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Vinyl Polymers Containing L-Valine and L-Leucine Residues: Thermodynamic Behavior of Homopolymers and Copolymers with *N*-Isopropylacrylamide

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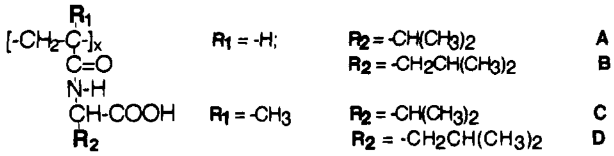
ABSTRACT: Vinyl polymers carrying carboxyl groups and the groups (amido and isopropyl) present in the well-known thermosensitive poly(*N*-isopropylacrylamide) (PNIPAAm) were studied for protonation reaction thermodynamics at different temperatures (25, 30, and 35 °C). The study was performed in aqueous solution (0.1 M NaCl) to elucidate the mutual influence of temperatures and pH on the mechanism responsible for phase separation of polymers having a lower critical solution temperature (LCST). The thermodynamic data (viscometry, basicity constants, enthalpy changes) for the protonation of carboxylate groups in homopolymers and copolymers with *N*-isopropylacrylamide (NIPAAm) showed that subtle conformational changes occurred at a critical degree of protonation (α). Beyond this critical α value, a larger endothermic effect was superimposed on that of the protonation of the COO^- group. The phenomenon was ascribed to hydrophobic forces between isopropyl groups outweighing the repulsive electrostatic interactions of the polymer in the ionized, unfolded state. The enthalpy changes ($-\Delta H°$) became larger as the NIPAAm content increased in the copolymers, and at higher temperatures the magnitude of this change dropped sharply. The critical α shifted to a lower value because higher temperatures enhanced hydrophobic interactions. The reduced amount of structured water molecules on the polymer, responsible for the LCST phenomenon, was revealed by the lower entropy change ($\Delta S°$), that confirmed that the process is entropy-driven and based on a critical balance between hydrophobic and electrostatic forces.

Introduction

In a previous paper[1] some polymers containing α-amino acid residues (L-valine, L-leucine) were prepared by radical polymerization of the corresponding vinyl monomers in order to study their conformational behavior on protonation and with a view to applications in solute separation and controlled delivery of drugs.[2–5] Macromolecular extension and contraction on a microscopic scale or in macroscopic systems can be magnified by fabricating a three-dimensional polymer network in hydrogels[6–8] or membranes having a "chemical valve" function.[9–12] The latter consist of porous substrates onto which stimuli-responsive polymers are graft-polymerized.[13,14] The regulation of the gating or valving function depends on the extension of the grafted polymer chains which are brought back to collapsed coil conformation by changes in environmental conditions. Physicochemical parameters, such as pH, temperature, and redox, cause changes in polymer chain conformation, and in most cases a combination of such stimuli overcomes the problem of designing intelligent materials.[15,16]

The polymers considered had poly(acrylic acid) or poly(methacrylic acid) structure and incorporated amido (hydrophilic) and isopropyl (hydrophobic) groups in the side chain:



Their thermodynamic study is of special interest because it enables a correlation to be established between increasing hydrophobicity and the appearance of compact structure.[17,18] The solution properties of these polymers are those of polyelectrolytes with compact conformation in water due to hydrophobic forces between isopropyl groups. These attractive forces outweigh the repulsive electrostatic interactions between negatively charged carboxyl groups when the polymer reaches a critical degree of protonation α. This critical α strongly depends on the nature of the α-amino acid residues. The magnitude of the hydrophobic character was revealed by calorimetric data when polymer A showed an endothermic peak superimposed on the protonation process of COO^-.[1] The peak, observed at $\alpha > 0.65$, decreased with increasing temperature, suggesting mutual dependence of pH and temperature on the conformational changes of polymer A. This result was correlated with lower hydration of the polymer, and an LCST (lower critical solution temperature) phenomenon similar to that of temperature-sensitive polymers was observed.[19–23] As is well-known for structurally related and uncharged poly(*N*-alkylacrylamide) polymers,[24,25] temperature-induced phase separation of their solutions is mainly driven by increased interaction between hydrophobic moieties on the polymer, caused by reduced structuring of water around hydrophobic polymer side groups as the temperature increases.[26] In water, the uncharged macromolecules elongate, presumably as a result of hydrogen-bonding between the amide group of the polymer and surrounding water molecules. As the solution temperature rises, H-bonds break and more and more water molecules are released. On a macroscopic scale, this release provokes the separation of a polymer-rich phase, concomitant, on the molecular level, with collapse of the polymer chains from extended coils to more compact conformation.[26,27] Poly(*N*-isopropylacrylamide) (PNIPAAm) has been studied more than other water soluble polymers for its thermoreversible properties, whereby aqueous solutions of it precipitate at an LCST of 32 °C.[20,28] Several copoly-

