Dual Stimuli-Responsive Polyamines Derived from Modified *N*-Vinylpyrrolidones Through CuAAC Click Chemistry

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ABSTRACT: The synthesis via copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) of three new monomer derivatives of *N*-vinyl-2-pyrrolidone (VP) carrying cyclic pyrrolidine, piperidine, and piperazine groups and the corresponding copolymers with unmodified VP is shown. The systems bearing pyrrolidine and piperidine displayed both thermo- and pH-response, which has not been reported previously for a polymer with polyvinylpyrrolidone (PVP) backbone. A broad modulation of the LCST with the copolymer composition and pH was observed in a temperature range 0–100 °C. The polymers carrying piperazine exhibited broad buffering regions and no thermosensitivity. © 2015 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2016**, *54*, 1098–1108

KEYWORDS: functionalization of polymers; polyamines; radical polymerization; stimuli-sensitive polymers; synthesis; thermal properties

INTRODUCTION Polyvinylpyrrolidone (PVP) is one of the most frequently used polymers due to its native properties (non-toxic, neutral, biocompatible, good solubility in water as well as in many organic solvents) that make it suitable for use in many biomedical and technical fields, either as coating,[1] surfactant,[2,3] stabilizer (E1201), as clarifying agent in drinks and support in tablets (it has been approved as food additive by the FDA), as antifouling material,[4–6] and so forth.

Modification of PVP has been pursued for the purpose of adding functional groups to its conventional form, trying to maintain its excellent properties. A commonly reported strategy for its functionalization is the copolymerization of the VP monomer with other monomers carrying a functional groups, obtaining a functionalized copolymer of VP.[7,8] However, VP belongs to a group of "less-activated" monomers, whose reactivity in radical polymerization is lower than that of typical commercial monomers such as acrylates, methacrylates, and styrenes. Therefore, besides losing the PVP backbone in the copolymers of VP with those monomeric families, materials which are structurally heterogeneous[9] are obtained what inevitably interferes in the final properties. Lately, numerous studies have been focused on the functionalization of PVP maintaining its backbone, using VP monomer modified with functional groups in the lactam ring. Among these functional groups like ester and amide groups,[10] alcohols and thiols,[11] alkyl groups,[12] and even cyclodextrins[13] can be pointed out. Recently, PVPs carrying primary amines were synthesized in our group and used as precursor for other derivatizations due to the high reactivity of the amine group.[14]

One interesting feature that may be accomplished by incorporating appropriate structures to polymeric VP-derivatives is the stimuli-responsiveness in aqueous media, that is, the preparation of smart PVP polymers. "Smart polymers," which have received much attention in recent years, are polymers that respond with dramatic property changes to variations of the environment triggering changes in their structural organization and morphology. When temperature is the stimulus, a water-soluble polymer (such as the well-known poly(*N*-isopropylacrylamide) PNIPAAm) undergoes a phase transition as a response to a temperature change. The most common thermosensitivity is the lower critical solution temperature phenomenon (LCST), which is the case when the inter and intramolecular interactions between soluble polymer chains increase above a critical temperature, leading to the non-solubility of the polymer and its subsequent precipitation.[15]

A particular and very interesting type of aqueous thermosensitivity is the case where the system is additionally sensitive

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to pH, that is, a scenario of double responsiveness where temperature and/or pH changes induce a change in the polymer microstructure. Although this may be obtained by copolymerization of thermosensitive units (like NIPAAm) and ionizable units (such as acrylic, methacrylic acids, or amine derivatives),[16–21] there is a type of structure that provides simultaneously both types of sensitivity: pendant aliphatic ionizable tertiary amines such as those included in poly(*N,N*-diethylaminoethyl methacrylate), poly-DEAEM,[22] poly(*N,N*-dimethylaminoethyl methacrylate), poly-DMAEM,[23] or poly(ethylpyrrolidine methacrylate), poly-EPyM.[24] As an example, Poly-DEAEM has LCST values around 40 °C at pH 7.[22–26]

Polymeric VP-derivatives showing LCST have been actually prepared by copolymerization of VP with thermosensitive units.[27–29] In addition, and pursuing the desire of maintaining the PVP backbone as mentioned above, some PVP systems with thermosensitive properties have been synthesized from native VP monomer and different alkylated VP monomers.[30,31] However, and to the best of our knowledge, no smart PVP polymers showing dual stimuli-response in aqueous media, to temperature and pH, has yet been reported. In this work, *N*-vinylpyrrolidone monomers modified with several cyclic aliphatic amines (pyrrolidine, piperidine, and piperazine) have been synthesized and copolymerized with pure VP, obtaining different aminated polymers—some of them showing dual sensitivity—with a true PVP backbone. VP monomers with amine groups were synthesized by copper(I)-catalyzed azide alkyne cycloaddition (CuAAC). Homopolymers and copolymers with unmodified VP have been prepared by conventional free radical polymerization. The sensitivity of these new polymers to pH and temperature has been studied.

EXPERIMENTAL

Materials

1-Vinyl-2-pyrrolidone (Sigma–Aldrich) was distilled under reduced pressure before use. 2,2′-Azobis(isobutyronitrile) (AIBN) 98% (Sigma–Aldrich) was used after recrystallization in methanol. Di-*tert*-butyldicarbonate 97% (Aefa Aesar) and Copper(II) sulfate pentahydrate 98.5% (Quimicen) were used as received. All other chemicals were purchased in Sigma–Aldrich and used as received.

Synthesis of VP Derivatives

1-(2-Azidoethyl)pyrrolidine (N_3-Pl) (1) and 1-(2-Azidoethyl)piperidine (N_3-Pp) (2)

Five grams of the hydrochloride salt (1 equiv.) was dissolved in deionized water (140 mL). Then, sodium azide (2 equiv.) was added and the solution was warmed up to 70 °C under magnetic stirring. After 5 h, the solution was cooled down using an ice bath and KOH (1.1 equiv.) was slowly added to the mixture. Finally, 150 mL of diethylether was added to the reaction mixture and the aqueous layer was extract twice with diethylether (2 × 100 mL). The organic layers were combined and dried over anhydrous sodium sulfate. For security reasons, the products were never completely dried but some THF was added before removing the diethylether under reduced pressure. Assuming a 100% yield, a 0.7 M THF solution was prepared for the next reaction (see Scheme 1)

N_3-pl. FTIR (cm^{-1}): 2964, 2876, 2789, 2095, 1459, 1442, 1349, 1278, 1150, 1056, 955, 861.

N_3-pp. FTIR (cm^{-1}): 2936, 2856, 2801, 2094, 1469, 1456, 1442, 1377, 1351, 1302, 1277, 1157, 1123, 1040, 931, 862, 758.

