on the order of three or more hours[12]) and exhibit broad pH transitions.[13] Figure 1 shows the degree of ionization vs pH curves for microgels functionalized with acrylic acid (AA), methacrylic acid (MAA), and vinylacetic acid (VAA). Both MAA−NIPAM and AA−NIPAM show the expected broad ionization profiles of polyions, with 95% of the total functional groups titrated over a minimum 3.5 pH unit range ($4.0 < pH < 8.1$ for MAA−NIPAM and $3.7 < pH < 7.4$ for AA−NIPAM). However, VAA-functionalized microgels show drastically different ionization profiles. In both the high and low VAA loading microgels, 95% of the available functional groups are titrated within the extremely narrow pH range of $4.0 < pH < 6.6$. Furthermore, as shown in Figure 2, the pK_a value of VAA−NIPAM gels is virtually independent of the degree of ionization while those of AA−NIPAM and MAA−NIPAM both increase systematically with α_d by 1.1 and 1.5 units, respectively.

The results shown in Figures 1 and 2 have two significant impacts. From a macroscopic and applica-

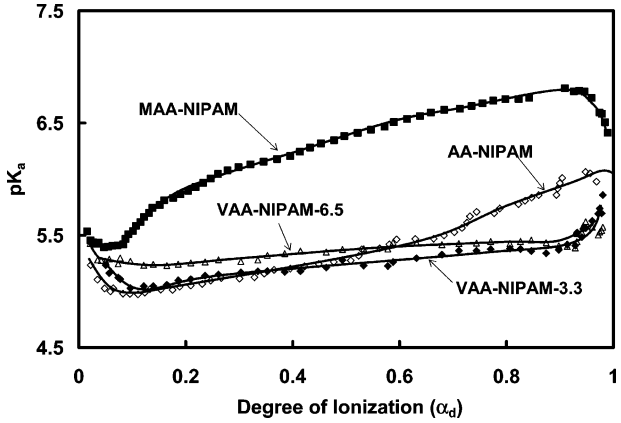

Figure 2. Carboxylic acid group pK_a values of acrylic acid, methacrylic acid, and vinylacetic acid-functionalized microgels as a function of the degree of ionization.

tions perspective, VAA−NIPAM copolymer microgels are much more responsive to changes in solution pH than are MAA−NIPAM or AA−NIPAM gels and can be switched from a fully deionized state to a fully ionized state by relatively subtle changes in solution properties. From a microstructure perspective, the near-constant pK_a suggests that the polyelectrolyte effect has virtually no impact on the titration of VAA−NIPAM microgels. Indeed, VAA−NIPAM appears to ionize much more like a small acid than a conventional polyacid. This observation has never before been reported for a carboxylic acid-functionalized microgel and sharply contrasts the observed behaviors of AA−NIPAM and MAA−NIPAM microgels both in this work and throughout the literature.[10,13] Such a pK_a profile is only possible if the functional groups in VAA−NIPAM are relatively well-isolated from each other (i.e., few VAA units are incorporated consecutively into the cross-linked polymer chains), and the functional groups are all present in similar chemical environments (i.e., all carboxylic acid groups are surrounded by similar polyion and polymer chain densities).

The unusual ionization behavior of VAA−NIPAM was further investigated using the technique of nonequilibrium titration. In our previous work,[10] we showed that performing a series of titrations at a variety of speeds can probe functional group distributions in microgel particles. Extremely fast titrations probe surface or near-surface groups, while titrations using very long stabilization times (>30 min per unit pH increase) appear to probe both surface and internal functional groups. To apply this method to the unusually responsive VAA−NIPAM system, conductometric titrations were performed using various titration speeds, the results of which are shown in Table 2. No statistical difference is observed between the titration results at various speeds, showing that minimal diffusion barriers exist to the titration of all the functional groups within the microgel. Furthermore, the potentiometric titration is readily reversible via back-titration with acid using even very short (2.2 min/unit pH) stabilization times. Conductometric titration profiles also show a classical, three-slope shape with clear end points corresponding well to those observed in the potentiometric titration (see Supporting Information). Given the absence of any nonequilibrium effects in these experiments, one would expect the functional groups to be localized at or near the particle surface such that the slow diffusion of acid or base into the more heavily cross-linked core of the microgel is not rate-limiting in terms of fully ionizing the microgel.