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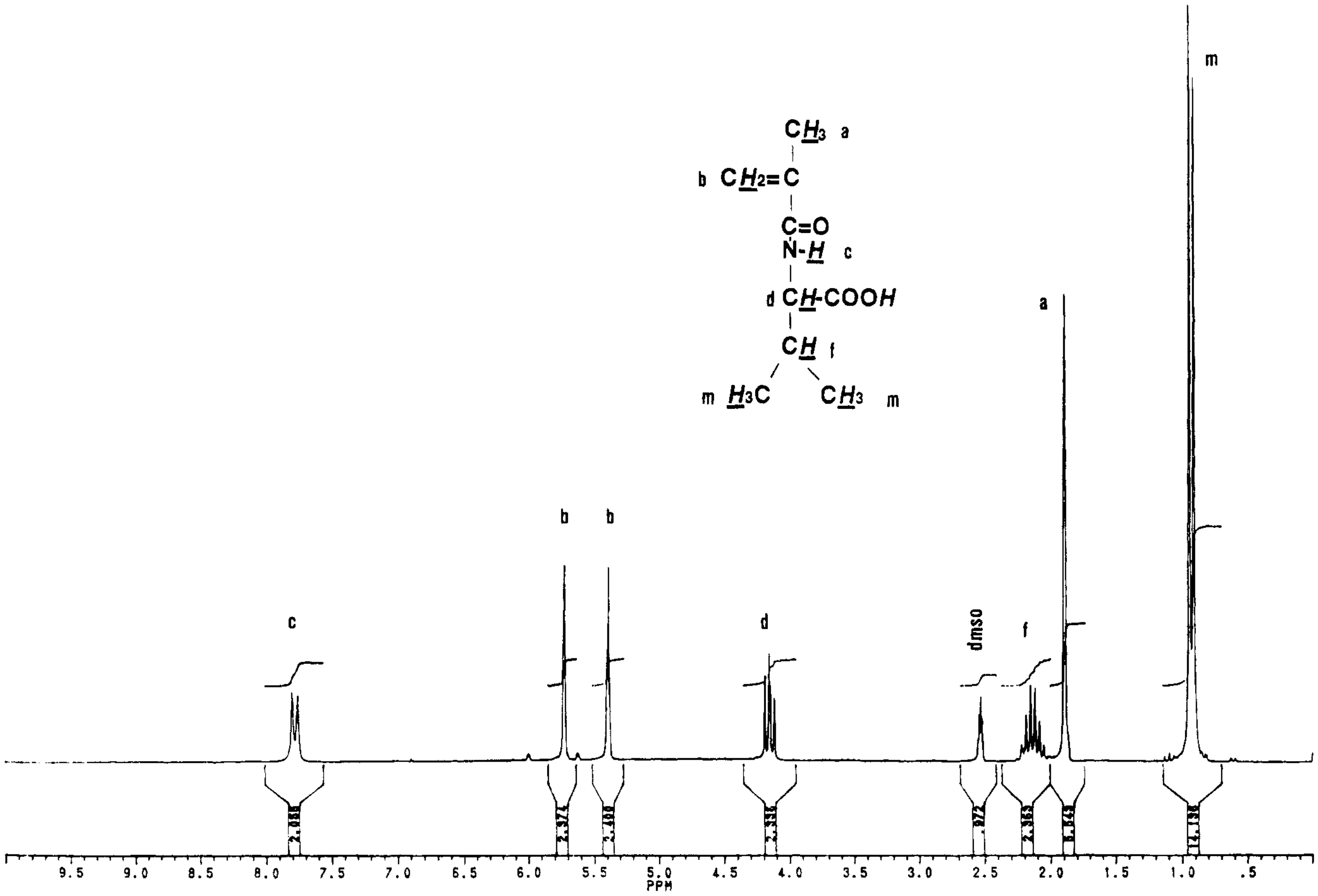
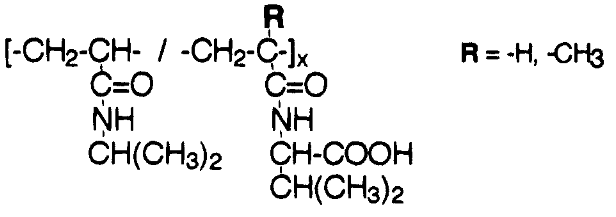


Figure 1. Proton NMR spectrum of *N*-methacryloyl-L-valine in DMSO-d_6 with the corresponding assignments of proton signals.

mers of *N*-isopropylacrylamide (NIPAAm) with acidic/basic or hydrophobic comonomers are being studied to improve pH and temperature responsivity. Thermosensitive polymers have the useful property of increasing or decreasing their LCST when hydrophilic or hydrophobic units, respectively, are added.[13,25]

This paper deals with the comparative protonation behavior of a series of polymers containing L-valine and L-leucine residues in acrylate and methacrylate structures. Moreover, the thermodynamic study was performed at different temperatures on a series of compounds containing *N*-acryloyl-L-valine (AVA) and *N*-methacryloyl-L-valine (MAVA) copolymerized with NIPAAm.

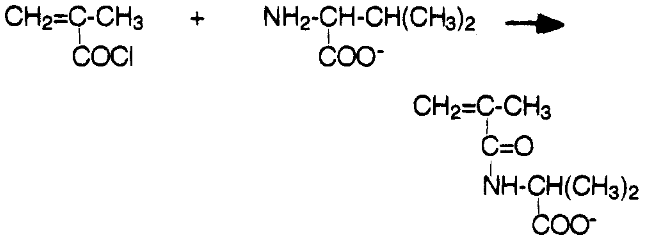


$$[\text{-CH}_2\text{-}\underset{\substack{|\\ \text{C=O}\\ |\\ \text{NH}\\ \text{CH(CH}_3)_2}}{\text{CH}}\text{-} \;/\; \text{-CH}_2\text{-}\overset{\text{R}}{\underset{\substack{|\\ \text{C=O}\\ |\\ \text{NH}\\ |\\ \text{CH-COOH}\\ |\\ \text{CH(CH}_3)_2}}{\text{C}}}\text{-}]_x \qquad \text{R = -H, -CH}_3$$

The protonation of COO^- groups in copolymers with NIPAAm was studied to clarify the role of comonomer hydrophilicity and charge on the mechanisms of the temperature-induced phase separation.[25]

Results and Discussion

Synthesis. Monomer. The vinyl monomer *N*-methacryloyl-L-valine (MAVA) was synthesized by the general techniques previously employed.[1,29,30] The acylation reaction of L-valine with methacryloyl chloride occurred in alkaline solution



$$\underset{\substack{|\\ \text{COCl}}}{\text{CH}_2\text{=C-CH}_3} + \underset{\substack{|\\ \text{COO}^-}}{\text{NH}_2\text{-CH-CH(CH}_3)_2} \longrightarrow \underset{\substack{|\\ \text{C=O}\\ |\\ \text{NH-CH(CH}_3)_2\\ |\\ \text{COO}^-}}{\text{CH}_2\text{=C-CH}_3}$$

Treatment with concentrated hydrochloric acid gave a white crystalline solid of analytical grade. The ^{1}H NMR and IR spectra were entirely consistent with the proposed structure. The main IR frequencies observed (COOH, 1740 cm^{-1}; Amide I, 1670 cm^{-1}; $-C{=}C-$, 1620 cm^{-1}) were close to those found in the previously synthesized *N*-acryloyl-L-valine.[1] A lower value was observed for the Amide II (N—H stretching, 1535 cm^{-1}) due to inductive effects.[31] A similar pattern was revealed in the proton NMR resonances. Figure 1 shows the ^{1}H NMR spectrum of MAVA together with the assignments of proton signals. Comparison of the methacrylate and acrylate proton NMR spectra showed that the amido proton falls to lower resonances in the former monomer.