Tert-*Butyl 4-(2-Hydroxyethyl)piperazine-1-Carboxylate (HO-pz-Boc) (3)*

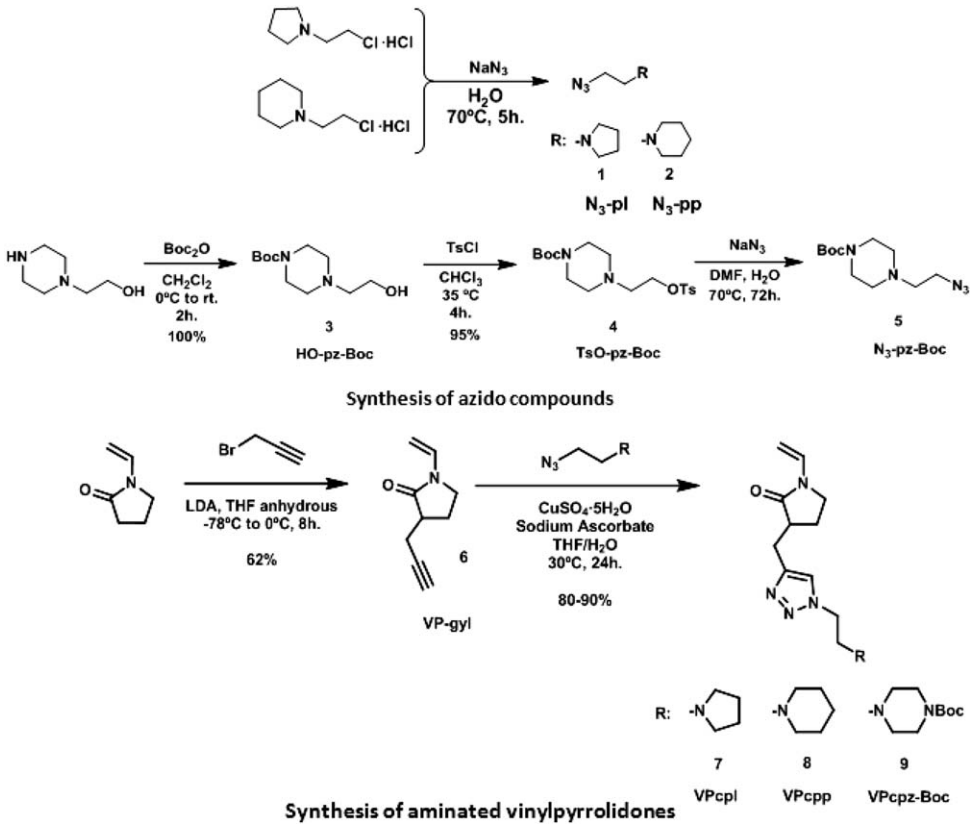
Di-*tert*-butyldicarbonate (10.9 mL, 46.09 mmol) was dissolved in 35 mL of CH_2Cl_2 and added dropwise to a solution of 5 g of 1-(2-hydroxyethyl)piperazine (5 g, 38.40 mmol) in dichloromethane (50 mL). During the addition, the reaction mixture was maintained at 0 °C and, then, was allowed to warm up to room temperature. After 2 h, saturated NH_4Cl solution was used to quench the reaction (30 mL). The organic layer was separated and the aqueous one was extracted with CH_2Cl_2 (2 × 40 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The white residue was purified by column chromatography using silica gel as stationary phase and hexane/ethyl acetate (3:1) as eluent to yield a white solid. Yield: 100%.

^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 3.60$ (t, 2H, HO-CH_2, $J = 5.6$ Hz), 3.40 (t, 4H, CH_2-CH$_2$-NCOOtBu-CH$_2$-CH_2, $J = 5.2$ Hz), 2.83 (s, 1H, -O*H*), 2.51 (t, 2H, HO-CH$_2$-CH_2, $J = 5.6$ Hz), (t, 4H, CH_2-NCOOtBu-CH_2, $J = 5.2$ Hz), 1.24, (s, 9H, NCOOtBu). ^{13}C RMN ($CDCl_3$, 100 MHz): $\delta = 154.76$ (N*C*OOtBu), 79.78 (HO-*C*H$_2$), 77.36 (NCOO*C*(CH$_3$)$_3$), 59.56 (*C*H$_2$-CH$_2$-NCOOtBu-CH$_2$-*C*H$_2$), 57.86 (HO-CH$_2$-*C*H$_2$), 52.82 (*C*H$_2$-NCOOtBu-*C*H$_2$), 28.48 (NCOOC(*C*H$_3$)$_3$). FTIR (cm^{-1}): 3437, 2975, 2933, 2864, 2811, 1692, 1457, 1419, 1365, 1290, 1244, 1167, 1126, 1077, 1054, 1003, 926, 865, 768.

Tert-*Butyl 4-(2-((Tosyloxy)ethyl)piperazine-1-Carboxylate (TsO-pz-Boc) (4)*

HO-pz-Boc (3.3 g, 14.33 mmol) was dissolved in 30 mL of CH_2Cl_2 and cooled using an ice bath. A solution of *p*-toluenesulfonyl chloride (2.79 g, 14.33 mmol) in 20 mL of CH_2Cl_2 was slowly added and the mixture was allowed to warm up to 35 °C under magnetic stirring. After 4 h, the reaction mixture was diluted with 10 mL CH_2Cl_2 and washed with 10 mL of a saturated aqueous solution of $NaHCO_3$ (three times). The organic layers were collected and dried over anhydrous sodium sulfate. The solid was removed by filtration and the solvent was evaporated under reduced pressure to yield a pale yellow solid. Yield: 95%.

^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.95$ (d, 2H, Ar-*H*, $J = 8.4$ Hz), 7.40 (d, 2H, Ar-*H*, $J = 8.40$ Hz), 3.66 (t, 2H, O-CH_2, $J = 5.2$ Hz), 3.47 (t, 4H, CH_2-CH$_2$-NCOOtBu-CH$_2$-CH_2, $J = 4.8$ Hz), 2.62 (t, 2H, O-CH$_2$-CH_2, $J = 5.2$ Hz), 2.53 (t, 4H, CH_2-NCOOtBu-CH_2, $J = 4.8$ Hz), 2.48 (s, 3H, CH_3-Ar), 1.45 (s, 9H, NCOOtBu). ^{13}C RMN ($CDCl_3$, 100 MHz): $\delta = 154.79$



SCHEME 1 Synthesis of aminated azido compounds (above) and its vinylpyrrolidone derivatives using CuAAC chemistry (below).

(N*C*OOtBu), 147.01, 141.85, 130.44, 127.25, 80.15 (HO-*C*H_2), 77.45 (NCOO*C*(CH_3)$_3$), 59.69 (*C*H_2-CH_2-NCOOtBu-CH_2-*C*H_2), 57.71 (HO-CH_2-*C*H_2), 52.96 (*C*H_2-NCOOtBu-*C*H_2), 28.60 (NCOOC(*C*H_3)$_3$), 22.04 (*C*H_3). FTIR (cm^{-1}): 3415, 2978, 2933, 2869, 2815, 1690, 1594, 1457, 1419, 1366, 1290, 1245, 1189, 1172, 1127, 1081, 1055, 1034, 1004, 926, 865, 813, 769, 699, 653.

Tert-*Butyl 4-(2-Azidoethyl)piperazine-1-Carboxylate (N$_3$-pz-Boc) (5)*

TsO-pz-Boc (3.7 g, 9.73 mmol) was dissolved in 50 mL of DMF. Then, sodium azide (1.26 g, 19.46 mmol) was dissolved in 10 mL of H_2O and added to the reaction mixture, that was warmed up to 70 °C under magnetic stirring. After 72 h, the solution was cooled down with an ice bath, and KOH (1.20 g, 20 mmol) dissolved in 20 mL of water was slowly added to the mixture. Finally, the reaction mixture was added to 100 mL of CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The same security protocol as in the preparation of N_3pl and N_3pp was used. Assuming 100% yield, a 0.1 g/mL THF solution was prepared for the next reaction.