Table 2. Conductometric Titration Dependence on Time for VAA−NIPAM Microgels[a]

titration speed (min/unit pH)	measured % VAA incorporated VAA−NIPAM-3.3	measured % VAA incorporated VAA−NIPAM-6.5
2.2	36.2 ± 2.1	26.0 ± 0.8
4.4	35.6 ± 2.0	25.8 ± 0.8
6.7	36.8 ± 2.1	24.8 ± 0.8
10	35.3 ± 2.0	25.5 ± 0.8
22.2	37.1 ± 2.1	26.1 ± 0.8
33.3	37.9 ± 2.1	26.4 ± 0.9
66.7	37.6 ± 2.1	26.6 ± 0.9

[a] The results are expressed in terms of the percentage of VAA added in the prepolymer solution which is incorporated into the product microgel.

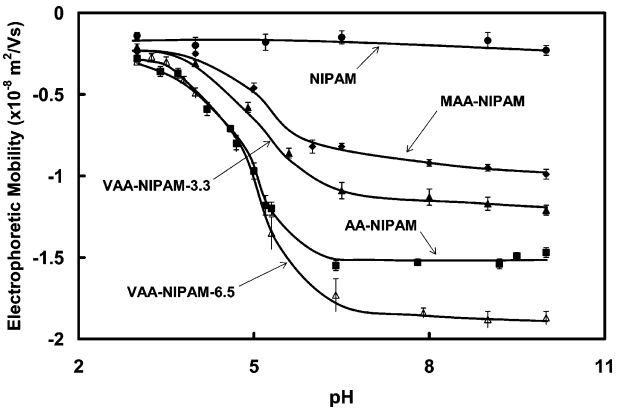

Figure 3. pH dependence of the electrophoretic mobilities (as measured at 25 °C) of vinylacetic acid, acrylic acid, and methacrylic acid-functionalized microgels compared with a nonfunctionalized PNIPAM microgel.

pH Sensitivity. The pH dependence of the electrophoretic mobility of the VAA−NIPAM, AA−NIPAM, and MAA−NIPAM microgels is shown in Figure 3. The narrow 4.0−6.6 pH ionization range observed in titrations of the VAA−NIPAM microgels is also reflected in the mobility results; no statistical difference in electrophoretic mobility was noted in the range 6.5 < pH < 10. In contrast, continuous mobility increases are observed up to pH 9 in the MAA−NIPAM system.

More remarkable, however, is the absolute magnitude of the electrophoretic mobility of the VAA−NIPAM microgels compared with, in particular, the MAA−NIPAM microgel. While MAA−NIPAM contains exactly the same bulk carboxylic acid content as VAA−NIPAM-6.5, the electrophoretic mobility of VAA−NIPAM-6.5 is more than double that of MAA−NIPAM when the microgels are both fully ionized. The contrast is even more dramatic with VAA−NIPAM-3.3, which contains 50% fewer functional groups than MAA−NIPAM but still exhibits a 20% higher mobility at pH 10. Even compared to AA−NIPAM, the electrophoretic mobility of VAA−NIPAM-6.5 is still 30% higher when both microgels are fully ionized. These results suggest that −COOH groups in the VAA−NIPAM system are significantly more localized at the particle surface than in AA−NIPAM and, in particular, MAA−NIPAM.

