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A novel route to substituted poly(vinyl pyrrolidone)s via simple functionalization of 1-vinyl-2-pyrrolidone in the 3-position by ring-opening reactions

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ABSTRACT

A general synthetic approach is described that allows to obtain novel 1-vinyl-2-pyrrolidone (VP) derivatives with different kinds of functional groups in its 3-position in a one-pot reaction. The strategy used to achieve this goal is the reaction of the carboxamide anion of 1-vinyl-2-pyrrolidone with cyclic precursors of these functionalities. While the driving force for the reactions of three-membered rings is their high annular tension, it is shown here that larger heterocycles can be opened with good yield when additional electron-withdrawing groups are present in the ring. This leads to VP with longer spacer groups between the functionality and the future polymeric main chain. Furthermore, the high versatility of this procedure is demonstrated by the preparation, for the first time, of VP modified with amine or sulfonic functionalities that allow to prepare the corresponding aminated and sulfonated PVPs.

1. Introduction

Poly(vinylpyrrolidone) (PVP) is a water-soluble amphiphilic nontoxic polymer commonly used in a wide range of applications in the pharmaceutical and nutritional area, as well as in cosmetics, personal hygiene, paintings, etc.

However, PVP lacks reactive groups what limits the possibility of adding new functions to the polymer in order to modify its physical and chemical properties. Furthermore, large differences in radical reactivity between 1-vinylpyrrolidin-2-one (VP) and most other monomers lead to compositional drift during copolymerization [1]. This complicates the introduction of reactive groups into the polymer using this method. Monomers that are derivatives of VP itself are expected to show smaller differences in radical reactivity and therefore provide a way of preparing PVP copolymers with a versatile control of the functions and microstructure of the polymer. The new functionalities of the PVP based polymers and copolymers can furthermore be used for the linkage of bioactive conjugates under mild conditions. For these reasons, the preparation of VP pre-activated with functional groups is of high interest.

Modification of VP under preservation of both, the lactam ring and the polymerizable vinylic double bond has first been described by White and co-workers [2] by alkylation of its 3-position. This reaction takes place when the enolate of the carboxamide is created using a strong base (e.g. lithium diisopropylamide (LDA) at low temperature [3] (−78 °C) or NaH at high temperature [4] (reflux of THF)). This carboxamide anion can then react with convenient alkyl halides as the coupling components when these do not contain acid hydrogen atoms.

A similar way for the preparation of functionalized VP has been used by Engström et al. [5,6], Bencini et al. [7], Kim et al. [8] and He et al. [9]. These authors used a two

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step approach creating protected functional groups in the first step that were deprotected in a second reaction step to yield the desired functionalities, more concretely VP with one or two OH or COOH groups in 3-position.

Our group has recently described a strategy that allows one to prepare VP functionalized with hydroxyl or mercapto groups in a one-step procedure using three-membered heterocyclic precursors of these functionalities [10]. After polymerization of these systems one obtains modified PVP where the distance from the functional groups to the polymer main chain is only two methylenic groups. However, the objective of many scientists is the use of functional groups for the covalent formation of conjugates between large bioactive molecules and PVP. For this purpose it is often convenient to dispose of functionalities located via flexible spacers at a larger distance from the polymeric chain. Interesting applications are also envisaged for PVP carrying amino or sulfonic groups.

In the present work, we have therefore amplified the approach of one-step functionalization of VP by ring-opening reactions to larger cycles with different hetero atoms that lead to VP monomers with longer spacers and new functional groups.

2. Experimental

2.1. Instrumentation

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer (300 and 75.4 MHz, respectively) in $CDCl_3$ or D_2O with TMS as the internal standard. The chemical shifts are given in the δ scale relative to TMS. ^{13}C NMR spectra were carried out with complete ^{1}H decoupling and the assignments were made by additional ^{13}C-DEPT experiments. The determination of carbon, hydrogen, and nitrogen content was recorded on a Perkin-Elmer 2400.