FTIR (cm^{-1}): 2978, 2933, 2814, 2099, 1692, 1457, 1416, 1365, 1281, 1241, 1167, 1126, 1004, 931, 866, 769.

3-Propargyl-*N*-vinyl-2-Pyrrolidone (VP-Gyl) (6)

Diisopropylamine (7 mL, 50 mmol) was added at −78 °C to a solution of butyllithium (17.3 mL, 43 mmol) in 80 mL of anhydrous THF. The mixture was warmed up to 0 °C under stirring for 10 min and was cooled back to −78 °C. VP (5 mL, 43 mmol) was dropwise added to this solution and was kept at −78 °C for 1 h. Then, propargyl bromide (4.8 mL, 43 mmol) was added to the solution, and the mixture was slowly warmed up to 0 °C and stirred during 5 h. Finally, the resulting yellow solution was quenched with water (40 mL). Dichloromethane (30 mL) was added and the organic layer was separated. The aqueous layer was then extracted three times with dichloromethane (30 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The solid was removed by simple filtration and the solvent was evaporated under reduced pressure. The yellow residue was purified by column chromatography using silica gel as stationary phase and hexane/ethyl acetate (5:1) as eluent to yield colorless oil. Yield: 62%.

^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.08$ (dd, 1H, N-C*H*=CH_2, $J = 16.0$ and 9.0 Hz), 4.46 (d, 1H, *cis* N-CH=CH*H*, $J = 9.0$ Hz), 4.42 (d, 1H, *trans* N-CH=C*H*H, $J = 16.0$ Hz), 3.56 (td, 1H, CO-N-C*H*H, $J = 10.0$ and 3.0 Hz), 3.41 (dt, 1H, CO-N-CH*H*, $J = 10.0$ and 8.0 Hz), 2.77–2.71 (m, 1H, C*H*-CO), 2.66 (ddd, 1H, C*H*H-C-CH, $J = 17.0$, 4.5 and 2.5), 2.48 (ddd, 1H, CH*H*-C-CH, $J = 17.0$, 4.5, and 2.5 Hz), 2.41–2.34 (m, 1H, CO-CH-C*H*H), 2.08–2.00 (m, 1H, CO-CH-CH*H*), 1.97 (t, 1H, C-C*H*,

$J = 2.5$ Hz). ^{13}C RMN ($CDCl_3$, 125 MHz): $\delta = 172.96$ (N*C*O), 129.39 (N-*C*H=CH_2), 94.70 (N-CH=*C*H_2), 80.93 (*C*≡CH), 70.00 (C≡*C*H), 42.81 (CO-N-*C*H_2), 41.36 (CO-*C*H), 23.40 (N-CH_2-*C*H_2), 20.21 (*C*H_2-C≡CH). FTIR (cm^{-1}): 3293, 3252, 2886, 2117, 1694, 1629, 1427, 1389, 1328, 1315, 1268, 980, 851. HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_9H_{11}NO$ 150.0913, found 150.0914.

Aminated N-*Vinyl-2-Pyrrolidone Compounds*

VP-gyl (2.00 g, 13.4 mmol) and sodium L-(+)-ascorbate (0.53 g, 2.68 mmol) were added to THF (10 mL). Separately, copper(II) sulfate pentahydrate (1.02g, 4.02 mmol) was dissolved in deionized water (6 mL). These two solutions were added at the same time to 20 mL of the azido tertiary amine compound solution (N_3-pl, N_3-pp, or N_3-pz-Boc) in THF previously prepared (13.4 mmol of azocompound) under stirring at 30 °C. After 24 h, the reaction was quenched adding 5 mL of MeOH and left stirring for 10 min. Then, 50 mL of an aqueous solution Na_2CO_3 0.1 M was added, followed by 50 mL of chloroform. The aqueous layer was then extracted twice with chloroform (30 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and purified by column chromatography using aluminum oxide as stationary phase and hexane/ethyl acetate/triethylamine (4:4:1) as eluent.

3-((1-(2-(Pyrrolidin-1-yl)ethyl)−1H-1,2,3-triazol-4-yl)methyl)−1-Vinyl-2-Pyrrolidone (VPcpl) (7)

(Yield: 90%) ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.47$ (s, 1H, C-C*H*-N), 7.06 (dd, 1H, N-C*H*=CH_2, $J = 16.0$ and 9.0 Hz), 4.43–4.35 (m, 4H, CH-N-CH_2 and N-CH=CH_2), 3.34 (dd, 2H, CO-N-CH_2, $J = 9.0$ and 5.5 Hz), 3.18 (dd, 1H, C*H*H-C, $J = 14.5$ and 4 Hz), 3.00–2.90 (m, 4H, CH*H*-C, C*H*-CO, and CH-N-CH_2-CH_2), 2.53–2.50 (m, 4H, N-CH_2-$(CH_2)_2$-CH_2), 2.33–2.27 (m, 1H, CO-CH-C*H*H), 2.00–1.93 (m, 1H, CO-CH-CH*H*), 1.78–1.75 (m, 4H, N-CH_2-(CH_2)$_2$). ^{13}C RMN ($CDCl_3$, 125 MHz): $\delta = 174.10$ (N*C*O), 144.50 (*C*-CH-N), 129.30 (N-*C*H=CH_2), 122.48 (C-*C*H-N), 94.56 (N-CH=*C*H_2), 55.51 (CH-N-CH_2-*C*H_2), 54.06 (N-*C*H_2-$(CH_2)_2$-*C*H_2), 49.33 (CH-N-*C*H_2-CH_2), 42.79 (CO-N-*C*H_2), 42.60 (CO-*C*H), 26.49 (CO-CH-*C*H_2), 23.55 (N-CH_2-(*C*H_2)$_2$-CH_2), 23.42 (N-CH_2-*C*H_2). FTIR (cm^{-1}): 2957, 2879, 2798, 1698, 1632, 1550, 1428, 1389, 1327, 1270, 1048, 981, 851. HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{15}H_{23}N_5O$ 290.1979, found 290.1975.

3-((1-(2-(Piperidin-1-yl)ethyl)−1H-1,2,3-Triazol-4-yl)methyl)−1-Vinyl-2-Pyrrolidone (VPcpp) (8)

(Yield: 82%) ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.50$ (s, 1H, C-C*H*-N), 7.06 (dd, 1H, N-C*H*=CH_2, $J = 16.0$ and 9.0 Hz), 4.44–4.35 (m, 4H, CH-N-CH_2 and N-CH=CH_2), 3.37–3.31 (m, 2H, CO-N-CH_2), 3.18 (dd, 1H, C*H*H-C, $J = 14$ and 3.5 Hz), 3.00–2.89 (m, 2H, CH*H*-C and C*H*-CO), 2.44–2.38 (m, 4H, N-CH_2-$(CH_2)_3$-CH_2), 2.26–2.33 (m, 1H, CO-CH-C*H*H), 2.03–1.92 (m, 1H, CO-CH-CH*H*), 1.60–1.53 (m, 4H, N-CH_2-CH_2-CH_2-CH_2), 1.44–1.40 (m, 2H, N-$(CH_2)_2$-CH_2. ^{13}C RMN ($CDCl_3$, 125 MHz): $\delta = 174.09$ (N*C*O), 144.40 (*C*-CH-N), 129.33 (N-*C*H=CH_2), 122.61 (C-*C*H-N), 94.53 (N-CH=*C*H_2), 58.29 (CH-N-CH_2-*C*H_2), 54.48 (N-*C*H_2-$(CH_2)_3$-*C*H_2), 47.75 (CH-N-*C*H_2-CH_2), 42.79 (CO-N-*C*H_2), 42.64 (CO-*C*H), 26.47 (CO-CH-*C*H_2), 25.97 (N-CH_2-*C*H_2-CH_2-*C*H_2), 24.12 (N-$(CH_2)_2$-*C*H_2-$(CH_2)_2$), 23.41 (N-CH_2-*C*H_2). FTIR (cm^{-1}): 2933, 2851, 2781, 1697, 1631, 1551, 1428, 1390, 1327, 1269, 1045, 982, 851. HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{16}H_{25}N_5O$ 304.2137, found 304.2132.