The functional group distributions imaged in the TEM micrographs in Figure 4 correlate directly with the electrophoretic mobility predictions. All of the functionalized microgels take up significantly more stain than does the nonfunctionalized PNIPAM microgel (Figure

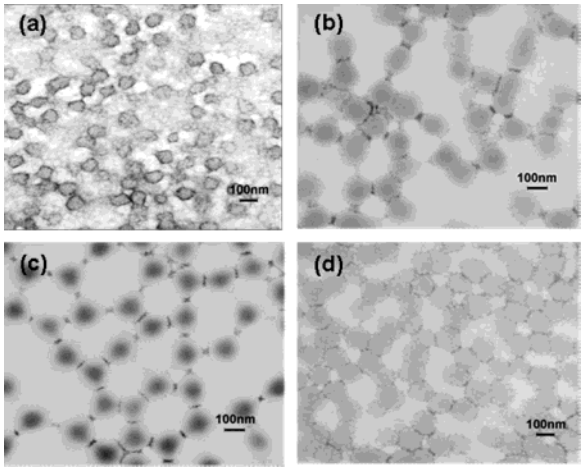

Figure 4. Transmission electron micrographs of microgels functionalized with vinylacetic acid (a), acrylic acid (b), and methacrylic acid (c) compared with a nonfunctionalized PNIPAM microgel (d). Anionic sites are selectively stained using uranyl acetate to appear darker in these images.

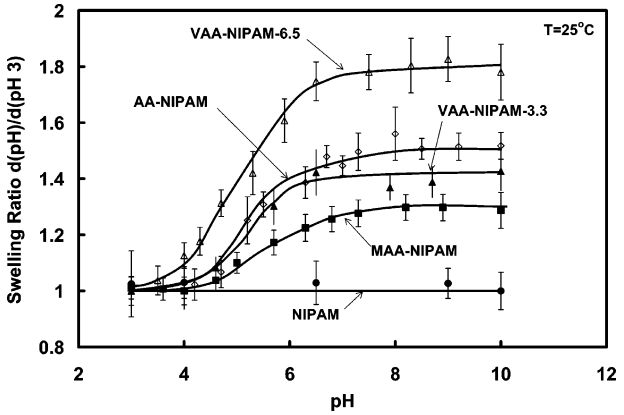

Figure 5. pH dependence of the hydrodynamic diameters (as measured at 25 °C) of vinylacetic acid-, acrylic acid-, and methacrylic acid-functionalized microgels compared with a nonfunctionalized PNIPAM microgel.

4d), confirming the utility of the uranyl acetate for selectively staining carboxylic acid groups. VAA−NIPAM (Figure 4a) exhibits a very discrete core−shell structure with the stained carboxylic acid groups highly localized in a thin shell on the microgel surface. Interestingly, this micrograph is very similar to that reported by Jones and Lyon for their PNIPAM-core, PNIPAM-*co*-AA shell microgels prepared via a multistep reaction.[14] On the other hand, AA−NIPAM (Figure 4b) shows no distinct core−shell structure while MAA−NIPAM (Figure 4c) exhibits somewhat of a "reverse" core−shell structure with the stained carboxylic acid functional groups localized more toward the core of the microgel. These results are particularly interesting given that both acrylic acid-[13] and methacrylic acid[6]-functionalized microgels prepared under similar conditions have been reported to exhibit core−shell structures with the functional monomer concentrated in the shell and, by extension, localized on the microgel surface.

