Novel Temperature-Responsive Water-Soluble Copolymers Based on 2-Hydroxyethylacrylate and Vinyl Butyl Ether and Their Interactions with Poly(carboxylic acids)

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ABSTRACT: Novel water-soluble amphiphilic copolymers have been synthesized by free radical copolymerization of 2-hydroxyethylacrylate with vinyl butyl ether. In water these copolymers exhibit lower critical solution temperature, which depends on the content of hydrophobic vinyl butyl ether units. The interaction between these copolymers and poly(acrylic acid) or poly(methacrylic acid) in aqueous solutions results in formation of interpolymer complexes stabilized by hydrogen bonds and hydrophobic interactions. An increase in hydrophobicity of the copolymers leads to the enhancement of their complex formation ability with respect to poly(acrylic acid) and poly(methacrylic acid). Poly(methacrylic acid) forms stronger complexes with the copolymers when compared with poly(acrylic acid). The complexes exhibit dual sensitivity to pH- and temperature and this property may be easily adjusted regulating the strength of interaction. © 2005 Wiley Periodicals, Inc. J Polym Sci Part B: Polym Phys 44: 195–204, 2006

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INTRODUCTION

Water-soluble polymers exhibiting lower critical solution temperature (LCST) in water have attracted considerable attention in recent years. Numerous applications of these polymers in controlled release systems,[1–3] biotechnology,[4] separation and enrichment technologies,[5] and stabilization of colloids[6,7] have stimulated researchers to develop new polymers and to optimize the properties of well-known systems.

N-isopropylacrylamide (NIPAAM) is one of the most studied monomers for the preparation of temperature-responsive polymers. The cloud point of homopolymer PNIPAAM is around 32 °C, but copolymerization of NIPAAM with different anionic,[8,9] cationic,[10,11] and nonionic monomers[12,13] can significantly change this value. In addition, NIPAAM was used for modification of the properties of polysaccharides by grafting,[14] preparation of thermosensitive colloidal crystals,[15] synthesis of temperature-sensitive mem-

branes,[16] and interpenetrating networks.[17] The other temperature-sensitive polymers, which are not based on NIPAAM, include poly(*N,N*-diethylacrylamide),[18] poly(vinyl methyl ether),[19,20] some cellulose ethers,[21,22] poly(*N*-vinylcaprolactame),[23] and poly(2-ethyl-2-oxazoline).[24] In summary, temperature-sensitive polymers can be prepared by homo- or copolymerization of monomers with certain structure and hydrophobic–hydrophilic balance.

Another possibility of preparing polymers with LCST is a copolymerization of hydrophilic monomers with hydrophobic ones. The resulting polymers should have a proper hydrophobic–hydrophilic balance and also exhibit temperature-induced phase separation. This possibility was demonstrated in our previous work, where thermosensitive polymers were synthesized by radiation-induced copolymerization of vinyl ether of ethyleneglycol with vinyl alkyl ethers.[25–27]

Water-soluble nonionic polymers are able to form hydrogen-bonded interpolymer complexes (IPC) with poly(carboxylic acids) in aqueous solutions. This topic in polymer research has received much attention since the sixties. At the moment several hundred research papers have been published on the subject and the general features of the complexation were summarized and analyzed in numerous reviews.[28–34] Among the nonionic polymers, which were mostly studied from the view point of their complexation with poly(carboxylic acids), several can be outlined: poly(ethylene oxide),[35–39] poly(vinyl pyrrolidone),[40–44] poly(vinyl alcohol),[45–47] poly(acrylamide) and poly(*N*-isopropylacrylamide),[48–51] poly(vinyl methyl ether),[52–54] and some polysaccharides.[34] Many papers were devoted to the study of complexation of nonionic copolymers with poly(carboxylic acids) and different effects were reported depending on the nature of copolymers. In case, one of the comonomers, for example, acrylic acid,[28] can form very weak hydrogen bond with a carboxylic group and if it is very hydrophilic it can disrupt the interaction and weaken the complexation. Also, if the copolymer consists of two hydrophilic nonionic monomers, for example, *N,N*-dimethylacrylamide-*co*-acrylamide,[55] then both monomeric units can participate in the complexation, and the major role in stabilization of IPC belongs to the more hydrophobic one. Finally, if one of the monomers form hydrogen bonds and the other one does not but it is relatively hydrophobic it can contribute to the hydrophobic stabilization of IPC. This stabilization effect was demonstrated in our earlier work on complexation between poly(acrylic acid) (PAA) and copolymers of hydrophilic vinyl ethers of glycols with vinyl butyl ether.[56,57] In addition, Koussathana and coworkers[58] have demonstrated that the hydrophobic stabilization of IPC is more efficient if the nonionic polymer exhibit LCST in aqueous solutions.