According to solubility of the polymers, two size exclusion chromatography (SEC) apparatus were used to determine the number and weight average molecular weights. Polymers soluble in DMF were analyzed using a Perkin-Elmer apparatus with an isocratic pump serial 200 connected to a differential refractometric detector (serial 200a). Two Resipore columns (Varian) were conditioned at 70 °C and used to elute the samples (1 mg/ml concentration) at 1 ml/min HPLC-Grade *N*,*N*′-dimethyl formamide (DMF) supplemented with 0.1% v/v LiBr. Calibration of SEC was carried out with monodisperse standard polymethylmetacrilate samples in the range of 2.9×10^3–480×10^3 obtained from Polymer Laboratories. Polymers soluble in water were analysed with a Shimadzu SIL 20A-HT with an isocratic pump serial LC-20D connected to a differential refractometric detector (serial RID-10A). Three columns of PL-aquarel OH 50, 40 and 30 (Polymer Laboratories) 8 μm, were conditioned at 40 °C and used to elute the samples (1 mg/ml concentration) with mobile phase 0.2 M $NaNO_3$, 0.01 M NaH_2PO_4 buffered solution at pH 9 at 1 ml/min. Calibration of SEC was carried out with monodisperse polyethyleneglycol standard in the range of 1.0×10^3–500×10^3 obtained from Scharlab.

2.2. Materials

All the starting products had been purchased by Sigma–Aldrich and were used without any further purification, except VP which was purified by distillation at low pressure.

2.3. General procedures

2.3.1. Preparation of compounds **1–13**

A freshly distilled solution of VP (10.0 mL, 94 mmol, 1.08 equiv) in anhydrous THF (30 mL) was added dropwise to a commercial solution of lithium diisopropylamide (2.0 M, in THF, hexane and ethylbenzene, 84.2 mL, 1.8 equiv) in inert atmosphere and at −78 °C. After its anion complete formation, the solution was kept at −78 °C for 2 h. Then the corresponding cyclic precursor (87.3 mmol, 1.0 equiv) was added dropwise. The resulting solution was magnetically stirred for the time and temperature specified in Table 1. At the end of the reaction, monitored by TLC, the solution was hydrolyzed in CH_2Cl_2–H_2O (2:1, 300 mL). The aqueous layer was extracted with CH_2Cl_2 (2×100 mL) and the organic layers were combined and dried over sodium sulfate (Na_2SO_4) and the solvent evaporated at low pressure. The residue was purified by column chromatography using CH_2Cl_2/THF (10:1) (**6**, **7**), CH_2Cl_2/Et_2O (50:1) (**11**), hexane/ethyl acetate (5:1) (**12**) or CH_2Cl_2/MeOH (4:1) (**13**) as eluent.

2.3.2. Polymerization and copolymerization with vinyl pyrrolidone (VP) and derivates of VP

Monomers and initiator (AIBN) were dissolved in the chosen solvent in a total concentration of 1 mol/L and 1.5×10^{-2} mol/L, respectively. Nitrogen was flushed through the polymerizing solution for 30 min. Then polymerization was carried out at 60 °C during 24 h. The formed polymer or copolymer was isolated and purified by precipitation in diethylether. In the case of water soluble products they were purified by dialysis in membranes of cut-off 3000.

2.4. Characterization of products

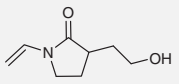
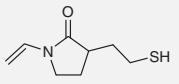
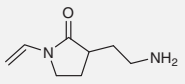
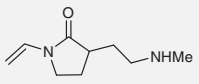
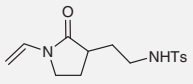
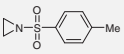
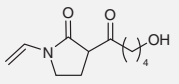
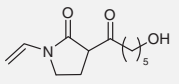
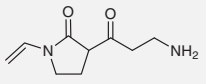
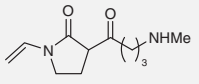
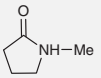
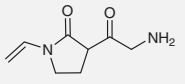
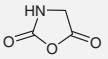
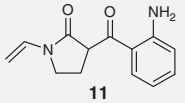
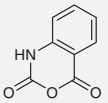
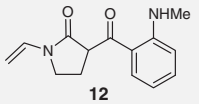
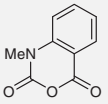
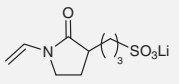
2.4.1. 3-(2-Hydroxyethyl)-1-vinyl-2-pyrrolidone (**1**) and 3-(2-mercaptoethyl)-1-vinyl-2-pyrrolidone (**2**)

These compounds are described in our previous article [10].