Polymers. The homopolymer and the corresponding copolymer with *N*-isopropylacrylamide (NIPAAm) were prepared in dioxane or benzene solutions by free radical polymerization, using azobis(isobutyronitrile) as initiator. The polymers, purified in water, were characterized by elemental analysis and spectroscopic techniques (IR and ^{1}H NMR). The vinyl double bond was absent from

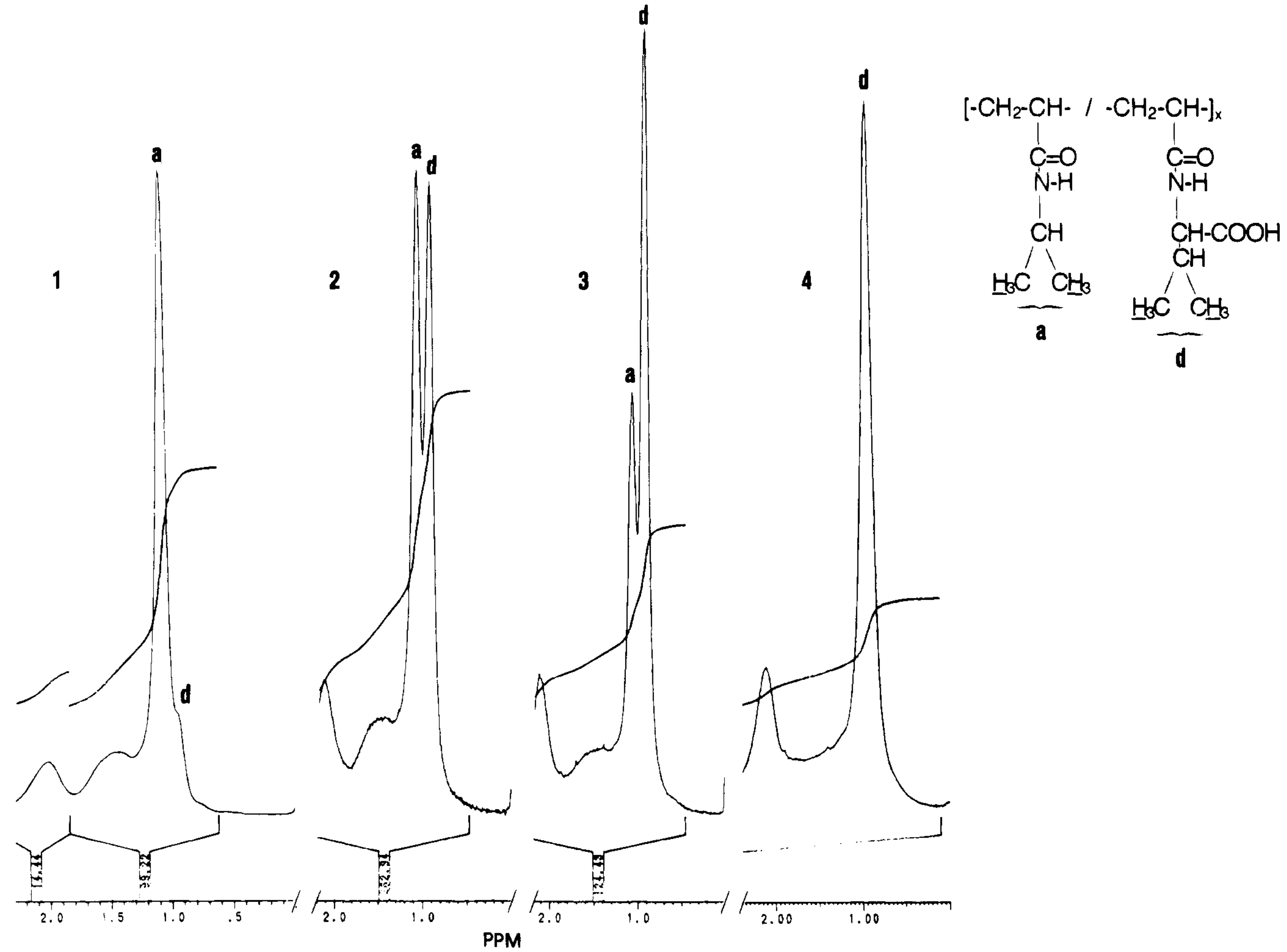


Figure 2. Proton NMR spectra (in DMSO-d_6) in the range of methyl resonances for copolymers made of *N*-isopropylacrylamide (NIPAAm, a) and *N*-acryloyl-L-valine (AVA, d) at different AVA/NIPAAm molar ratios: 1/10 (1); 1/1 (2); 2/1 (3); poly(*N*-acryloyl-L-valine) (4).

the polymer when checked by infrared and NMR spectra. The latter showed broad lines for backbone and side-chain resonances, consistent with the presence of a slowly tumbling macromolecular species in solution.

A series of copolymers were obtained with different comonomer (NIPAAm/acidic monomer) compositions. Unlike for the methacrylate, the acid–base titrations of the acrylate analogue indicated good agreement between the quantity of carboxyl groups in the copolymer and feed compositions. These results suggest that the comonomer feed ratios reflected the relative comonomer incorporation levels when a similar structure of acrylic nature was considered. For the two acrylate monomers (NIPAAm and AVA), radical polymerization probably obeys Bernouillian statistics, forming copolymers with a random distribution of carboxyl groups along the chain.[32] Figure 2 shows the ^{1}H NMR spectra of a series of copolymers with different AVA incorporation. The proton resonances of the methyl groups in NIPAAm, falling to higher magnetic field, recognized the relative comonomer content. Although a similar pattern was revealed for compounds incorporating *N*-methacryloyl-L-valine units in copolymers, the acid–base titrations showed a slightly larger quantity of carboxyl groups, probably due to the different monomer reactivity ratios of the radicals.