Water-soluble polymers of 2-hydroxyethylacrylate received little attention in the study of interpolymer complexation reactions. Previously we reported the results on complexation between poly(2-hydroxyethylacrylate) (PHEA) and PAA in aqueous solutions for the first time.[59] It was found that PHEA exhibits relatively low complexation ability, which is related to its highly hydrophilic nature.

The goal of the present study was to synthesize new copolymers of HEA with vinyl butyl ether (VBE) and study the solution and complexation behavior of these copolymers. We expected that the copolymerization of these monomers may result in formation of copolymers exhibiting LCST in aqueous solutions and enhanced complexation potential.

EXPERIMENTAL

Materials

HEA, azoisobutyronitrile (AIBN), HCl, and NaOH were purchased from Aldrich (USA), and used without purification. HEA for kinetics analyses was purified from inhibitor by careful distillation in vacuum. VBE was purchased from Alash (Kazakhstan), and was purified by distillation using rectification column (Fisher Technology, Germany). PAA with weight-average molecular weight 2.5×10^5 Da was purchased from Aldrich and used without purification.

Synthesis of Copolymers and PMAA

Copolymers HEA–VBE and PMAA were synthesized by radical copolymerization at 60 °C in ethanol solutions. The polymerization time was 30 min. The concentration of monomers in ethanol was 30 vol %. AIBN (0.01 mol/L) was used as a radical initiator. Before copolymerization the monomer mixture was saturated with argon and sealed into glass ampoules. The copolymers were purified by several re-precipitations from ethanol to diethyl ether. They were dried under vacuum for 3 days until the constant weight was achieved.

The molecular weight of PMAA was 350 ± 10 kDa, which was determined viscometrically using the following equation: $[\eta] = 6.6 \times 10^{-4} \cdot M_v^{0.5}$ (solvent: 0.002 M HCl aqueous solution at 30 °C)

Kinetics of Copolymerization (Dilatometric Measurements)

Various ratios of HEA/VBE were dissolved in ethanol to form 30 vol % solutions. AIBN was used as an initiator. Before polymerization the solutions were saturated with argon and sealed into glass dilatometer. The kinetics of HEA–VBE copolymerization was investigated by dilatometry technique, which utilizes the volume change that occurs upon polymerization to follow conversion versus time. The dilatometers containing different monomer mixtures were placed in a constant temperature bath at 60 °C and the volume change of the polymerizing system, which is quantitatively related to the percent of conversion, was monitored visually using cathetometer B-630 (USSR, accuracy ± 0.01 mm). As the dilatometers containing monomer mixtures with different ratios were placed into the constant temperature bath, initial meniscus moved up, showing an increase in reaction mixture volume due to the thermal expansion of the monomer mixture. After approximately 5–10 min the effects due to thermal expansion become negligible and the reaction mixtures began to contract because of copolymerization. Conversion of monomers was calculated by the following equation

$$C = \frac{\Delta V'}{V'K} 100\%$$

where V' is the initial volume of feed mixture, $V' = \pi r^2 \Delta h$, r is the radius of the capillary; Δh is the change in the meniscus position; $k = (V'_{sp\,m} - V'_{sp\,p})/(V'_{sp\,m})$ is the contraction coefficient ($V'_{sp\,m} = 1/\rho_m$ is the specific volume of the feed mixture, $V'_{sp\,m} = 1/\rho_p$ is the specific volume of the polymer). The density was found to be slightly different for obtained copolymers. The average density ranged from 1.15 to 1.16 g/mL.

Characterization of Copolymers

Molecular weights and molecular weight distributions were determined using a GPC equipped with an Agilent 1100 series RI detector, quaternary pump, and three PL gel 5 μm MIXED-D columns in set. The eluent was DMF containing Bu$_4$NBr (0.1% (w/v)) with a flow rate of 0.8 mL/min. The molecular weights were calibrated with polystyrene standards.