2.4.2. 3-(1-Oxo-5-hydroxypentyl)-1-vinyl-2-pyrrolidone (**6**)

Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02 (dd, 1H, N–C*H*═, J = 16.0 y 9.0 Hz), 4.52 (d, 1H, cis N–CH═CH*H*, J = 16.0 Hz), 4.48 (d, 1H, trans N–CH═C*H*H, J = 9.0 Hz), 3.67–3.49 (m, 4H, C*H*$_2$–N, C*H*$_2$–OH), 3.09–2.98 (m, 1H, CH–CO), 2.69–2.51 (m, 2H, OC–CH$_2$), 2.20–2.05 (m, 1H, CH*H*–CH$_2$–N), 1.72–1.49 (m, 5H, C*H*$_2$–C*H*$_2$–CH$_2$–OH, C*H*H–CH$_2$–N). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 206.2 (O*C*–CH$_2$), 171.6 (OC–N), 125.3 (N–*C*H═), 96.9 (N–CH═*C*H$_2$), 63.4 (CH$_2$–OH), 55.2 (OC–*C*H–CO), 43.0 (CH$_2$–N), 41.8 (OC–*C*H$_2$), 31.6 (*C*H$_2$–CH$_2$–OH), 24.7 (OC–CH$_2$–*C*H$_2$), 22.9 (*C*H$_2$–CH$_2$–N). Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.71; H, 8.02; N, 6.56.

Table 1
Functionalization of VP by ring-opening reactions.

Monomer	Cyclic precursor	Reaction temperature	Yield[a]%
 **1**		−78 °C → −30 °C	28
 **2**		−78 °C → −30 °C	27
 **3**		−78 °C → −30 °C −78 °C → r.t.	–
 **4**		−78 °C → −30 °C −78 °C → r.t.	–
 **5**		−78 °C → −30 °C −78 °C → r.t.	–
 **6**		−78 °C → r.t.	28
 **7**		−78 °C → r.t.	55
 **8**		−78 °C → −30 °C −78 °C → r.t.	–
 **9**		−78 °C → −30 °C −78 °C → r.t.	–
 **10**		−78 °C → −30 °C −78 °C → r.t.	–
 **11**		−78 °C → r.t.	40
 **12**		−78 °C → r.t.	45
 **13**		−78 °C → r.t.	50

[a] After purification of the products by column chromatography.

*2.4.3. 3-(1-Oxo-6-hydroxyhexyl)-1-vinyl-2-pyrrolidone (**7**)*

Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02 (dd, 1H, N–C*H*═, J = 11.9 and 7.0 Hz), 4.52 (d, 1H, cis N–CH═CH*H*, J = 17.5 Hz), 4.48 (d, 1H, trans N–CH═C*H*H, J = 11.6 Hz), 3.67–3.48 (m, 4H, CH_2–N–, CH_2–OH), 3.10–2.98 (m, 1H, C*H*–CO), 2.68–2.52 (m, 2H, OC–CH_2), 2.19–2.05 (m, 1H, CH*H*–CH_2–N), 1.72–1.48 (m, 5H, CH_2–CH_2–CH_2–CH_2–OH, C*H*H–CH_2–N), 1.45–1.31 (m, 2H, CH_2–CH_2–OH). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 206.2 (OC–CH_2), 174.0 (O*C*–N), 125.9 (N–*C*H═), 96.3 (N–CH = *C*H_2), 63.2 (*C*H_2–OH), 54.3

(OC–*C*H–CO), 43.0 (*C*H$_2$–N), 42.0 (OC–*C*H$_2$), 32.8 (*C*H$_2$–CH$_2$–OH), 25.5 (*C*H$_2$–CH$_2$–CH$_2$–OH), 24.3 (CO–CH$_2$–*C*H$_2$), 23.2 (*C*H$_2$–CH$_2$–N). Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.12; H, 8.44; N, 6.10.