Thermodynamics of Protonation

Homopolymers. The protonation behavior of poly(*N*-methacryloyl-L-valine) (polymer C) was studied at 25 °C in 0.1 M NaCl. Its polyelectrolyte behavior was quite similar to that observed for polymer A. In both cases the basicity constants (log *K*) decreased linearly during protonation of the COO^- group, reaching the same critical degree of protonation ($\alpha = 0.7$), where log K/α slopes drastically changed (Figure 3). Before this critical α value, log K (Table 1) obeyed the modified Henderson–Hasselbalch equation:[33]

$$\log K = \log K^\circ + (n - 1) \log[(1 - \alpha)/\alpha] \qquad (1)$$

Compared to polymer A, the lower *n* value of polymer C was ascribed to greater hydrophobic character due to the methyl group on the main chain. This was in agreement with the behavior already reported for other classes of vinyl polymers.[17] The log K° value of polymer C was lower than that of A due to the inductive effect. The additional methylene group, inserted in the side chain of the polymer containing the L-leucine residues (polymer B), produced a subtle change in the log K/α slope at lower α values ($\alpha = 0.3$). It was evident that the conformational changes were mainly determined by the nature of the α-amino acid residues. For the polymers considered, calorimetric titration data revealed increasing endothermicity as the degree of protonation approached the critical α value, beyond which a strong endothermic peak was superimposed on the protonation of the COO^- group (Figure 3). The endothermic jump, larger in polymer C due to its more hydrophobic character, was ascribed to hydrophobic

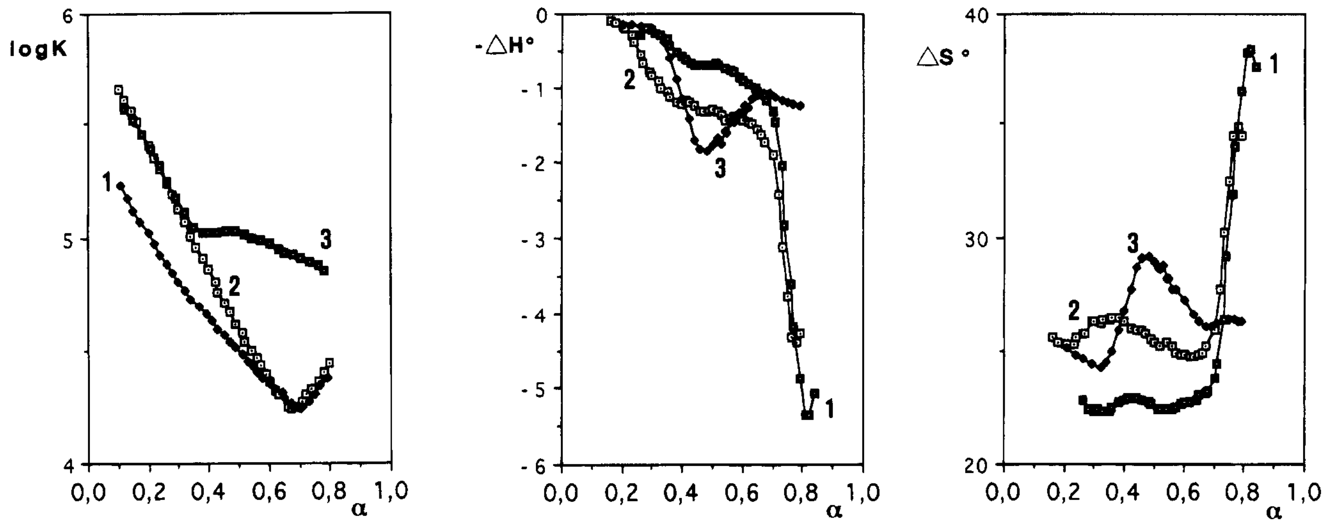


Figure 3. Basicity constants (log *K*), enthalpy ($-\Delta H°$, kcal mol^{-1}), and entropy ($\Delta S°$, cal mol^{-1} K^{-1}) changes for the protonation of COO$^-$ groups in poly(*N*-methacryloyl-L-valine) (1), poly(*N*-acryloyl-L-valine) (2) and poly(*N*-acryloyl-L-leucine) (3) in relation to the degree of protonation α at 25 °C in 0.1 M NaCl.

Table 1. Henderson–Hasselbalch Parameters for Polymers and Copolymers in 0.1 M NaCl at Different Temperatures

compd	temp/°C	α-range	log $K°$ [a]	n[a]
A[b]	25	0.10–0.66	4.59	2.26
	30	0.10–0.67	4.82	2.28
	35	0.11–0.66	4.80	2.39
A_1	25	0.10–0.61	4.44	1.93
A_2	25	0.10–0.57	4.27	1.84
A_3	25	0.11–0.57	3.83	1.14
C	25	0.11–0.70	4.50	1.82
	30	0.11–0.68	4.49	1.86
	35	0.10–0.66	4.50	1.81
B	25	0.11–0.34	4.86	1.96

[a] $\log K = \log K° + (n-1)\log[(1-\alpha)/\alpha]$. [b] A: poly(*N*-acryloyl-L-valine). A_1: copolymer with 75 wt % AVA. A_2: copolymer with 62 wt % AVA. A_3: copolymer with 12 wt % AVA. B: poly(*N*-acryloyl-L-leucine). C: poly(*N*-methacryloyl-L-valine).

forces between isopropyl groups outweighing the repulsive electrostatic interactions of the partially ionized polymer in more extended conformation. A different calorimetric pattern was revealed for the protonation of polymer B. A smaller endothermic jump (Figure 3) occurred at lower α values, suggesting different conformational behavior on uptake of protons. Subtle changes in macromolecular coiling were revealed by viscometric titration data. Figure 4 shows reduced viscosity (η/C) in relation to α for polymers B and C. The ionized macromolecule coiled slowly at lower α, due to reduced electrostatic interactions between charged carboxylate groups. As the critical α value was approached, a sharp drop in viscosity was observed. The whole protonation process was entropy-driven, because water molecules were released from the carboxylate anion being protonated and the hydrophobic groups. Clustering of the latter above the critical α value, suddenly increased $\Delta S°$ (Figure 3) due to a destroying water layer surrounding the whole macromolecule. In polymers A and C, electrostatic forces were competitive with hydrophobic forces, the latter predominating above the critical value of α when the macromolecule shrank into a compact, tightly coiled conformation. The hydrophobic groups clustered in microdomains, the COO$^-$ groups coming closer together to increase the free-energy terms and thus the log K/α slopes (Figure 3). A cloudy solution was observed when cohesive interactions predominated under conditions of almost complete neutralization of the charged groups on the polymer.[1,34]