^{1}H and ^{13}C NMR spectra of the (co)polymers were recorded in DMSO solutions using NMR spectrometer Bruker ARX300 at 300 and 75 MHz, respectively.

Preparation of Polymers and Polycomplexes Solutions

Aqueous solutions of polymers were prepared by direct dissolution of known amounts of PAA (PMAA) and copolymers in distilled water with overnight stirring. The concentration of [HEA–VBE] in base-moles was calculated by computing the molar weight of the average repeating unit by the following formula

$$M = (A\,M_{HEA} + B\,M_{VBE})/100$$

Where M_{HEA} and M_{VBE} are molar weights of HEA and VBE units, and A and B are their percentage in copolymers, respectively. Polycomplexes were prepared by simple mixing of components aqueous solutions at the required ratio and stiring for several minutes before measurements.

Turbidimetric and pH Measurements

Turbidimetric measurements were performed using Shimadzu UV/VIS-2401 PC spectrophotometer (Japan) at 400 nm. The temperature of solutions was regulated with the help of thermoelectrically temperature-controlled cell positioner CPS-240A (Shimadzu, Japan). Cloud points of polymer solutions were determined from turbidity–temperature curves as a temperature at which an abrupt increase in turbidity is observed. The pH of solutions was measured with the pH-meter Ion Meter 3345 (Jenway, UK) and was adjusted by the addition of small amounts of 0.1 M HCl or NaOH.

RESULTS AND DISCUSSION

Synthesis and Characterization of HEA–VBE Copolymers

The conversion degrees of the monomer mixtures versus time were calculated based on the dilatometry data and presented as kinetic curves (Fig. 1). It is clearly seen that the pure monomer
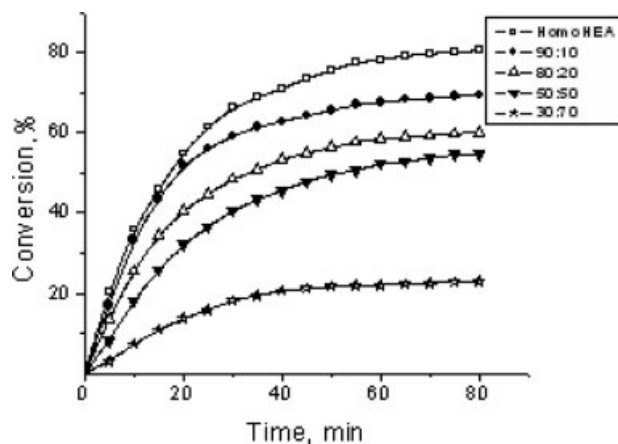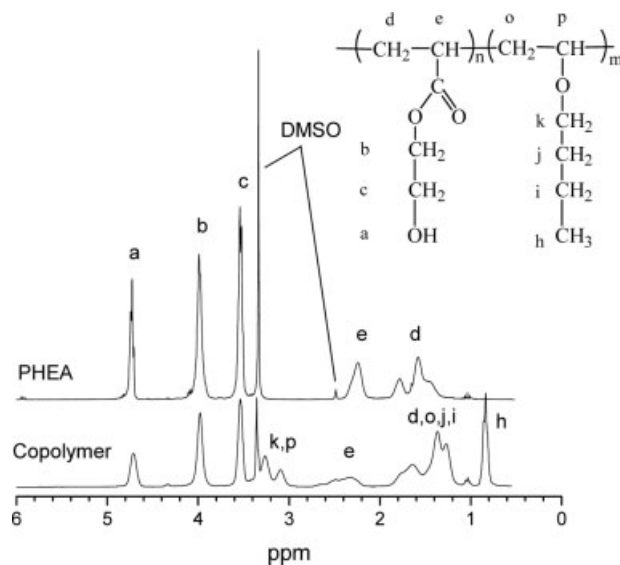
Figure 1. Kinetics of copolymerization at different monomer ratios in Feed ([HEA]:[VBE], mol %).

Figure 2. ^{1}H NMR spectrum of PHEA and HEA–VBE copolymer. Monomer ratio in Feed—[HEA]:[VBE] = 30.0:70.0, mol %.