*2.4.4. 3-(2-Aminobenzoyl)-1-vinyl-2-pyrrolidone (**11**)*

Yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, 2H, CH, J = 4.0 Hz), 7.28 (t, 2H, CH, J = 4.0 Hz), 7.07 (dd, 1H, N–CH=, J = 16.0 and 9.0 Hz), 6.70 (t, 2H, CH J = 4.0 Hz), 6.65 (d, 2H, CH, J = 4.0 Hz), 6.30 (br, 2H, NH_2), 4.58 (dd, 1H, CO–C*H*–CO, J = 5.2 and J = 9.6 Hz), 4.45 (d, 1H, cis N–CH=CH*H*, J = 9.0 Hz), 4.40 (d, 1H, trans N–CH–C*H*H, J = 16.0 Hz), 3.68 (m, 1H, N–C*H*H), 3.55 (td, N–CH*H*, J = 4.4 and J = 9.2 Hz), 2.63 (m, 1H, N–CH$_2$–CH*H*), 2.32 (m, 1H, N–CH$_2$–C*H*H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.9 (CO), 169.4 (CO–N), 151.2 (C–NH_2), 135.0 (*C*H–CH–C–NH_2), 132.7 (N–*C*H=), 129.3 (CH–C–CO),117.1 (*C*H–CH–C–CO), 117.0 (*C*–CO), 116.0 (H–C–NH_2), 95.3 (*C*H$_2$=CH–N), 51.0 (CO–*C*H–CO), 43.6 (*C*H$_2$–N), 22.1 (*C*H$_2$–CH$_2$–N). Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17; O, 13.90. Found: C, 68.01; H, 6.08; N, 12.05.

*2.4.5. 3-(2-Methylaminobenzoyl)-1-vinyl-2-pyrrolidone (**12**)*

Yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (br, 1H, N*H*Me), 7.94 (d, 2H, CH, J = 4.0 Hz), 7.40 (t, 2H, CH, J = 4.0 Hz), 7.07 (dd, 1H, N–C*H*=, J = 16.0 and 9.0 Hz), 6.70–6.62 (m, 2H, 2=CH), 4.59 (dd, 1H, CO–C*H*–CO, J = 4.8 and J = 9.3 Hz), 4.50 (d,1H, cis N–CH = CH*H*, J = 9.0 Hz), 4.45 (d, 1H, trans N–CH–C*H*H, J = 16.0 Hz), 3.68 (m, 1H, N–C*H*H), 3.55 (m, N–CH*H*), 2.90 (d, 3H, N–C*H*$_3$, J = 5.1 Hz), 2.60 (m, 1H, N–CH$_2$–CH*H*), 2.35 (m, 1H, N–CH$_2$–C*H*H). ^{13}C RMN ($CDCl_3$, 100 MHz) δ 197.2 (CO), 169.9 (CO–N), 153.0 (C–NH_2), 135.9 (*C*H–CH–C–NH_2), 133.6 (N–*C*H=), 129.6 (*C*H–C–CO), 116.6 (*C*H–CH–C–CO), 114.7 (*C*–CO), 111.6 (CH–C–NH_2), 95.5 (*C*H$_2$=CH–N), 51.2 (CO–*C*H–CO), 43.9 (*C*H$_2$–N), 29.6 (*C*H$_3$–N), 22.7 (*C*H$_2$–CH$_2$–N). Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; O, 13.10. Found: C, 69.98; H, 6.54; N, 11.37.