A comparison of the pH-induced swelling ratios for the different functionalized microgels, shown in Figure 5, also yields interesting results. The swelling ratios reported in Figure 5 are calculated by dividing the observed particle size at the pH given on the *x*-axis by the particle size of the same microgel in its fully protonated state at pH 3. Error bars represent the

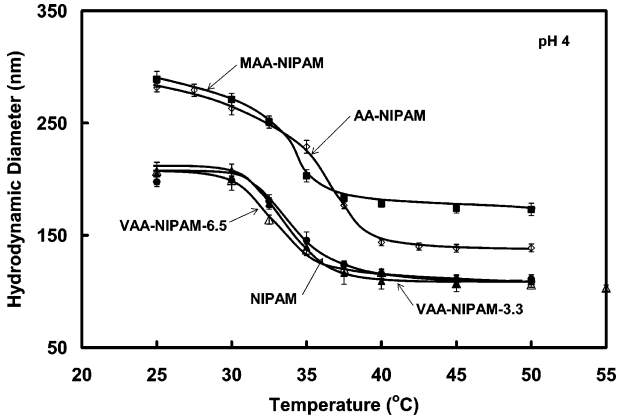

Figure 6. Temperature dependence of the pH 4 hydrodynamic diameters of vinylacetic acid-, acrylic acid-, and methacrylic acid-functionalized microgels compared with a nonfunctionalized PNIPAM microgel.

standard error of the mean swelling ratio. VAA−NIPAM-6.5 and VAA−NIPAM-3.3 exhibit high d(pH 10)/d(pH 3) ratios of 1.8 and 1.4, respectively, ratios which are in exact proportion to the total amount of functional monomer present within each microgel (6.5 and 3.3 mol %, respectively). Both MAA−NIPAM and AA−NIPAM are significantly less responsive to ionization. AA−NIPAM exhibits a d(pH 10)/d(pH 3) ratio just slightly higher than that of VAA−NIPAM-3.3, which contains only half as many carboxylic acid groups; furthermore, d(pH 10)/d(pH 3) for MAA−NIPAM is 4 times smaller than that observed for the equally functionalized VAA−NIPAM-6.5. Thus, the presence of one additional functional group has a significantly higher impact on the swelling of the VAA−NIPAM copolymer microgels than does the presence of one additional functional residue in the AA- or MAA-functionalized microgels. Given that the TEM and electrophoretic mobility results show an increased localization of carboxylic acid functional groups on the surface of VAA−NIPAM, the large degree of swelling observed again emphasizes the critical importance of local polyanion concentrations in regulating the swelling of PNIPAM-based microgels.

Volume Phase Transition Behavior. The volume phase transition behavior of VAA−NIPAM was characterized using dynamic light scattering and electrophoresis. The particle size variation with temperature at pH 3 (the fully protonated state) is shown in Figure 6. The particle size profiles are nearly identical for the nonfunctionalized NIPAM microgel and both of the vinylacetic acid-functionalized microgels, similarities also observed in the electrophoretic mobility results (see Supporting Information). Interestingly, VAA−NIPAM-6.5 has a 1−2 °C lower VPTT than the NIPAM homopolymer microgel according to both particle size and mobility data, suggesting that VAA in its protonated state is slightly more hydrophobic than NIPAM. Vinylacetic acid is reported to be insoluble in water at temperatures below 15 °C,[15] and some phase separation is observed when small quantities of water are added to the monomer even at room temperature. However, the more significant observation is that protonated VAA−NIPAM microgels display the same sharp temperature sensitivity of nonfunctionalized PNIPAM gels, in terms of both the narrow temperature range of their volume phase transition and the degree of volumetric deswelling observed upon heating. This sharply thermo-

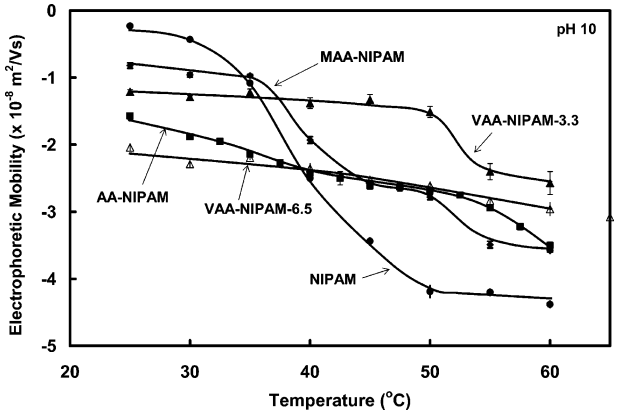

Figure 7. Temperature dependence of the pH 10 electrophoretic mobilities of vinylacetic acid-, acrylic acid-, and methacrylic acid-functionalized microgels compared with a nonfunctionalized PNIPAM microgel.