HEA was converted into homopolymer very fast and 80% conversion was achieved after approximately 60–70 min. An addition of VBE into the feed mixture, however, significantly reduced the copolymerization rate, which was likely due to low activity of this monomer in reactions of radical polymerization.[25–27]

To quantify the reaction ability of these monomers in copolymerization, the copolymers were synthesized from the feed mixtures of different ratios at low degree of conversion (<10%). After purification the copolymers were characterized by ^{1}H and ^{13}C NMR spectroscopy. Figure 2 shows the ^{1}H NMR spectrum of PHEA and HEA–VBE. The —CH and —CH$_2$ backbone protons of PHEA (d and e) resonate at 2.25 ppm and from 1.46 to 1.8 ppm, respectively. Signals at δ = 4.00 and 3.54 ppm are assigned to —CH$_2$ protons of the hydroxyethyl group (c and b), and a resonance at δ = 4.73 ppm corresponds to the —OH of the hydroxyethyl group (a). These data are in good agreement with those obtained by Coca et al.[60] The methyl protons of butyl group in the spectrum of copolymers give the strong signal at δ = 0.85 ppm (h). Methylene protons (i, j, o,) resonate from δ = 1.22 to 1.38 ppm. The —CH protons (p) of VBE backbone and —CH$_2$ protons (k) of VBE substituent resonate at δ = 3.09 ppm and 3.27 ppm, respectively. These data are also in good agreement with those obtained by Keki et al.[61]

Figure 3 shows a ^{13}C NMR spectrum of PHEA and HEA–VBE with complete assignments of the chemical shifts. The spectral data are in a good agreement with the data of Keki et al.,[61] who reported the spectral features of poly(butyl vinyl ether).

The data of ^{1}H NMR spectroscopy was used for determination of copolymers compositions, which allowed the calculation of the reactivity ratios (r_1 and r_2) of the monomers in radical copolymerization. The molecular weights of the same copolymers were determined by gel permeation chromatography. The characteristics of the feed mixture, compositions, molecular weights, as well as polydispersities of the copolymers are summarized in Table 1. It is clearly seen that the copolymers are slightly enriched by HEA when compared with the feed mixture, which is related to the lower activity of VBE in copolymerization. The following r_1 and r_2 values were obtained for HEA and
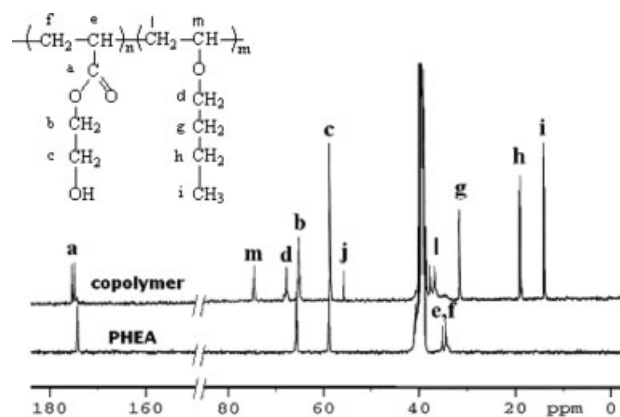
Figure 3. ^{13}C NMR spectrum of PHEA and HEA–VBE (84.3:15.7 mol %) copolymer. The signal at 40 ppm corresponds to carbons of DMSO.

Table 1. Composition Ratios of HEA-VBE Copolymers and their Molecular Weight Characteristics

| Sample	Feed Ratio (HEA:VBE, mol %)	Composition Ratio[a] (HEA:VBE, mol %)	M_n (kDa)	M_w/M_n
1	95.0:5.0	97.6:2.4	173.3	1.82
2	90.0:1 0.0	95.0:5.0	242.6	1.47
3	85.0:1 5.0	92.9:7.2	165.9	1.47
4	80.0:20.0	90.6:9.4	320.5	1.29
5	70.0:30.0	84.3:15.7	274.2	1.30
6	50.0:50.0	74.0:26.0	–	–
7	30:70	62.4:37.6	129.5	1.49
8	100:0	100.0:0.0	109.8	1.60

[a] Estimated by ^{1}H NMR in DMSO-d_6.

VBE: 2.12 and 0.03, respectively, (from calculations by Mayo-Lewis method); and 2.05 and 0.03, respectively, from calculations by Finemann-Ross approach.[62] These data confirm a significantly higher activity of HEA in copolymerization when compared with VBE. Taking into account the significant difference in monomer reactivity ratios and a very low probability of VBE for adding to the growing radicals ended with VBE units (r_2 = 0.03), one can assume that the structure of copolymers is presented by relatively long sequences of HEA divided by single units of VBE.