*2.4.6. 3-(3-Sulfopropyl)-1-vinyl-2-pyrrolidone (**13**)*

Yellow solid. ^{1}H NMR (D_2O, 300 MHz) δ 6.79 (dd, 1H, N–C*H*=, J = 15.9 and 9.1 Hz), 4.52 (d, 1H, cis N–CH=CH*H*, J = 15.9 Hz), 4.48 (d, 1H, trans N–CH=C*H*H, J = 9.1 Hz), 3.48–3.44 (m, 1H, C*H*H–N), 3.38–3.34 (m, 1H, CH*H*–N), 2.85–2.70 (m, 2H, C*H*$_2$–SO_3^-), 2.59–2.51 (m, 1H, C*H*–CO), 2.23–2.14 (m, 1H, CH*H*–CH$_2$–N), 1.80–1.59 (m, 4H, C*H*H–CH$_2$–N, C*H*H–C*H*$_2$–CH$_2$–SO_3^-), 1.41–1.33 (m, 1H, CH*H*–C*H*$_2$–CH$_2$–SO_3^-). ^{13}C NMR (D_2O, 75.4 MHz) δ 178.2 (OC–N), 128.6 (N–CH=), 97.8 (N–CH=C*H*$_2$), 50.9 (CH$_2$–SO_3^-), 43.9 (CH$_2$–N), 42.4 (OC–*C*H), 29.3 (*C*H$_2$–CH$_2$–CH$_2$–SO_3^-), 23.4 (*C*H$_2$–CH$_2$–N), 21.8 (*C*H$_2$–CH$_2$–SO_3^-). Anal. Calcd. for $C_9H_{15}NO_4S$: C, 46.34; H, 6.48; N, 6.00; O, 27.43; S, 13.75. Found: C, 46.62; H, 6.41; N, 5.93.

3. Results and discussion

The first step of the synthetic route to functionalized VP monomers is the formation of the corresponding enolate of the carboxamide. Different bases for the selective abstraction of a proton in 3-position had been tested in previous work [10] showing that the best results concerning a complete formation of the carboxamide anion were obtained using lithium diisopropylamide (LDA).

In Table 1 the chemical structures of the heterocyclic starting compounds as well as those of the products obtained by reaction with the carboxamide anion of VP are summarized.

The first two products in this table correspond to VP modified with protic functional groups and short spacers between these functional groups and the polymerizable group. More concretely, VP with pending OH- and SH-groups in 3-position could be realized using ethylene oxide (**1**) and ethylene sulfide (**2**), respectively [10]. Ring-opening of these systems is thermodynamically feasible due to the high annular tension of these 3-membered cycles. In an analogue way we also tried to synthesize VP modified with primary, secondary and protected primary amine groups using aziridine (**3**), *N*-methylaziridine (**4**) and *N*-tosyl aziridine (**5**). Although the experimental procedure in these cases was very similar to that used for the ring-opening reactions of ethylene oxide and ethylene sulfide the susceptibility of the nitrogen containing cycles towards the nucleophilic attack by the carboxamide anion was not high enough and the desired products were not formed in a detectable quantity.

In order to open larger heterocyclic rings by the reaction with the carboxamide anion their susceptibility towards nucleophilic attack had to be increased. This can be achieved by using heterocycles that are activated by electron-withdrawing groups in the vicinity of the heteroatom. This approach leads to the use of lactones, lactames, sultones and cyclic carboxy anhydrides. From Table 1 it becomes evident that 6 and 7-membered lactones like δ-valerolactone (**6**) and ε-caprolactone (**7**) react in satisfactory yield to form hydroxyl functionalized VP monomer with a keto-group in α-position of the spacer group.

Table 2
Polymers and copolymers prepared in this work.

	Polymer medium	Mn	PDI	Solubility
Poly-(7)	Dioxan	–[a]	–	DMSO, dioxan
Poly-(7-co-VP) (50:50 mol%)	Dioxan	–[a]	–	DMSO, dioxan
Poly-(11)	DMF	14100[b]	1.6	Acid H_2O, DMF
Poly-(11-co-VP) (50:50 mol%)	DMF	16400[b]	2.0	Acid H_2O, DMF
Poly-(13)	H_2O	20900[c]	1.9	H_2O
Poly-(13-co-VP) (50:50 mol%)	H_2O	32100[c]	1.6	H_2O

[a] Polymer was not soluble in the eluents used in GPC.
[b] GPC eluent was DMF. Data relative to PMMA standards.
[c] GPC eluent was water. Data relative to PEG standards.