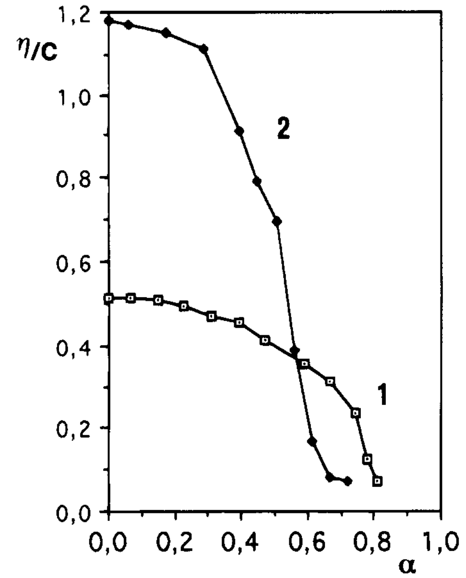


Figure 4. Reduced viscosity (η/C, dL g^{-1}) in relation to α for the protonation of poly(*N*-methacryloyl-L-valine) (1) and poly(*N*-acryloyl-L-leucine) (2) at 25 °C in 0.1 M NaCl.

Poly(NIPAAm-*co*-AVA). As stated above, PNIPAAm is a water-soluble polymer below its LCST (32 °C), behaving like a flexible chain. Thermal behavior is only attributed to its hydrated structure.[35] Thus, copolymers with NIPAAm are expected to be temperature-dependent only above the LCST, due among other factors to the presence of charges.[25] Figure 5 shows the thermodynamic data obtained at 25 °C for a series of copolymers with NIPAAm at different AVA contents. As revealed by log *K* in relation to α, the low AVA content in copolymers reflected lower electrostatic effects. In all cases, before the critical α value, the linear decrease in log *K* agreed well with eq 1 (Table 1). When the copolymer contains small numbers of charged units, the trend of log *K* versus α becomes lower and flatter. This can be attributed to randomly charged COO$^-$ groups distributed along the macromolecular chain. These groups induce low electrostatic interaction and low cooperation between monomer units. The NIPAAm units shield charges, decreasing the polyelectrolyte

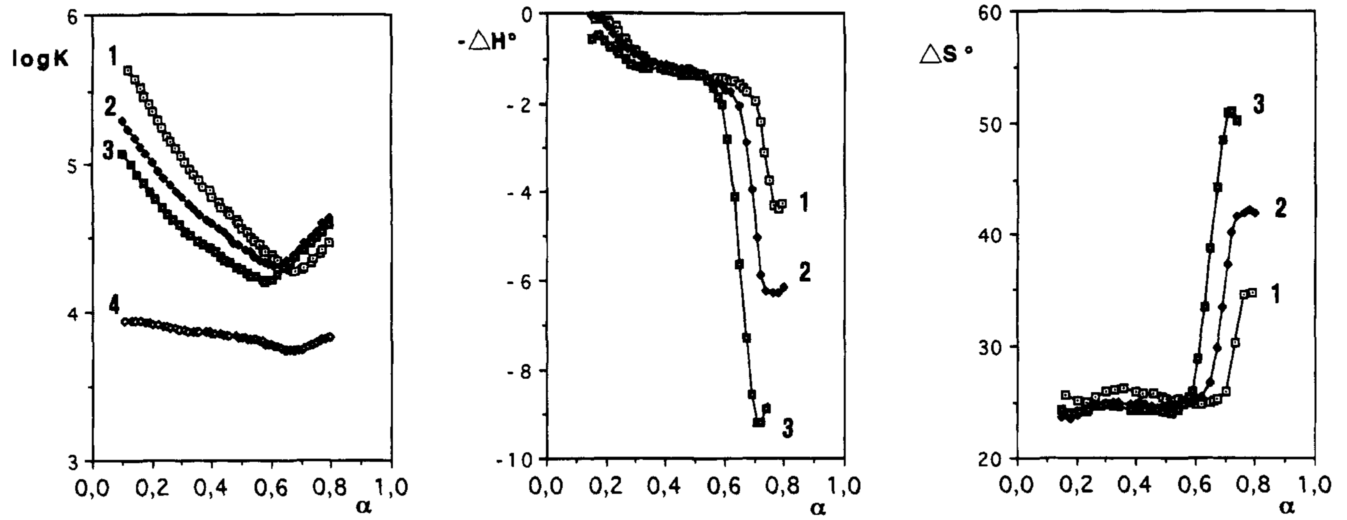


Figure 5. Basicity constants (log K), enthalpy ($-\Delta H°$, kcal mol^{-1}), and entropy ($\Delta S°$, cal mol^{-1} K^{-1}) changes in relation to α for the protonation of COO$^-$ groups in copolymers made of NIPAAm and AVA with different wt % of AVA: 100% (1); 75% (2); 62% (3); 12% (4), at 25 °C in 0.1 M NaCl.