Tert-*Butyl 4-(2-(4-((1-Vinyl-2-pyrrolidon-3-yl)methyl)-1H-1,2,3-Triazol-1-yl)ethyl) Piperazine-1-Carboxylate (VPcpz-Boc) (9)*

(Yield: 80%) ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.48$ (s, 1H, C-C*H*-N), 7.05 (dd, 1H, N-C*H*=CH_2, $J = 16.0$ and 9.0 Hz), 4.44–4.35 (m, 4H, CH-N-CH_2 and N-CH=CH_2), 3.40–3.33 (m, 6H, CH_2-NCOOtBu-CH_2 and CO-N-CH_2), 3.17 (dd, 1H, C*H*H-C, $J = 10$ and 4.5 Hz), 3.00 (dd, 1H, CH*H*-C, $J = 15.0$ and 7.5 Hz), 2.95–2.89 (m, 1H, C*H*-CO), 2.79 (t, 2H, CH-N-CH_2-CH_2, $J = 6.0$ Hz), 2.41–2.38 (m, 4H, CH_2-CH_2-NCOOtBu-CH_2-CH_2), 2.33–2.27 (m, 1H, CO-CH-C*H*H), 2.00–2.92 (m, 1H, CO-CH-CH*H*), 1.47–1.43 (m, 9H, NCOOtBu). ^{13}C RMN ($CDCl_3$, 125 MHz): $\delta = 174.03$ (N*C*O), 154.62 (N*C*OOtBu), 144.49 (*C*-CH-N), 129.27 (N-*C*H=CH_2), 122.63 (C-*C*H-N), 94.63 (N-CH=*C*H_2), 79.74 (NCOO*C*(CH_3), 57.50 (CH-N-CH_2-*C*H_2), 52.83 (*C*H_2-CH_2-NCOOtBu-CH_2-*C*H_2), 47.55 (CH-N-*C*H_2-CH_2), 45.66 (CH_2-*C*H_2-NCOOtBu-*C*H_2-CH_2), 42.77 (CO-N-*C*H_2), 42.58 (CO-*C*H), 28.38 (NCOOC(*C*H_3)$_3$), 26.35 (CO-CH-*C*H_2), 23.35 (N-CH_2-*C*H_2). FTIR (cm^{-1}): 2933, 2859, 2818, 1690, 1633, 1551, 1458, 1424, 1391, 1365, 1328, 1276, 1249, 1170, 1130, 1048, 1005, 865, 770. HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{20}H_{32}N_6O_3$ 405.2609, found 405.2609.

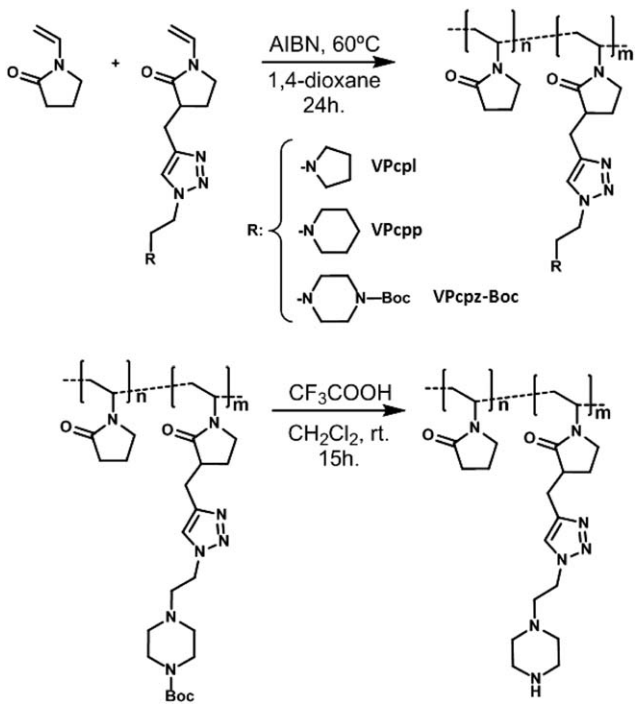
Polymerization Reactions

All polymers were synthesized using a conventional free radical polymerization procedure: monomers and initiator (AIBN) were dissolved in 1,4-dioxane at concentrations of 1.0 mol/L and 1.5×10^{-2} mol/L, respectively. Gaseous N_2 was flushed through the solutions for 20 min. The polymerization reactions were performed at 60 °C during 24 h to attain total conversion. Copolymers of VP and the modified VPs were prepared using four different molar monomer feed ratios F_{VPcpx} of 0.2, 0.4, 0.6, and 0.8, being *VPcpx* VPcpl, VPcpp, or VPcpz-Boc (see Scheme 2). The obtained copolymers have been labeled as poly (VP-*co*-VPcpx)-*Z*, being *Z* the nominal molar percentage of the aminated unit (i.e., 20, 40, 60, or 80). Homopolymers were also synthesized. The molar fractions of VPcpl, VPcpp, and VPcpz-Boc (f_{VPcpx}) in the copolymers were determined by ^{1}H NMR in $CDCl_3$. These compositions were calculated comparing the area of the CH-N-CH_2 band (corresponding to the *k* band in Fig. 2) with that of the group of signals between 2.50 and 4.30 ppm, using the following equations:

$$A_{4.5\text{-}4.7} = 2H_{VPcpx} \quad (1)$$

$$A_{2.50\text{-}4.30} = 5H_{VP} + 12H_{VPcpl} \quad (2)$$

$$A_{2.50\text{-}4.30} = 5H_{VP} + 8H_{VPcpp} \quad (3)$$



SCHEME 2 Synthesis of poly vinylpyrrolidones carrying pyrrolidine (VPcpl), piperidine (VPcpp), or piperazine (VPcpz-Boc and VPcpz) groups.

$$A_{2.50\text{-}4.30} = 5H_{VP} + 12H_{VPcpz\text{-}Boc} \quad (4)$$

$$f_{VPcpx} = \frac{H_{VPcpx}}{H_{VPcpx} + H_{VP}} 100 \quad (5)$$

A schematic representation of the polymerization is shown in Scheme 2.

Homopolymers and copolymers from VPcpl and VPcpp were isolated and purified by dialysis in water using membranes of cut-off 1000 Da, followed by freeze drying.