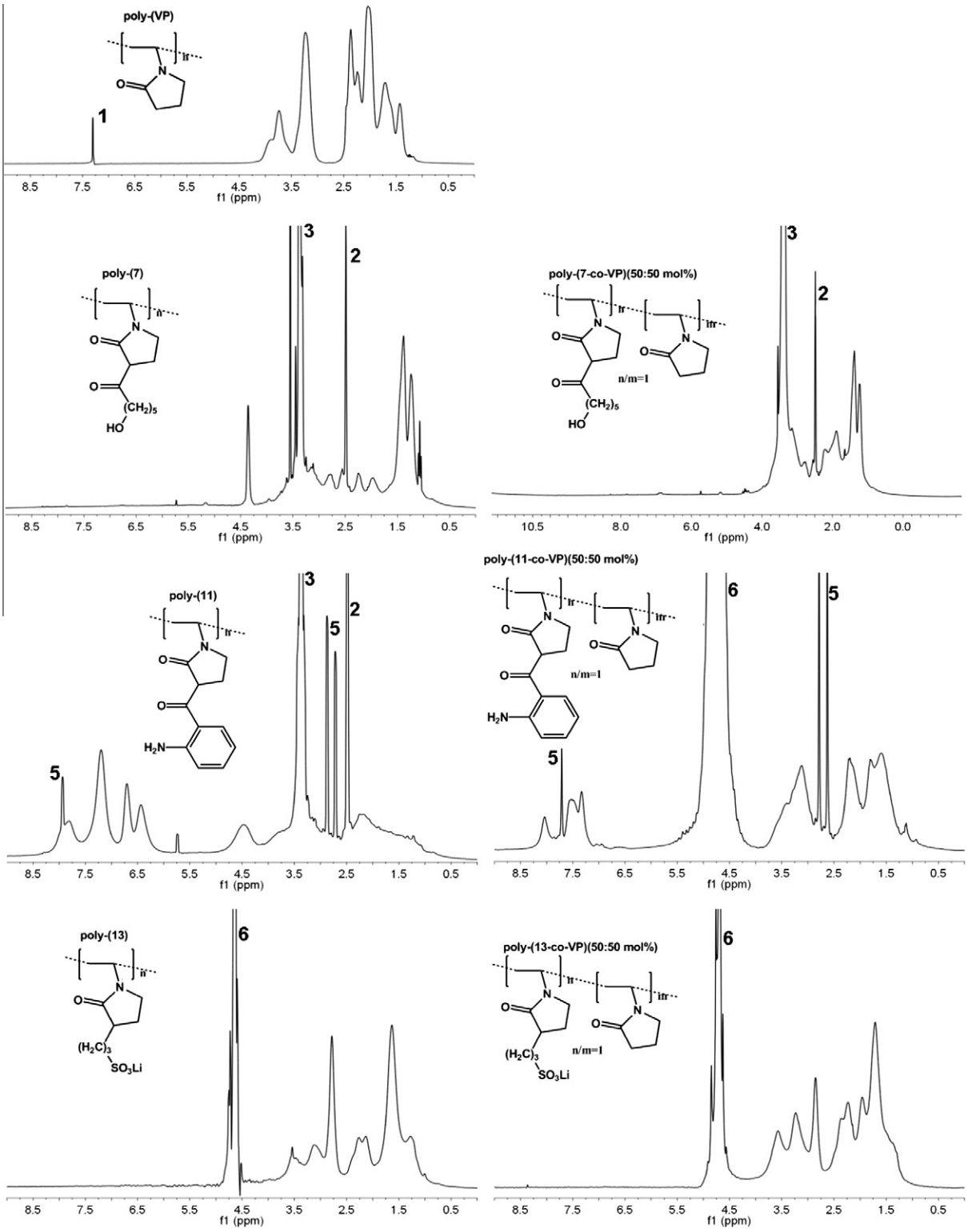


Fig. 1. ^{1}H NMR spectra of the polymers and copolymers prepared in this work. Numbers refer to residual solvents: 1 – chloroform from deuterated $CDCl_3$. 2 – DMSO from deuterated DMSO-d_6. 3 – H_2O in deuterated DMSO-d_6. 5 – residual DMF. 6 – H_2O from deuterated D_2O.

Also here the analogue nitrogen containing lactames like azetidone (**8**) or *N*-methylpyrrolidone (**9**) are not sufficiently reactive to give the desired monomer with aliphatic amine groups.

An alternative way to achieve functionalization of VP with aliphatic amine moieties is the use of cyclic carboxyanhydrides that are known to eliminate CO_2 upon nucleophilic attack under simultaneous formation of an aliphatic primary NH_2 group. Unfortunately, 2,5-oxazolidinedione (**10**), the most simple and promising cyclic precursor for this case, is insoluble in the reaction medium so that no reaction took place here. On the other hand, its benzo-analogue compound, isatoic anhydride (**11**) as well as the *N*-methyl derivative (**12**) presented the required solubility in THF. Consequently ring opening of these heterocycles takes place and leads in satisfactory yield to VP modified with aromatic primary and secondary amine groups.

Of special interest is the product formed between VP and 5- and 6-membered ring sultones (**13**) because reactions of these compounds with a wide variety of nucleophilic reagents such as alcohols, amines, alkoxides, and metal alkyls have been reported to lead invariably to derivatives of sulfonic acids [11,12]. This type of reaction has been of considerable industrial importance since it has allowed the introduction of a water-solubilizing group into a variety of organic molecules. As can be seen in Table 1 using the carboxamide anion of VP also in this case ring opening takes place in this way and leads in good yield to VP containing sulfonic groups.