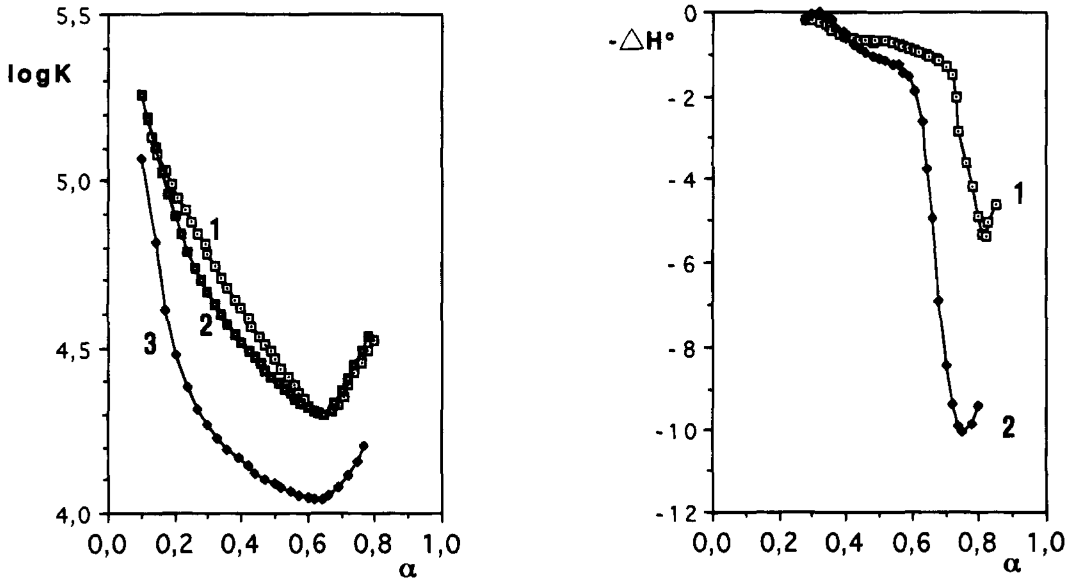


Figure 6. Basicity constants (log K) and enthalpy ($-\Delta H°$, kcal mol^{-1}) changes in relation to α for the protonation of COO$^-$ groups in copolymers made of NIPAAm and N-methacryloyl-L-valine (MAVA) with different wt % of MAVA: 100% (1); 63% (2); 14% (3), at 25 °C in 0.1 M NaCl.

effect (n of eq 1).[33] Calorimetric data (Figure 5) showed the hydrophobic interaction phenomenon with a sharp endothermic peak above the critical α value. In the series of copolymers, the close enthalpy changes for the protonation of COO$^-$ were slightly endothermic. As α approached the critical value, endothermicity was stronger and became larger with increasing NIPAAm content.[27] These results show that the protonation process is entropy-driven and based on a critical balance between hydrophobic and electrostatic forces. As in the case of free polymers, strong hydrogen bonding between amide groups and surrounding water molecules triggers the formation of a layer of highly organized water around the polymer chain.[26,36,37] At critical α values the layer is destroyed and water molecules are liberated, sharply increasing entropy (Figure 5). These results show the protonation behavior of copolymers obtained with monomers of close acrylic structure.

Poly(NIPAAm-*co*-MAVA). The copolymer of the acrylate NIPAAm and the methacrylate MAVA, gave a log K/α plot that was substantially different from the previous case. Figure 6 shows the trend of log K in relation to α for the protonation of COO$^-$ groups in a series of copolymers. Electrostatic effects predominated at low α, and the log K values were close to those of the homopolymer. This is probably related to copolymer microstructure, i.e., to a random or blocky distribution of the charged units.[38] The further increase in α decreased log K for electrostatic reasons in the copolymer with the lowest amount of MAVA. As in copolymers with AVA, a critical α value was reached during the protonation of COO$^-$ groups in copolymers with MAVA. This was always attributed to collapse of the macromolecular coil, forcing the isopropyl groups in the side chain of both comonomers into close contact. Micelle-like behavior is induced by hydrophobic forces which bring the polar COO$^-$ groups close together, making protonation easier.[19] Calorimetric data (Figure 6) revealed the same pattern as above, with the methyl group on the backbone chain imparting a slight increase in endothermicity due to its more hydrophobic character.

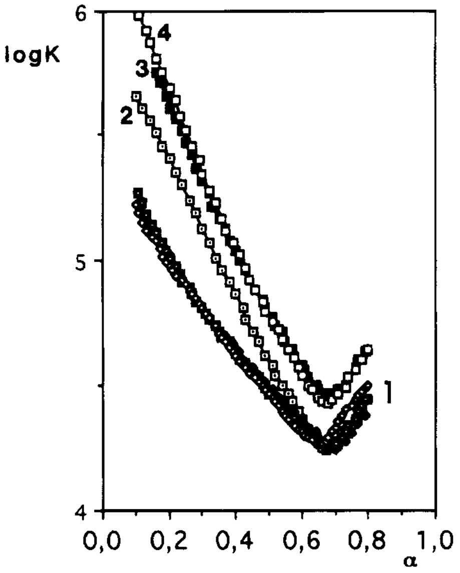


Figure 7. Basicity constants (log K) in relation to α at different temperatures for poly(N-methacryloyl-L-valine) (1: 25, 30, and 35 °C) and poly(N-acryloyl-L-valine) (2, 25 °C; 3, 30 °C; 4, 35 °C), in 0.1 M NaCl.

Effect of Temperature. Both polymers containing the L-valine residues (A and C) and the corresponding copolymers with NIPAAm, were studied at higher temperatures (30 and 35 °C) and constant ionic strength (0.1 M NaCl). The log K/α pattern of polymer A showed a small shift to higher basicities of COO^- groups at 30 °C that overlapped the trend at 35 °C (Figure 7). Unlike in polymer C, the increased log K values at 30 °C and above were due to the lower hydration of polymer A and its increased hydrophobicity. This particular trend also occurred for the corresponding copolymers. A temperature increase to 30 °C led to increased log K values for copolymers containing the AVA comonomer (Figure 8). The general phenomenon was ascribed to a decreased dielectric constant in the polymer environment, and thus to decreased ionization of the COOH groups.[25,39,40] In all copolymers, however, the critical α values shifted to lower values as the temperature rose (Figures 8 and 9). This general trend was correlated with the LCST phenomenon and was ascribed to hydrophobic forces that first predominated on the electrostatic repulsion of charged groups, because there is less structured water around more hydrophobic polymers. Calorimetric titration data (Figure 8) revealed that less water was bound to the polymer when protonation occurred at 30 °C or more.[41]

Conclusions

The results of this thermodynamic study contribute to the understanding of the temperature-induced phase separation mechanisms of charged polymers showing the LCST phenomenon.[25] Examples of polymers having multiple stimuli-response characteristics are given. Unlike uncharged PNIPAAm, vinyl polymers containing the carboxyl group together with amido and isopropyl groups may develop mutual temperature- and pH-sensitivity. Polymers with specific stimuli-induced swelling transitions may be of interest in designing gels[6,16,25] or systems for the purification and separation of substances.[1,15,28]

The protonation thermodynamics of homopolymers and copolymers with NIPAAm showed that hydrophobic and electrostatic forces competed at a critical degree of protonation α. During the protonation process the polymer gradually coiled due to the lower electrostatic interaction of the COO^- groups. When a critical α value was reached, hydrophobic forces between isopropyl groups outweighed the repulsive electrostatic interactions. Abrupt collapse of the macromolecular coil was revealed by low reduced viscosity and higher endothermicity. The latter increased with the content of NIPAAm units in copolymers, confirming that the thermosensitivity of PNIPAAm is most peculiar[22,36,37,39] because it contains amido and isopropyl groups at a suitable distance to balance the hydrophobic–hydrophilic quality in a critical manner. More water molecules were structured around hydrophobic isopropyl moieties, enhanced by the presence of NIPAAm units, and were thus released in great numbers under particular environmental conditions, i.e. above the critical α value. The effect of temperature was to decrease the enthalpy and entropy contribution and suggested that the process is entropy-driven by virtue of the few water molecules liberated at higher temperatures, due to LCST behavior.