Homopolymer and copolymers from VPcpz-Boc were isolated and purified by several precipitation–solution–precipitation cycles in diethylether–chloroform–diethylether. Deprotected poly-VPcpz and poly(VP-*co*-VPcpz) were prepared from the corresponding VPcpz-Boc polymers by reaction with an excess of trifluoroacetic acid (CF_3COOH/VPcpz 4:1 molar ratio) in CH_2Cl_2 at room temperature. After 15 h, the solvent was removed at low pressure and the residue obtained was dissolved in 5 mL of water, the pH adjusted to 7 with 1 M NaOH and the polymers were isolated and purified by dialysis in water using membranes of cut-off 1000 Da, followed by freeze drying.

Methods and Characterization

Thin layer chromatography (TLC) was performed on aluminum sheets 60 F254 Merck silica gel and compounds were visualized by irradiation with UV light and/or by treatment with a solution of Ninhydrin in *n*-BuOH/EtOH or H_2SO_4 (5%) in EtOH followed by heating. Flash chromatography was performed using thick walled columns, using silica gel

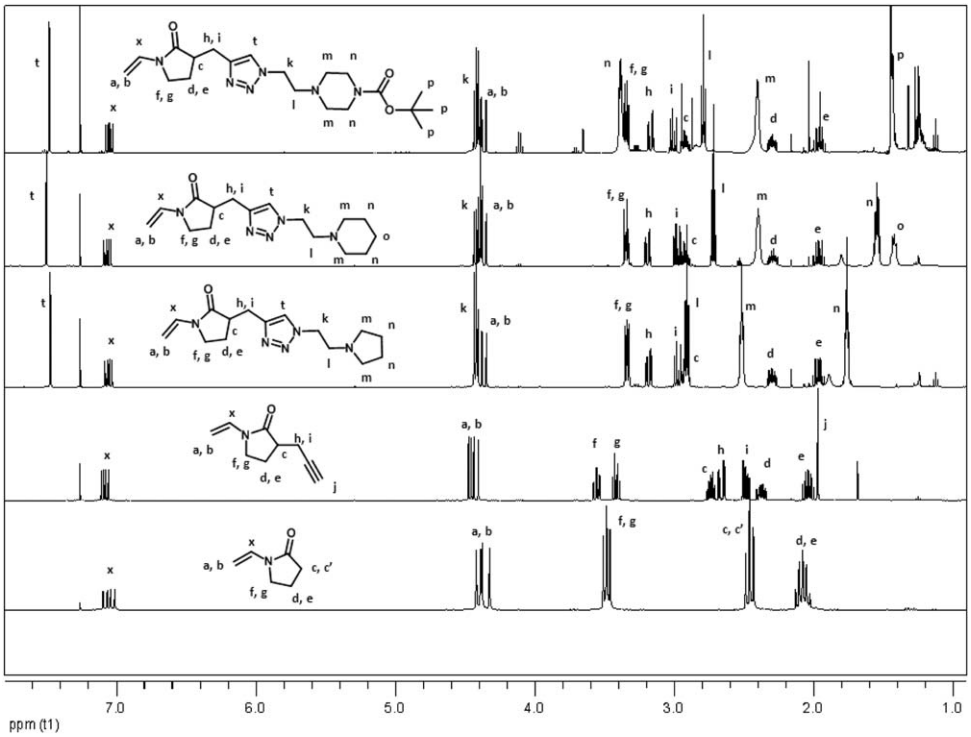


FIGURE 1 ^{1}H NMR spectra of the modified vinylpyrrolidone monomers in $CDCl_3$.

TABLE 1 Characterization of the Synthesized Polymers

Poly(VP-*co*-VPcpl)					
F_{VPcpl}	f_{VPcpl}[a]	M_n (kDa)[b]	DI[b]	Buffering Region[c]	T_g (°C)[d]
0.2	0.18	46.2	1.54	8.8–8.9	125
0.4	0.43	46.4	1.65	8.3–9.2	105
0.6	0.54	44.0	1.75	7.7–9.2	89
0.8	0.78	41.9	1.78	7.5–9.1	83
1.0	1.00	33.4	1.72	7.0–9.0	72

Poly(VP-*co*-VPcpp)					
F_{VPcpp}	f_{VPcpp}[a]	M_n (kDa)[b]	DI[b]	Buffering Region[c]	T_g (°C)[d]
0.20	0.17	42.9	1.46	8.7–8.8	126
0.40	0.44	39.2	1.44	8.0–8.8	109
0.60	0.60	36.7	1.49	8.0–8.7	102
0.80	0.83	28.2	1.52	7.7–8.5	91
1.00	1.00	23.2	1.51	7.5–8.5	77

Poly(VP-*co*-VPcpz-Boc)					
$F_{VPcpz\text{-}Boc}$	$f_{VPcpz\text{-}Boc}$[a]	M_n (kDa)[b]	DI[b]	Buffering Region[c,e]	T_g (°C)[d,e]
0.20	0.19	41.9	2.10	>9.0	157
0.40	0.36	42.3	2.15	>8.0	145
0.60	0.58	45.7	1.94	>8.0	125
0.80	0.78	48.3	1.82	>8.0	112
1.00	1.00	63.3	1.49	>8.0	105

[a] Calculated by ^{1}H NMR analysis.
[b] Determined by GPC in DMF with LiBr 1%.
[c] Determined by acid–base titration with NaOH 0.1 M.
[d] Determined by DSC (T_g PVP: 170 °C).
[e] Experiment performed on the deprotected polymers P(VP-*co*-VPcpz).

(Merck 60) or deactivated aluminum oxide, Brockmann II (Aldrich).

Monomers ^{1}H NMR and ^{13}C NMR spectra were recorded on a VARIAN NMR system (400 and 500 MHz for ^{1}H, and 100 and 125 MHz for ^{13}C, respectively) using $CDCl_3$ as solvent at room temperature and trimethylsilane (TMS) as the internal standard. Chemical shift values (δ) are reported in parts per million (ppm) relative to TMS. Coupling constants (J values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), td (triplet of doublets), and m (multiplet or unresolved). The ^{1}H NMR spectra of the polymers were measured on an Inova 300 spectrometer (300 MHz) using $CDCl_3$ or D_2O as solvents at room temperature and trimethylsilane (TMS) as the internal standard.

Mass spectrometry (MS) analyses were performed as high resolution ESI measurements on a VG AutoSpec mass spectrometer. Fourier Transform Infrared (FTIR) spectra were recorded on a Perkin Elmer RX-1 instrument with a Universal Attenuated Total Reflectance (ATR) device using diamond/ZnSe as internal reflection elements.

Raman spectra were recorded on a Renishaw *InVia* Reflex Raman system. An optical microscope is coupled to the system. The Raman scattering is excited using a diode laser at a wavelength of 785 nm. The laser beam is focused on the sample with a 0.75 50× microscope objective. The laser power, exposure time, and number of accumulations correspond to 320 mW, 10 s, and 5, respectively.

The number-average molecular weight (M_n) and polydispersity index (DI) of the polymers were measured by gel permeation chromatography (GPC) with a Perkin Elmer chromatographic system equipped with a Waters model 2414 refractive index detector, using Styragel (300 × 7.8 mm, 5 μm nominal particle size) HR3 and HR5 water columns. DMF with 1 wt % LiBr was used as eluent. Measurements were performed at 70 °C at a flow rate of 0.7 mL/min using a polymer concentration of 4 mg/mL. The calibration was performed with monodispersed polystyrene standards in the range of 2.0 and 9000.0 kDa.