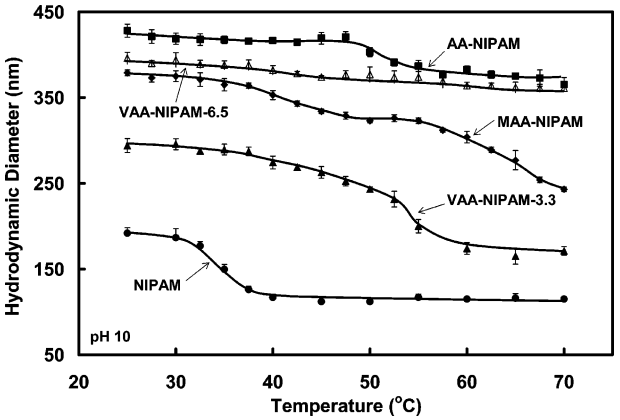

Figure 8. Temperature dependence of the pH 10 hydrodynamic diameters of vinylacetic acid-, acrylic acid-, and methacrylic acid-functionalized microgels compared with a nonfunctionalized PNIPAM microgel.

sensitive behavior is highly preferable to that observed in the deswelling profiles of both AA−NIPAM and MAA−NIPAM, which show broader volume phase transitions, slightly higher onset phase transition temperatures, and lower overall degrees of deswelling.

At pH 10, all VAA groups are in their ionized state, and the volume phase transition behaviors of the microgels become dramatically different. Figure 7 shows the electrophoretic mobility response, and Figure 8 shows the particle size response of the functionalized microgels as the temperature is varied. Ionized VAA−NIPAM microgels undergo volume phase transitions at significantly higher temperatures than do MAA- and AA-functionalized microgels. The VPTT of VAA−NIPAM−3.3 is shifted to $T > 50$ °C, and VAA−NIPAM-6.5 collapse is fully retarded until at least 70 °C, with no significant volume phase transition whatsoever observed within the operating range of our dynamic light scattering system. Given the relatively low 6.5 mol % incorporation of functional monomer in these microgels, VPTT shifts of this magnitude are, to our knowledge, unprecedented in the literature. This is certainly true in comparison to both AA−NIPAM and MAA−NIPAM in this work. The two-step, core−shell collapse of MAA−NIPAM is initiated between 30 and 35 °C and completed at 60 °C, while AA−NIPAM exhibits a small but discrete deswelling transition between 50 and 60 °C.

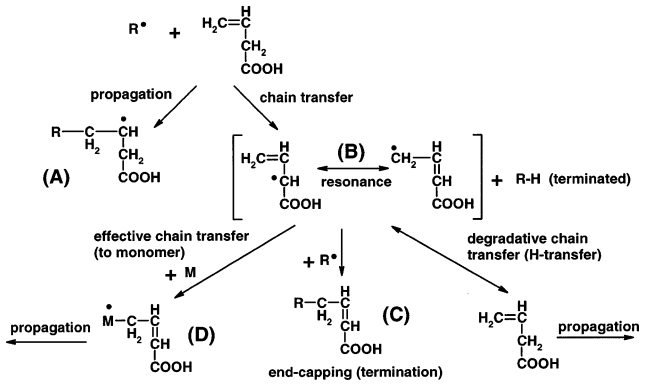

Figure 9. Potential reaction pathways for vinylacetic acid in the free radical environment of microgel polymerization.