Experimental Section

Spectroscopic Measurements. A Bruker AC200 spectrometer was used to record the proton NMR spectra of monomers and polymers (about 20 mg) dissolved in deuterated dimethyl sulfoxide (0.5 mL) using tetramethylsilane as the internal reference. Infrared spectra in the range 4000–600 cm^{-1} were recorded in KBr pellets and Nujol.

Viscometric Measurements. Viscometric titration data were obtained with an AVS 310 automatic Schott-Gerate viscometer at 25 °C. Polymer solutions were freshly prepared by dissolving a weighed amount of solid material (about 50 mg) in 25 mL of 0.1 M NaCl containing a known amount of standard sodium hydroxide solution. Standard hydrochloric acid solution (0.1 M), delivered by a Metrohm Multidosimat piston buret, was used as titrant in the stepwise neutralization of the charged polymer. The titration was blocked when the solution became cloudy. The FITH program[33] was used to calculate α from the log K values. The intrinsic viscosity was obtained at 30 °C using a similar polymer concentration in DMF.

Potentiometric Measurements. Potentiometric titrations were carried out in aqueous solution at different temperatures (25, 30, and 35 °C), following a previously described procedure.[33] A digital PHM-84 Radiometer potentiometer, equipped with a glass (Ross, model 81-01) and a reference electrode (Ross, model 80-05) and connected to an Olivetti M20 computer together with a Metrohm Multidosimat piston burette, was used for titration experiments. For each experiment the glass cell, thermostated to the desired temperature, was filled with about 100 mL of 0.1 M NaCl in which a weighed amount of solid material (monomer, about 60 mg; polymer, about 60 mg; copolymer, 60–120 mg depending on the carboxyl group content) and a known amount of standard sodium hydroxide solution were dispersed by magnetic stirring. A presaturated nitrogen stream was maintained over the surface of the solution to avoid carbon dioxide contamination. All titrations were made with standard 0.1 M HCl solution and the data (voltage, mV; volume of added titrant, mL) were contemporaneously printed and stored on disk for further processing. The end point of the potentiometric titration curve was taken to calculate the excess of sodium hydroxide equivalents. The difference between the initial amount and the equivalents of hydroxide ions was attributed to the carboxyl proton equivalent of the polymer and copolymer. Calibrations were performed (with Tris) before and after each titration to determine the reference $E°$ potential and the titrant concentration of each run. The basicity constants of polymers and copolymers were computed with the APPARK program.[33]

Calorimetric Measurements. Calorimetric titrations were performed according to a previously described method with a Tronac calorimeter (model 1250) in the isothermal

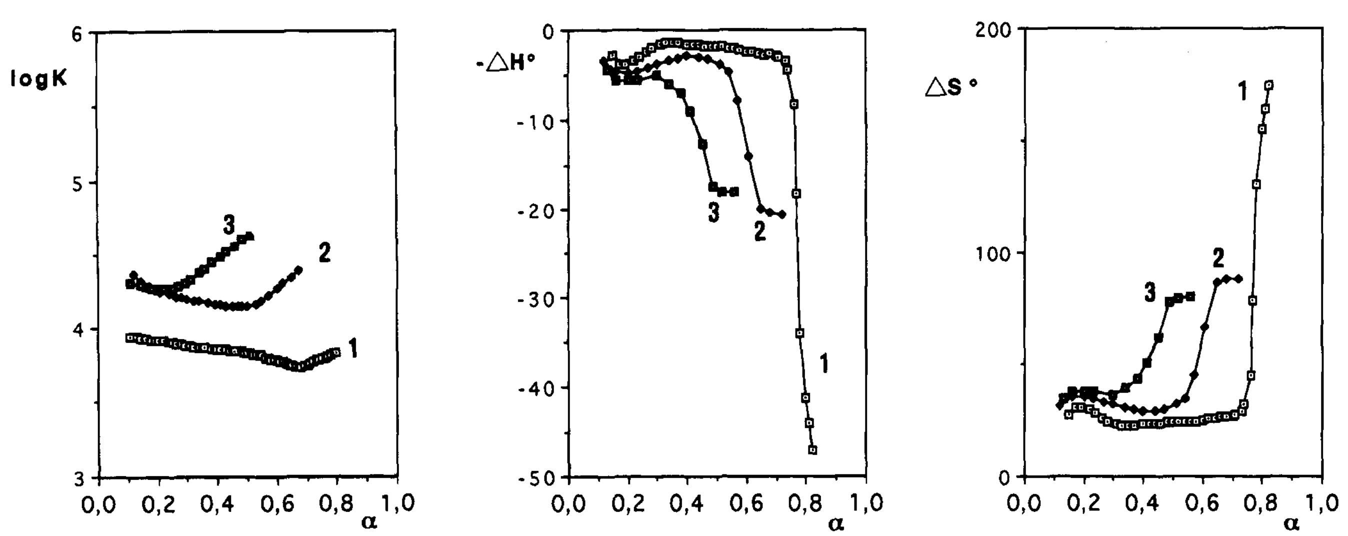


Figure 8. Basicity constants (log K), enthalpy ($-\Delta H°$, kcal mol^{-1}), and entropy ($\Delta S°$, cal mol^{-1} K^{-1}) changes in relation to α for the protonation of COO^- groups in the copolymer made of NIPAAm and AVA (AVA content: 12 wt %) in 0.1 M NaCl at different temperatures (°C): 25 (1); 30 (2); 35 (3).