The glass transition temperature (T_g) of the polymers was determined by Differential Scanning Calorimetry (DSC) using a Perkin-Elmer DSC-7 calorimeter. Thermal transition temperature measurements were conducted by heating the samples from 30 to 180 °C at 20 °C/min. T_g was estimated form the inflexion point of the second run. Typical sample weights were 8–10 mg.

The dissociation constant (pK_a) values of the polymers were determined by acid–base titration of 5 mg of polymer in 5 mL aqueous 0.15 M NaCl. An aqueous solution of NaOH (0.1 M) was used to carry out the titration using small amounts (20 μL) to avoid the modification of the ionic strength. Initially, a small volume of HCl (1 M) was added to ensure the ionization of the amine groups (around pH 3.0). The changes of pH were measured with a SCHOTT® Instruments handylab pH11 pH-meter.

The LCST of the aqueous polymer solutions was determined measuring the optical transmittance at 600 nm wavelength in several buffer solutions at different pH (7, 7.4, 8, and 9 performed in phosphate buffer solution, while the pH 10 measurement was performed in ammonia buffer solution). The measurements were accomplished using a polymer concentration of 2 mg/mL. The analysis was performed in a UV–visible spectrometer Cary 3 BIO-Varian. The temperature was gradually increased from 5 to 85 °C at a heating rate of 1 °C/min. The LSCT was estimated as the temperature at 50% transmittance.

The compositional variation of the copolymerization reactions versus the conversion has been described theoretically using the software Copol,[32] assuming that the copolymerization is governed by the terminal model, and using the reactivity ratios from a similar reaction of literature.[33] The terminal model considers the reactivity of the growing chain

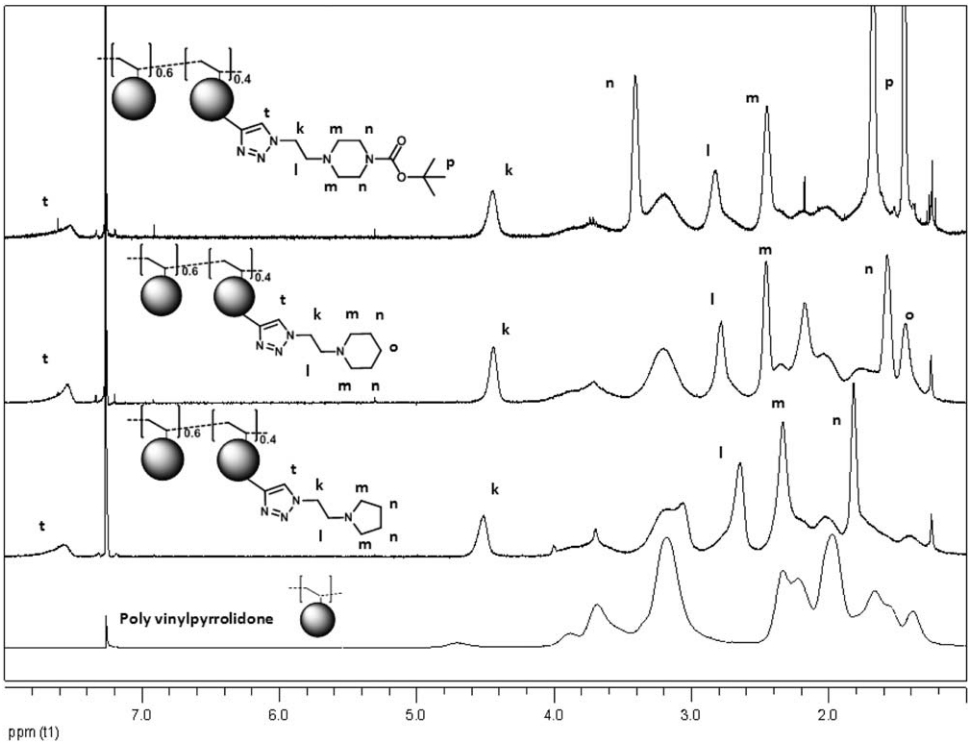


FIGURE 2 ^{1}H NMR spectra of the functionalized polyvinylpyrrolidone copolymers with $F_{VPcpx} = 0.4$.

to depend on the nature of the terminal unit, and in the case of binary copolymerizations needs two parameters—namely, the reactivity ratios—to describe the reaction. These reactivity ratios are given by eqs 6 and 7,

$$r_1 = \frac{k_{11}}{k_{12}} \quad (6)$$

$$r_2 = \frac{k_{22}}{k_{21}} \quad (7)$$

where k_{ij} ($i, j = 1, 2$) is the rate constant for the addition of a monomer M_j to a propagating chain end $\sim M_i$. A reactivity ratio value r_1 higher or lower than 1, means that a growing chain end $\sim M_1$ is more reactive towards monomer 1 or 2, respectively. This terminal model can be used for the description of these systems having in mind that it is an approximation to the reality.[34]

RESULTS AND DISCUSSION

Three new aminated monomers based on *N*-vinylpyrrolidone have been synthesized using CuAAC click chemistry. On one hand, VP monomer functionalized with an alkyne group (VP-gyl), whose synthesis have been previously reported[13] (Scheme 1), was used as alkyne precursor. On the other hand, azido compounds carrying pyrrolidine (N_3-pl), piperidine (N_3-pp), and a protected piperazine (N_3-pz-Boc) group were obtained by substitution of a leaving group (chloride or tosylate group). For security reasons, these intermediates were not isolated due to the high reactivity of these low molecular weight azido compounds. IR spectra of the synthesized products are reported in supporting information (Supporting Information Figs. 1.1–3), where an intense band appears around 2100 cm^{-1} corresponding to the azide groups. Then, using CuAAC click reactions under mild conditions (30 °C and 24 h), the aminated vinylpyrrolidones were obtained in high yields (always higher than 80%).

Figure 1 shows the ^{1}H NMR spectra of the synthesized vinylpyrrolidone derivatives, using a VP spectrum at the bottom as a reference. VP-gyl, VP modified with a propargyl group, was obtained in a 62% yield and its proton spectrum is characterized by a C-C*H* proton at 1.97 ppm and the splitting of the protons in the lactame cycle due to the monoalkylation. After the click reaction with the different azides, a singlet at 7.50–7.45 ppm appears indicating clearly the 1,2,3-triazole ring formed in each case. Comparing the spectra of VPcpl, VPcpp, and VPcpz-Boc, the peaks corresponding to the lactame cycle are maintained, as well as the vinyl group necessary for its subsequent polymerization. Figure 1 shows the assignments of the different protons.