Clear differences are also apparent in the magnitude of microgel deswelling across the volume phase transition. AA−NIPAM and VAA−NIPAM-3.3 both have onset VPTTs of approximately 50 °C; however, by 70 °C, the volume of VAA−NIPAM-3.3 has decreased 5-fold while that of AA−NIPAM has decreased less than 2-fold. Thus, VAA functionalization can be used to dramatically increase the volume phase transition temperature of a microgel without compromising the occurrence of a large and relatively sharp deswelling transition at temperatures above the shifted VPTT.

Discussion

The ionization and swelling profiles observed for VAA-functionalized microgels suggest that the carboxylic acid functional groups in VAA−NIPAM systems are well-isolated from each other (constant pK_a) while at the same time being localized at the microgel surface (high electrophoretic mobility). This would only be possible if VAA−NIPAM has a microstructure similar to the "ideal" NIPAM-rich core, carboxy-terminated oligomer shell morphology described in the Introduction. The formation of such a microstructure in the single-step VAA−NIPAM synthesis can be rationalized by considering the different reaction pathways undertaken by a single molecule of vinylacetic acid in a free radical environment, as illustrated in Figure 9.

As an allylic monomer with the general structure $CH_2{=}CH{-}CH_2{-}X$, vinylacetic acid can react via two distinct routes: standard free radical propagation through the C−C double bond (forming species A) or chain transfer via abstraction of the methylene protons (forming species B).[11] Attempts to homopolymerize vinylacetic acid have largely failed in that the products are highly branched and of low molecular weight; indeed, vinylacetic acid is rarely even cited among lists of carboxylic acid-containing monomers in recent literature and patents[16] and is even more rarely used in polymer-related applications.[17] On the basis of this observation, the chain transfer pathway is certainly nonnegligible; in fact, it may be dominant in situations where vinylacetic acid is highly diluted and a large number of different radical centers are present, as is the case in microgel synthesis.

During a chain transfer event, methylene proton abstraction creates a resonance-stabilized allylic radical (species B) which, in most allylic monomer systems, remains a stable free radical until it is terminated by some other mechanism or quenched at the end of the polymerization.[11] This is the well-known process of degradative chain transfer to monomer which termi-

nates growing polymer chains and excludes the incorporation of the transfer agent into the microgel.

However, in the case of vinylacetic acid, this degradative chain transfer reaction route is suppressed by two factors. First, the presence of the electronegative, electron-withdrawing carboxylic acid group strengthens the C−H bond at the methylene position and inductively destabilizes the electron-deficient resonance structure generated upon proton abstraction. Thus, the probability of degradative chain transfer is dramatically reduced and, in particular, the alternative processes of polymer chain end-capping (forming species C) and effective chain transfer to monomer (forming species D) become much more probable.[18] In either of these alternative reaction pathways, single vinylacetic acid groups are incorporated on the chain ends of NIPAM-rich polymer chains. This is physically consistent with the absence of a polyelectrolyte effect during the titration of the carboxylic acid groups in VAA−NIPAM microgels.

Second, protonated carboxylic acid residues form strong hydrogen-bonding networks, both with the surrounding water molecules and with the amide group in NIPAM residues.[5b] Previous research has confirmed that hydrogen bonding to species containing a radical center will reduce the termination rate constant of radicals.[11] Given that a pH of 2.2 < pH < 2.6 is maintained throughout the polymerization, strong hydrogen bonding should occur in the VAA−NIPAM system, and allylic radicals should thus terminate more slowly. This factor dramatically increases the probability of effective chain transfer over degradative chain transfer. Zubov et al. confirmed this effect by polymerizing VAA in the presence of phosphoric acid and sulfuric acid; heavily branched polymers were produced indicative of the occurrence of multiple effective chain transfer reactions.[18]