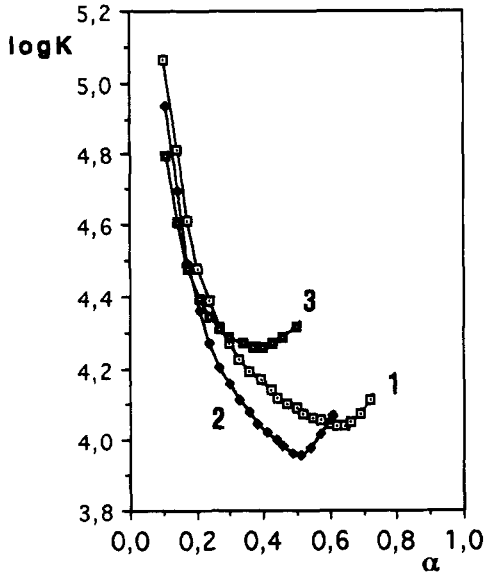


Figure 9. Basicity constants (log K) in relation to α for the protonation of COO^- groups in the copolymer made of NIPAAm and MAVA (MAVA content: 14 wt %) in 0.1 M NaCl at different temperatures (°C): 25 (1); 30 (2); 35 (3).

mode, using a stainless-steel reaction vessel of 25-mL capacity.[33] The water bath was thermostated to the desired temperature (25, 30, and 35 °C) by means of a precision temperature controller (PTC 40, from Tronac Inc). The aqueous solution (0.1 M NaCl), containing a weighed amount of polymer (about 50 mg) or copolymer (about 60−120 mg, depending on the content of carboxyl groups) and a measured volume of standard sodium hydroxide, was titrated with standard 0.1 M HCl solution with a constant burette delivery rate of 0.1000 mL min^{-1} through a Gilmont burette. Calibration of the instrument and corrections for the heats of dilution of the titrant were made before each titration experiment. All the experiments were automatically controlled by a North Star CCP 930 computer, running the Thermal program, and the titration data (heat, cal; volume of added titrant, mL) were stored on disk. The enthalpy change values were evaluated with the FITH program on the Olivetti M24 computer,[33] and the $\Delta S°$ values were calculated by means of the equation $\Delta S° = (\Delta H° - \Delta G°)/T$.

Synthesis of Monomers. *N*-Methacryloyl-L-valine (MAVA) was obtained by the general procedure used to introduce the vinyl group[29,30] in other monomers. A mixture of 11.7 g (0.1 mol) of L-valine (from Aldrich), 40 mL of double-distilled water, and 8.0 g (0.2 mol) of sodium hydroxide pellets (from Aldrich) were stirred with an external ice bath. To this solution was added 10.5 g (0.1 mol) of freshly distilled methacryloyl chloride (from Aldrich) dropwise over a 30-min period. The reaction mixture was stirred for 30 min more, and then concentrated hydrochloric acid (0.1 mol) was added dropwise to reach a low pH, whereupon a voluminous white precipitate formed on standing. The viscous solid was removed by filtration and washed with water. The product was crystallized from benzene to give about 10 g of white crystals. Anal. Calcd for $C_9H_{15}NO_3{\cdot}0.25H_2O$: C, 56.98; H, 8.23; N, 7.38. Found: C, 56.83; H, 7.89; N, 7.24. The infrared and ^{1}H NMR (in DMSO-d_6) spectra, together with the potentiometric purity, showed that the product was of analytical grade.

Synthesis of Polymers. Polymers were obtained by radical polymerization of the monomers initiated by azobis(isobutyronitrile) (AIBN), as previously reported.[1,14] Poly(*N*-methacryloyl-L-valine) was obtained as follows. To a solution of 2.1 g of MAVA in 50 mL of benzene was added 15 mg of recrystallized AIBN. The mixture was purged with nitrogen and allowed to stand in a thermostated oil bath at 60 °C for 24 h. The polymer precipitated out and was filtered and washed with fresh benzene. The compound recovered was brown and viscous. It was washed with petroleum ether (from Fluka) and vacuum dried to give 1.76 g of white powder (85% yield). The intrinsic viscosity was 0.92 dL/g in DMF at 30 °C. Anal. Calcd for $C_9H_{15}NO_3{\cdot}0.75H_2O$: C, 53.96; H, 8.37; N, 7.05. Found: C, 54.39; H, 8.55; N, 6.94. The spectroscopic data (IR and ^{1}H NMR in DMSO-d_6) was consistent with the proposed structure. The potentiometric purity was higher than 95 wt %.

Synthesis of Copolymers. Copolymers of *N*-acryloyl-L-valine (AVA) and *N*-methacryloyl-L-valine (MAVA) with NIPAAm (from Eastman Kodak) were obtained in dioxane or benzene solutions, respectively. Radical polymerization was initiated by AIBN at 60 °C for 20 h after degassing and purging the monomer solution with nitrogen. Different molar ratios of comonomers were used, and the experimental details are reported in Table 2.

Copolymers A_1 and A_3 were precipitated from their solutions with ethyl ether, while compound A_2 was precipitated in double-distilled water. In all cases a fine white powder was obtained. Copolymers C_1 and C_2 both formed a voluminous gel-like solid in the reactor. They were first washed with fresh benzene (three times) and then with petroleum ether to a give a dry white powder.

The acid−base titration of the carboxyl groups, in conjunction with elemental analysis and IR and ^{1}H NMR (DMSO-d_6) spectra, was consistent with the molar ratios of comonomers in the feed composition.

Table 2. Feed Compositions for the Copolymerization of NIPAAm with Vinyl Monomers

	amt of NIPAAm[a]		amt of AVA[b]		amt of MAVA[c]					
compd	g	mol	g	mol	g	mol	amt of AIBN/mg	vol/mL	yield/g	COOH groups content[d]/wt %
A_1	0.285	0.0025	0.86	0.005			11.5	10	1.02	75
A_2	0.285	0.0025	0.43	0.0025			7.2	10	0.60	62
A_3	1.130	0.010	0.17	0.001			13.0	10	1.20	12
C_1	0.640	0.006			1.08	0.006	20.0	30	1.56	63
C_2	3.180	0.030			0.53	0.003	40.0	30	3.50	14

[a] Dissolved in 9 mL of dioxane for compounds with AVA and 15 mL of benzene for compounds with MAVA. [b] Dissolved in 1 mL of double-distilled water. [c] Dissolved in 15 mL of benzene. [d] From the acid–base titration.

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