Figure 2 shows the ^{1}H NMR spectra of the three copolymers synthesized with a nominal feed molar fraction of $F_{VPcpx} = 0.4$, selected as example. A spectrum of pure PVP is shown at the bottom as a reference. One band at 7.70–7.40 ppm indicated the presence of the triazole in the polymers, as well as a band at 4.60–4.40 corresponding to the methylene group next to the triazole (*k*) moiety. In addition, the rest of the highlighted signals in the figure show the successful synthesis of the polymers with the corresponding amine in the side chain of each PVP. The copolymer composition,

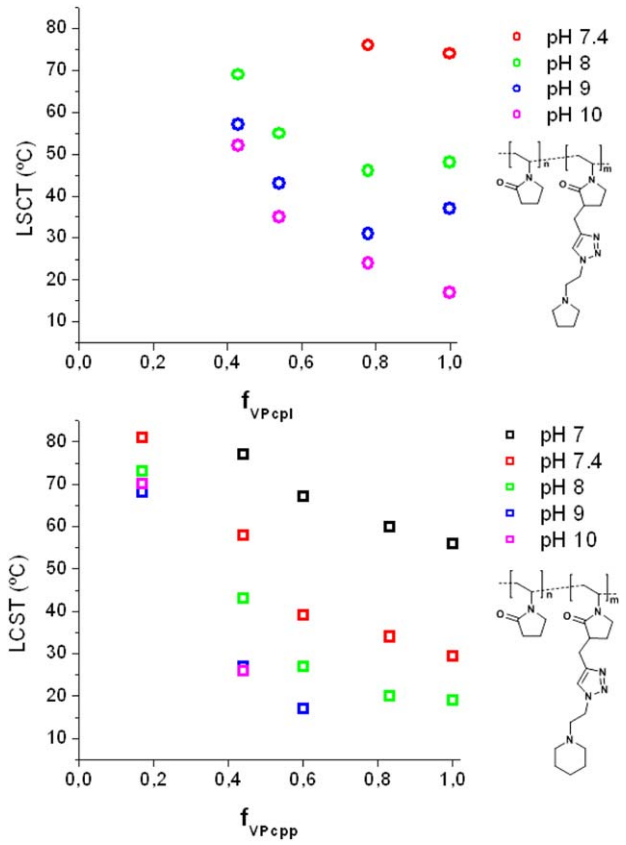


FIGURE 3 LCST values of pyrrolidine (poly(VP-*co*-VPcpl), above) and piperidine (poly(VP-*co*-VPcpp), below) polymers versus amine composition in the polymer under different pH values. LCST values were determined at 50% transmittance. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

calculated as indicated in the experimental section, agrees well with the nominal feed composition indicating that both units are properly incorporated to the polymeric chains (see Table 1). The copolymers synthesized from VP and VPcpz-Boc were treated with CF_3COOH in CH_2Cl_2 to deprotect the piperazine rings in the polymer, disappearing completely the bands from the protecting group (p protons) at 1.80–1.40 ppm. The spectra of the deprotected VPcpz polymers are included in supporting information (Supporting Information Fig. S2).

The polymers were also characterized using Infrared and Raman spectroscopy, where a characteristic band around 1550 cm^{-1} demonstrates the presence of the triazole group. Its intensity is more sensitive in Raman than in Infrared spectroscopy. Infrared and Raman characterization of these homopolymers and copolymers are included in supporting information (Supporting Information Fig. S2).

The molecular weights of the polymers and the molecular weight distributions were obtained from the GPC measurement using DMF with LiBr (1 wt %) as the eluent. The results are listed in Table 1 showing a higher average M_n for the copolymers than for their respective homopolymers, except for VPcpz-Boc polymers. Polydispersity indexes between 1.4 and 2.0 were obtained, typical of the conventional free radical polymerization used in this work.

The T_gs of the prepared polymers are included in Table 1. The T_gs of statistical copolymers and miscible polymers are normally predicted using the Fox equation:

$$\frac{1}{T_g} = \frac{w_1}{T_g 1} + \frac{w_2}{T_g 2} \tag{8}$$

where T_g1 and T_g2 are the T_g of the corresponding homopolymers, and w_1 and w_2 are the weight fractions of the components. Polymer DSC analysis was performed comparing the T_gs with theoretical T_g values calculated using the Fox equation considering VP as component 1 (which T_g is 170 °C) and the aminated VP as component 2 (whose T_gs are 72, 77, and 101 °C for the homopolymers poly-VPcpl, poly-VPcpp, and poly-VPcpp-Boc, respectively).

The obtained T_g for all copolymers in each aminated VP series decreases linearly when increasing the amount of the modified component in the copolymer. This behavior is consistent with the Fox equation. However, theoretical T_gs obtained by the Fox equation mismatched with the obtained T_gs in poly(VP-*co*-VPcpz) polymers, approaching the theoretical values when increasing the functionalized composition, (see Supporting Information Fig. S3). This behavior could be due to the possible formation of intra and intermolecular hydrogen bonding between secondary amines.

Thermo- and pH-Responsive Behavior

The aminated PVPs display pH sensitivity due to the presence of secondary and tertiary amines in their structure, exhibiting buffering regions of 8.0–9.2 for VPcpl polymers, 7.8–8.8 for VPcpp polymers, and higher than 8.0 for VPcpz polymers (see Supporting Information Fig. S4). The range of the polymers buffering region depends on the nature of the amine groups, on the so-called polyelectrolytic effect[35,36] and on the copolymer composition (amine content). The higher the amine

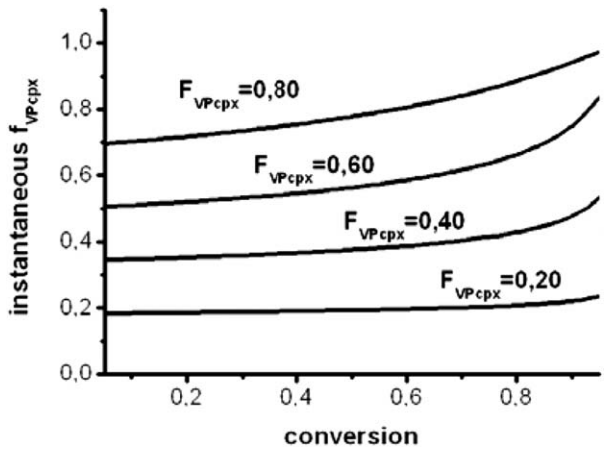


FIGURE 4 Theoretical instantaneous copolymer molar fraction of VPcpx versus the conversion.