Phase Behavior of HEA–VBE Copolymers in Aqueous Solutions

The copolymers synthesized in the present study consist of hydrophilic fragments of HEA and hydrophobic fragments of VBE. Although the homopolymers PHEA and PVBE do not exhibit any temperature sensitive behavior the copolymerization of HEA and VBE results in the forma-

tion of copolymers exhibiting LCST in aqueous solutions. It should be noted that this behavior was observed for water-soluble copolymers only, that is for copolymers, where the content of VBE does not exceed 20 mol %. A higher content of VBE in the copolymers makes them very hydrophobic and insoluble in water. The temperature-induced phase transitions in aqueous solutions of HEA–VBE copolymers were assessed by measurement of their turbidity upon heating (cloud points method). Figure 4 shows the dependence of solution turbidity on temperature at different concentrations of HEA–VBE (95.0:5.0 mol %). It is clearly seen that the phase separation occurs upon heating at some fixed temperature, which depends on concentration. The higher content of copolymer in solution results in lower value of a cloud point. Figure 5 presents the dependence of cloud point temperature on concentration for copolymers with different composition. An increase in copolymer concentrations leads to a decrease in the cloud point temperature. This concentration dependence of cloud point was
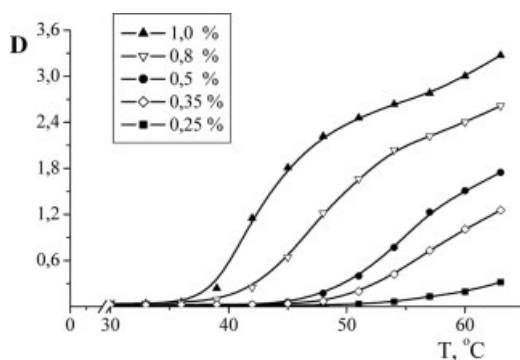
Figure 4. Dependence of HEA–VBE copolymer (95.0:5.0 mol %) aqueous solution turbidity on temperature at different concentrations of the copolymer (wt %).
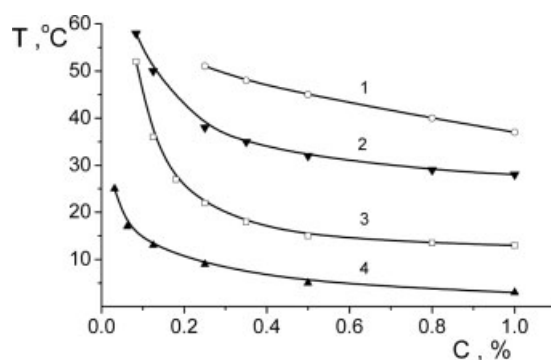
Figure 5. Effect of copolymers composition and concentration on the cloud points in solution. VBE content in copolymers: 5.0 (1), 7.2 (2), 9.4 (3), and 15.7 (4) mol %.

reported for many temperature-sensitive polymers (see, for example, ref. 63 and references cited therein). It is generally explained by easier aggregation of polymers above LCST at higher concentration. An increase in hydrophobic monomer VBE content in the copolymers leads to the lowering of cloud point temperatures. The reason for such a phase transition at the molecular level is hydrophobic interactions as well as formation/ dissociation of hydrogen bonds between water molecules and hydrophilic groups of macromolecules. At low temperature these hydrogen bonds are strong enough, helping to retain macromolecules in solution. As temperature increases a portion of hydrogen bonds are destroyed and the hydrophobic interactions become stronger, and the polymer is no longer stabilized by solvation layer and undergoes phase separation. The main reason of phase separation of HEA–VBE copolymers aqueous solutions at low temperature (lower than 40 °C) is hydrophobic interactions with participation of VBE chain of copolymers. As the hydrophobic interactions are intensified upon increase in VBE content in the copolymers the temperatures of phase separation are lowered.

The cloud point values observed for HEA–VBE copolymers of different compositions are in a broad temperature range of 5–60 °C, depending on the composition of copolymers and their concentration in solution, which opens various possibilities for their potential applications.