The relatively high proportions of both cross-linker and initiator used in microgel formulations are also important in ensuring that a maximum number of the end-capped or reinitiated polymer chains are attached to the growing microgel particles instead of being effectively wasted as soluble oligomers. Given that ∼5 mol % cross-linker is present in the microgel recipe, both the microgel and the growing oligomers are likely to contain a number of pendant vinyl groups (i.e., unreacted ends of the bifunctional MBA cross-linker). The high initiator concentration maintains a high concentration of free radicals throughout the polymerization process, making it more likely these pendant vinyl groups will be "activated" to cross-link the carboxy-terminal oligomers to the microgel particles. Experimentally, this effect was confirmed when an additional shot of APS added 6 h into the polymerization increased the degree of VAA incorporation by 20%. Thus, both the cross-linker and the initiator are important in achieving the reasonable degrees of VAA incorporation shown in Table 2 and maintaining the microgel yield above 80% of the total monomer weight in the prepolymer solution, as observed in both VAA recipes.

The apparent localization of functional groups on the surface of VAA−NIPAM microgels can be rationalized on the basis of the kinetics the chain transfer reactions. Kinetically, the fact that linear vinylacetic acid homopolymers can be synthesized at all[11] indicates that chain transfer is typically at least somewhat slower than VAA propagation. In turn, several studies have shown that allylic monomers such as vinylacetic acid propagate several orders of magnitude more slowly than acrylic monomers such as NIPAM.[11] Thus, VAA-containing oligomers produced via effective chain transfer or end-capping are more likely to be formed later in the polymerization at high NIPAM and MBA conversions. As a result, these VAA-containing oligomers would most likely be grafted to a pendant unsaturated group at or near the microgel surface in the later stages of particle formation.

In addition to the inherent kinetic concentration of VAA at the microgel surface, reorientation of surface polymer chains in VAA−NIPAM may also influence the high observed electrophoretic mobilities. Since only ∼5 mol % cross-linker is present, polymer chains terminated with VAA would (on average) have 20 monofunctional monomer units separating the nearest cross-link junction from the free functionalized chain end. As a result, terminal VAA-derived carboxylic acid groups should be relatively more mobile and better able to reorient to their lowest-energy states than −COOH groups incorporated primarily between cross-links (as in AA−NIPAM and MAA−NIPAM). In the latter case, mobility and reorientation are restricted by the multiple contact points effectively pinning the functional group to the rest of the gel network. Chain-transferred VAA groups are therefore better able to orient themselves toward the gel−aqueous interface (their thermodynamically preferred position in the charged state) and reconfigure laterally along the surface to minimize local charge−charge repulsions between the ionized carboxylic acid groups.

The proposed end-functionalized oligomer shell microstructure is also consistent with the much higher degree of swelling and strongly delayed volume phase transition observed in VAA−NIPAM upon ionization. A single chain transfer process effectively removes one cross-linking point from the microgel. Since the kinetics suggest most chain transfer reactions are associated with near-surface polymer chains, the cross-linking density in this near-surface "shell" should therefore be dramatically lower than that in the polymer core. This is particularly true when the inherent kinetic concentration of MBA in the microgel core is also taken into account.[19] Furthermore, TEM and electrophoresis results indicate that most of the ionizable functional groups are incorporated into the microgel within this near-surface region. As a result, the high degree of local polyanion−polyanion repulsion between charged VAA residues can effectively push the near-surface polymer chains apart with little elastic resistance from the lightly cross-linked local network. This should cause the gel volume to increase upon ionization to a far greater degree than could be achieved in other microgels with similar bulk cross-linker contents. In addition, the strong repulsive interactions in the highly hydrophilic, expanded, and ionized VAA-rich shell can effectively oppose the hydrophobic interactions driving the collapse of the PNIPAM-rich core, greatly increasing the volume phase transition temperature of the ionized VAA−NIPAM microgel (as observed). This behavior is similar to that reported by Jones and Lyon for their multistep PNIPAM-core, PNIPAM-*co*-AA shell microgel particles.[14]