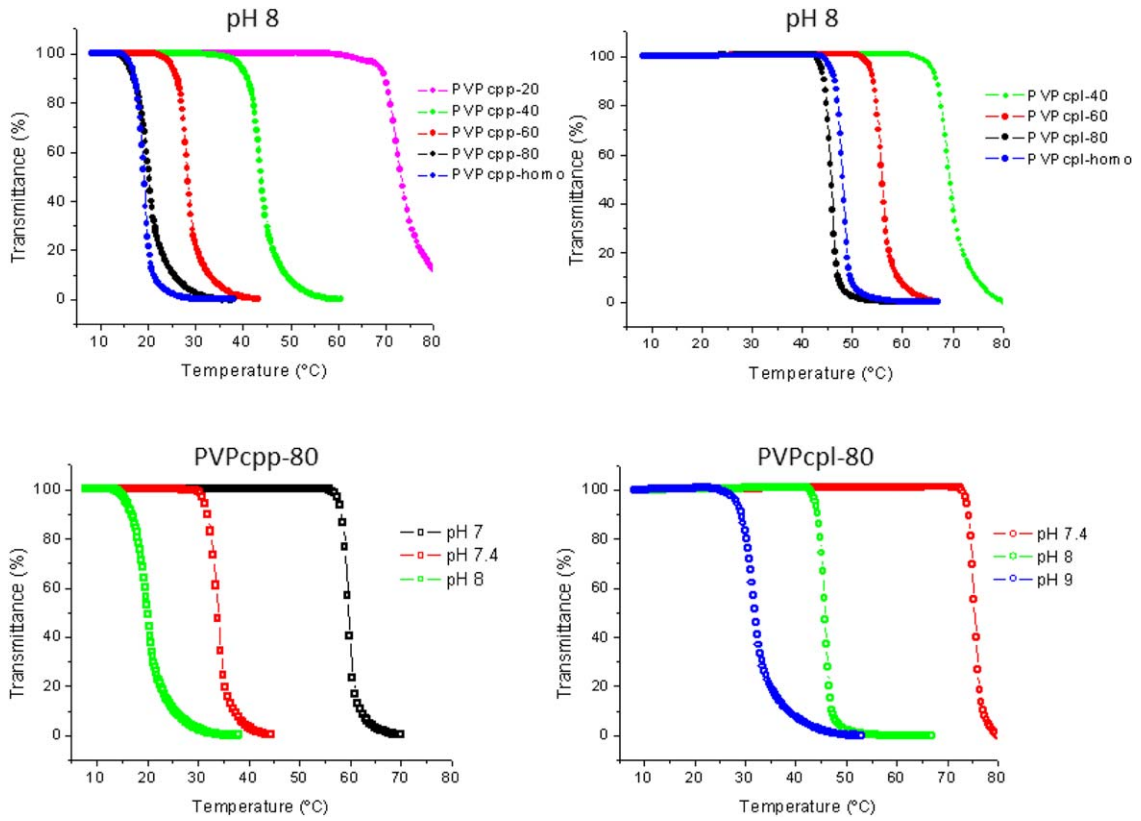


FIGURE 5 Thermal response of the VPcpl (right) and VPcpp (left) polymers at pH 8 (above), and thermal response of poly(VP-*co*-VPcpl)−80 copolymer (left) and poly(VP-*co*-VPcpp)−80 copolymer (right) at different pH values (below). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

content, the broader the buffering region. Polymers carrying piperazine groups showed wider pK_a ranges than polymers modified with pyrrolidine and piperidine groups, due to the presence of a secondary amine in its structure in addition to the tertiary amine. This large buffering region may be of interest in gene therapy applications of these polymers as non-viral vectors, by participating in the so-called "proton sponge effect."[37] The polymers bearing pendant pyrrolidine or piperidine groups also exhibit a cloud point during the titration (performed at room temperature), which has been related to a temperature-induced phase transition of the polymers (LCST phenomenon). Therefore, a complete study of the thermosensitivity was performed by turbidimetric measurements in pH buffer solutions as described in Experimental section. Figure 3 collects all LCST values.

PVP with pendant piperazine groups did not displayed any observable thermosensitivity in any buffer conditions. This behavior may be related to the presence of an additional secondary amine moiety that shifts the hydrophilic/hydrophobic balance to a scenario of total aqueous solubility in the observable region.

Copolymers and homopolymers of VPcpl and VPcpp did show LCST at pH 7 or higher. Below this critical temperature, the polymers are soluble. Above the LCST, inter- and/or intra-molecular interactions dominate and phase separation occurs. For each copolymer system, the thermosensitivity clearly depends on the composition and pH (see Fig. 3).

On one hand and for a given pH, the higher is the content of unmodified VP (which is more hydrophilic than the modified aminated units), the higher is the LCST. Similar compositional dependencies have been described for other systems in which thermosensitive units had been copolymerized with hydrophilic units.[16–21] It has to be noted that this dependence is not linear. The higher the amine content, the less pronounced the variation of the LCST. This behavior may be related, to some extent, to the compositional heterogeneity of the chains as it has been described for similar couples (VP/VP modified in 3 position with CH_2-R groups) that unmodified VP is slightly more reactive.[33] Assuming that the reaction can be compositionally described by the terminal model and using the reactivity ratios from ref. 15, which have also been determined in dioxane, the Copol software can theoretically describe the reaction in terms of instantaneous copolymer composition versus the conversion.[32]

Figure 4 shows that the higher the initial feed F_{VPcpx}, the higher the compositional heterogeneity. This tendency may explain—to some extent—the non-lineal shape of the graphs in Figure 3. If a heterogeneous collection of chains exists, the turbidimetry may mainly be related to the chains with higher amine content (because these chains suffer the

transition at lower temperatures than the rest of the chains). The shape of the curves would then be related to the higher deviation of the curves from the nominal values at increasing F_{VPcpx}.

On the other hand and for a given composition, the higher the pH, the lower is the LCST. This behavior has also been found in similar alkylated tertiary amines[38] and is related to the protonation, which increases the hydrophilia and hinders the polymer–polymer interactions responsible for the phase separation. Selected turbidimetric graphs have been depicted in Figure 5 showing these dependences on composition and pH: the upper graphs show the turbidimetric studies of copolymers with different compositions for a selected pH (8), while the lower graphs show the influence of the pH for a selected composition ($F_{VPcpx} = 0.8$). The abrupt transition observed for most of the systems has to be noted.

When comparing both copolymeric systems, remarkable differences have been found. The copolymers carrying piperidine moieties (the VPcpp system) exhibited for each pH lower LCST values than the system bearing pyrrolidine moieties (the VPcpl system). This is in agreement with the higher hydrophobicity of the piperidine cycle which has one more methylene group in its structure. In addition, the LCST values of the VPcpp system did not change when pH increased from 9 to 10, which may indicate that the piperidine system is totally deprotonated at pH 9, having the same interactions at both pHs. Moreover, it has to be noted that the poly(VP-*co*-VPcpp)−20 copolymer exhibited thermosensitivity despite of the very low content of sensitive units, whereas poly(VP-*co*-VPcpl)−20 which is homologous in composition did not show a LCST at any condition. This behavior of the VPcpp system may suggest a participation of the amphiphilic VP structure in the polymer–polymer interactions responsible for the phase separation.

CONCLUSIONS

Polymers with PVP backbone exhibiting sensitivity to pH and temperature have been obtained by synthesizing sensitive monomer units carrying different tertiary aliphatic amines (pyrrolidine, piperidine, and piperazine; the latter includes an additional secondary amine in the cycle) followed by copolymerization with unmodified VP. The piperazine derivatives have shown broad buffering regions and no thermosensitivity, while the pyrrolidine and piperidine systems do exhibit dual sensitivity to pH and temperature. To the best of our knowledge, this dual behavior has not been previously reported for any type of PVP polymer. For these two systems with dual sensitivity, a thermosensitivity at pH of 7 or higher has been found, that is, in the vicinities of the pK_a where amines become neutral and may participate in the polymer–polymer interactions and phase separation. Because of this influence of pH on protonation, the LCST values increased with increasing pH (above pH 7). Besides, the thermosensitivity depends on the copolymer composition. The higher the amount of VP, the higher the LCST values. For a given pH, the LCST value may be tuned by the proper selection of the cyclic structure and the composition. The thermosensitivity exhibited by the copolymer with only a 20 mol % of piperidine is remarkable, and may indicate a participation of VP units in the LCST phenomenon.

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