Interpolymer Complexation of HEA–VBE Copolymers with Poly(carboxylic acids)

The ability of HEA polymers to form hydrogen bonded IPC with poly(carboxylic acids) demonstrated in our previous work[59] opens a unique possibility to prepare polymeric system with dual stimuli-sensitivity with respect to both temperature and pH. As was demonstrated in the previous section, the copolymers HEA–VBE are temperature-sensitive. On the other hand, poly(carboxylic acids) are sensitive to changes in pH and their combination within IPC may result in dual sensitivity. In the present section it is demonstrated that the complexation of HEA–VBE copolymers with PAA and poly(methacrylic acid) (PMAA) leads to the appearance of this dual sensitivity.

Previously[59] we demonstrated that the complexes between PAA and PHEA are formed at 1:4 component ratio, therefore we studied the effect of pH on the complexation using the same ratio.
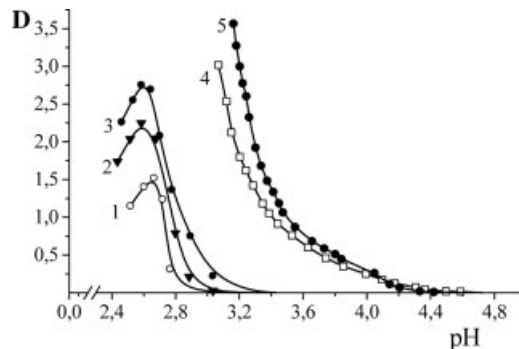
Figure 6. Effect of pH on turbidity of binary mixtures of PAA (1–3) and PMAA (4,5) with HEA–VBE copolymers containing 0 (1,4), 2.4 (2,5), and 5.0 (3) mol. % of VBE Components ratio [polyacid]/[copolymer] is 1:4. Concentrations of PAA and PMAA is 0.02 mol/L Concentration of copolymers is 0.25 wt %.

Figure 6 presents the dependence of solution turbidity on pH for mixtures of HEA–VBE with PAA and PMAA. It can be seen that at higher pH the binary system remains clear without any sign of phase separation. Upon decrease in pH the system starts to undergo phase separation, and the pH value at which this process occurs is called critical pH of complexation.[44,56,57,64,65] Below this value the formation of IPC with hydrophobic structure takes place and polycomplex particles undergo further aggregation and precipitation. It should be noted that the critical pH values observed for complexes of HEA–VBE with PAA are relatively low (within 2.9–3.3) and just slightly higher than the pH_{crit} of PHEA–PAA. This is an indication of low complexation ability of both PHEA and HEA–VBE. Moreover an increase in the hydrophobic VBE groups content in copolymers results in higher pH_{crit} values, which proves the significance of hydrophobic interactions contribution into stabilization of IPC. The complexes of HEA and HEA–VBE with more hydrophobic PMAA exhibit much higher pH_{crit} values and can be classified as strongly complexing polymer pair.[65] This is likely to be due to more efficient additional stabilization of IPC by hydrophobic interactions with participation of PMAA methyl groups.