Selected monomers **7**, **11** and **13**, bearing different functionalities like hydroxy, aromatic amine or sulfonic groups, have been shown to be easily polymerizable and copolymerizable with VP. Polymerization of monomer **1** has been described previously [10]. Main data of the polymerization and products are summarized in Table 2. The solvent used in polymerization has been chosen according to the solubility requirements of monomers and polymers. The homopolymer and copolymer bearing sulfonic groups are very soluble in water as it could be expected. The polymers with aromatic amine groups are soluble in acidic water and DMF, and the polymers derived from monomer **7** bearing OH groups, are soluble in DMSO or dioxane but not in water. Table 2 shows that the relative molecular weight of the obtained polymers and copolymers is relatively low. The proton NMR spectra of the polymers are shown in Fig. 1. The spectra show broad peaks typical for polymeric species, and changes in agreement with the structural variations. Poly-(**7**) shows the aliphatic protons of the side chain between 1 and 1.7 ppm, and the OH group at 4.4 ppm. The spectrum of poly-(**11**) exhibits the aromatic protons (overlapped with the amine) between 6.0 and 8.4 ppm, and the acid CO*CH*CO proton at 4.5 ppm. Poly-(**13**) shows also aliphatic protons between 1.0 and 2.0 ppm, and a distinctive signal at 2.8 ppm corresponding to the $-CH_2-S$ protons. The 1:1 copolymers show intermediate spectra between both homopolymers.

4. Conclusions

It has been shown that the presented approach describes the preparation of VP and PVP functionalized with hydroxyl group that are located at a certain distance from the polymerizable group. Furthermore, the synthesis of true aminated VP and PVP and true sulfonated VP and PVP could be realized for the first time. Both polymers are liable to have high potential in the biomedical area. Applications may be as PVP-based DNA vectors or in surface modification. True sulfonated PVP is furthermore of high interest in other technological fields, i.e. to prepare novel proton-conducting materials or to mimic biological sulfonated polymers.

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