Theoretical calculations can be used to confirm that the carboxylic acid functional groups in VAA−NIPAM may be both surface-localized and electrostatically independent in their equilibrium swelling state (as

suggested by the potentiometric titration data in Figure 2). The maximum average charge-to-charge separation distance in the VAA−NIPAM microgels was estimated to be 1.7 nm at 25 °C, assuming all of the charges are on exterior surface of the microgel. This distance is greater than the Bjerrum length λ_B, which serves as an estimate of the distance over which two charges significantly interact.

$$\lambda_B = \frac{{e_0}^2}{4\pi\epsilon_0\epsilon_r k_b T} = 0.71 \text{ nm} \quad (2)$$

where e_0 is the elementary charge, $\epsilon_0\epsilon_r$ is the permittivity of water, k_b is Boltzmann's constant, and T is the absolute temperature. AA−NIPAM and MAA−NIPAM microgels show significant charge−charge interactions in their titrations since NIPAM−AA and NIPAM−MAA copolymerizations always result in some neighboring AA and MAA groups (via random propagation reactions); conversely, the chain-transferring nature of VAA excludes the possibility of neighboring groups in VAA−NIPAM gels (see Figure 9).

The unique physical behavior of VAA−NIPAM microgels has important consequences for applications. In using vinylacetic acid, fewer functional monomers need to be incorporated into the microgel to induce swelling transitions of similar magnitudes to those observed in AA or MAA copolymer systems. Since thermosensitivity is maximized when the NIPAM content of the microgels is maximized, VAA−NIPAM systems can be designed which exhibit sharp pH responsiveness without compromising temperature sensitivity in the protonated state or in the ionized state at high temperatures. A comparison of the pH and temperature-induced swelling profiles of AA−NIPAM and VAA−NIPAM-3.3 in Figures 5 and 8 clearly illustrates this advantage of VAA-functionalized systems, particularly useful in applications where both pH and temperature triggers are of interest for controlling the microgel swelling (i.e., rheological modifiers).

The remarkable change in VAA−NIPAM microgels from being highly thermoresponsive at low pH to virtually nonresponsive at high pH also suggests the utility of these microgels in switching or delivery applications. As an example, the volume of VAA−NIPAM-6.5 increases 40-fold when the solution pH is changed from 4 to 6.5 at physiological temperature. This volume change is more than 3 times that observed for AA−NIPAM and 5 times that observed for MAA−NIPAM under the same conditions. Interestingly, even VAA−NIPAM-3.3 exhibits a higher responsiveness than either of the two conventional copolymer microgels despite containing only half the total number of functional groups.

Conclusions

Vinylacetic acid/*N*-isopropylacrylamide copolymer microgels contain carboxylic acid functional groups which are highly localized on the microgel surface yet remain relatively isolated from each other such that the ionization of one functional group has no significant impact on the ionization of other functional groups. This unique NIPAM-rich core/carboxy-terminated oligomer shell morphology allows VAA−NIPAM microgels to ionize over a much narrower pH range and exhibit larger increases in volume upon ionization than conventional AA−NIPAM and MAA−NIPAM microgels. The volume phase transition behavior of VAA−NIPAM microgels can also be tuned precisely in terms of both the transition temperature and the degree of deswelling induced. When fully protonated, VAA−NIPAM copolymer microgels give sharp, highly responsive thermal deswelling profiles similar to those of nonfunctionalized PNIPAM microgels. However, when fully ionized, volume phase transitions in VAA−NIPAM copolymer microgels are shifted to dramatically higher temperatures by even small amounts of comonomer; a relatively small 6.5 mol % VAA loading shifts the VPTT of the microgel higher by at least 40 °C.

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Supporting Information Available: Potentiometric and conductometric titration data for the VAA−NIPAM microgels, electrophoretic mobility profiles of the ionized microgels, and a mathematical model comparing the experimental and theoretical packings of vinylacetic residues on the microgel surface are attached. This material is available free of charge via the Internet at http://pubs.acs.org.

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