Slightly above pH_{crit}[64] the interaction product exist in the form of hydrophilic associate with extended structure, in which a significant part of functional groups is free from hydrogen bonding. Under these conditions the component ratio is expected to influence the structure of the associate significantly. The free functional groups help to maintain the interpolymer associate in solution
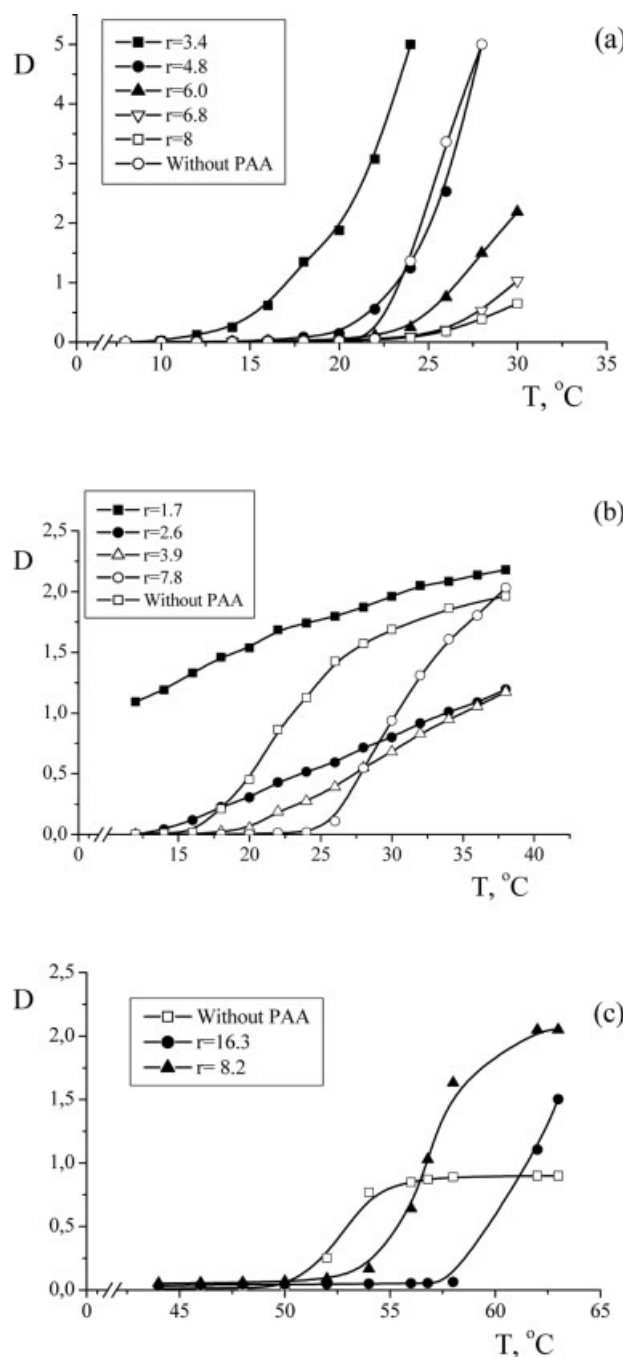
Figure 7. Temperature-induced phase separation of HEA:VBE copolymer aqueous solution with the following compositions 90.6:9.4 (a), 92.9:7.1 (b) and 95.0:5.0 (c) mol % in the presence of PAA with various components ratio, $r =$ [PAA]/[copolymer].

ments the pH of solution was not adjusted, which resulted in mixing of copolymers with PAA without precipitation of IPC. The pH values for initial PAA and the copolymers solutions were 3.6 and more than 4.0, respectively. For comparison the dependence of copolymers turbidity on temperature in the absence of PAA was also plotted. It is clearly seen that the ratio $r =$ [PAA]/[copolymer] affects the temperature-induced phase separation significantly. At relatively lower amount of PAA in the mixture, the phase separation occurs at temperatures lower than that of the pure copolymer. Probably in this case the binding of PAA by copolymer via intermolecular hydrogen bonding results in partial blockade of functional hydrophilic groups resulting in a slight hydrophobization of the whole associate, which starts to aggregate at lower temperature. In the presence of excessive amount of PAA the formation of a hydrophilic associate with a lot of free PAA segments is possible, which makes it even more hydrophilic and susceptible to aggregation only at higher temperatures. The speculative structures of the associates formed in these conditions are schematically shown in Figure 8. It should be noted that the content of VBE groups in copolymer affects the temperature-sensitive behavior of
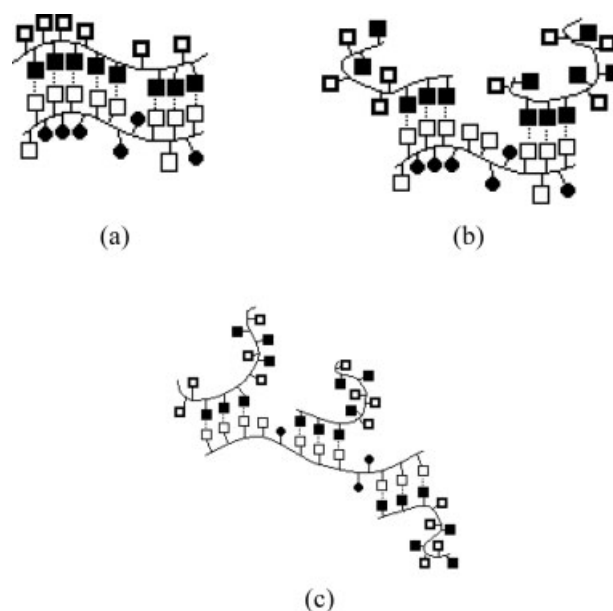
Figure 8. The speculative structures of the interpolymer associates formed at stoichiometric ratio of the components (a), in the presence of insignificant excess of PAA (b) and significant excess of PAA (c). ■, ionized groups COO$^-$; ■, nonionized groups COOH; □, hydroxyl groups of HEA; ●, inactive groups of VBE.

without phase separation and simultaneously they are sensitive to the changes in environment. The behavior of these associates at different temperatures is shown on Figure 7(a–c) for copolymers of different compositions. In these experi-

the interpolymer associates significantly. This may be due to variations in copolymer binding ability with respect to PAA because of contribution of hydrophobic effects. Different authors have demonstrated earlier the effect of interpolymer complexation on the temperature induced phase separation of poly(vinyl methyl ether),[53] poly(N,N-diethylacrylamide) (PDEA),[18] hydroxypropylcellulose,[22] methylcellulose.[66] Bian and Liu[18] have shown that 0.2 wt % poly(N,N-diethylacrylamide) aqueous solution starts to turn cloudy at 29.8 °C. However in the presence of PAA as long as $r = $ [PAA]/[PDEA] remains low (0.01–0.15) a gradual displacement of the turbidity curves to a higher temperature is observed. When r is higher than 0.3, the solutions are turbid irrespective of the temperature. Similar observations were reported by Karayanni and Staikos[53] for poly(vinyl methyl ether) and PAA. It was additionally shown that the changes in temperature induced phase separation behavior of the system are more pronounced in the case of PAA of 450 kDa in comparison with PAA of 50 kDa. Both authors[18,53] explained the increase in phase separation temperature by associations of negatively charged PAA groups with nonionic polymer via hydrogen bonding. When the components ratio r approaches stoichiometric 1:1, the complexes become insoluble at any temperature because of the blockade of all functional groups of both polymers and shifting the dissociation equilibrium toward nonionized carboxylic groups of PAA bound via hydrogen bonding with proton-accepting groups of a nonionic polymer. The complexation of hydroxypropylcellulose and methylcellulose with PAA reported in the literature[22,66] results in significant decrease of the phase separation temperature of a binary polymer system as compared with cellulose ether alone. In both studies the authors used relatively high amounts of PAA, which are close to IPC stoichiometry and the complex formation resulted in a blockade of functional groups. This situation resembles the observations of Bian and Liu[18] as well as Karayanni and Staikos,[53] when the components ratio [PAA]/[nonionic polymer] was relatively high.

Unlike the polymeric pairs reported in the literature[18,22,53,66] our VBE-HEA copolymers exhibited relatively low complexation ability and even a slight excess of PAA over stoichiometric ratio resulted in a decrease of the phase separation temperature solely due to partial binding of polymers. However when this excess is significant we observe an increase in phase separation temperature,

which is likely due to binding of extra PAA chains. It is interesting to note that the copolymer containing the highest amount of VBE (9.4 mol %) and exhibiting the highest complexation ability formed a turbid solution with PAA in a broad temperature range (Fig. 7(b), $r = 1.7$). However when extra PAA ($r = 4.8/7.8$) was added, the binary system became soluble at low temperatures and resulted in phase separation only upon heating. Similar behavior is expected for complexes between copolymers and PMAA but the dual sensitivity can be possibly observed at higher pH values.

CONCLUSIONS

In the present work it was demonstrated that a free-radical copolymerization of hydrophilic hydroxyethyl acrylate with hydrophobic VBE may result in formation of the copolymers with LCST if the content of the hydrophobic monomer in the feed mixture is ranged within 0–30 mol %. At higher VBE content in the feed the resulting copolymers are insoluble in water. An increase in VBE content within 0–30 mol % in the feed leads to the formation of the copolymers with lower LCST, which is caused by hydrophobization of the macromolecules. The data about the composition of resulting copolymers as well as the copolymerization kinetics show that HEA is much more active in copolymerization in comparison with VBE and the resulting copolymers are always enriched by this monomer.

The thermal sensitivity of these copolymers can be combined with pH-sensitivity of PAA or PMAA when these polymers interact in aqueous solutions via hydrogen bonding. The interaction affects both pH-induced and temperature-induced phase transition and can be used for adjustment of these properties by variation in the interaction strength. The copolymers with higher content of VBE form stronger complexes with PAA due to their additional stabilization by hydrophobic interactions. Several examples from the literature as well as our data on HEA-VBE/PAA show that the existence of dual sensitivity to pH and temperature is expected to be the common property typical for hydrogen bonded complexes of poly(carboxylic acids) and nonionic polymers exhibiting LCST.

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