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Polymer-analogous transformations of poly(*N*-vinylpyrrolidone) to produce new complexing macromolecular systems

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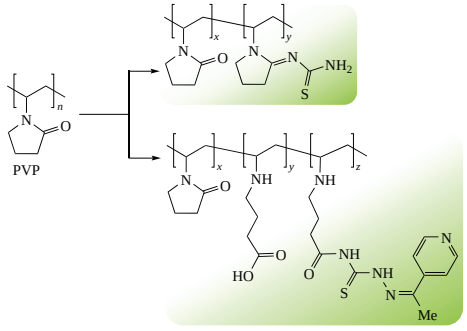
A new polymer-analogous transformations of poly(*N*-vinylpyrrolidone) was used to prepare new complex-forming macromolecular systems containing thiourea and thiosemicarbazone sites. Two variants of modification were realized, namely, the method including the preliminary *in situ* activation of nucleophilic centres of the polymer amide fragments with dimethyl sulfate followed by introducing nucleophilic agents into the system, and the method including partial hydrolysis of poly(*N*-vinylpyrrolidone) followed by the amide coupling. The obtained modified polymeric materials react with silver ions in aqueous solution.



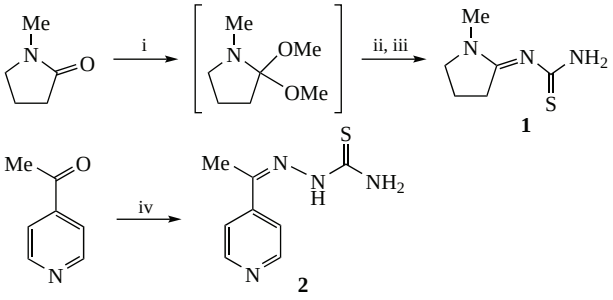
Keywords: poly(*N*-vinylpyrrolidone), polymer-analogous transformations, post-polymerization modification, complex-forming polymers, pyridine-containing polymers, thiourea, silver ion.

Due to its inertness,[1] non-toxicity,[2] thermostability,[2,3] pH stability in water fluids,[1] biocompatibility,[1–3] and compatibility with pharmaceutical preparations,[1,4] poly(*N*-vinylpyrrolidone) (PVP) finds wide application in pharmacology,[2,3] food[5] and cosmetic industry,[6] and medicine.[7,8] It is also used as a carrier and stabilizer of drugs due to its polar structure, amphiphilicity, and proton accepting ability.[1,3,9,10] The PVP structure enables formation of non-specific labile coordination compounds between its macromolecules and solvated metal ions with low stability constants.[11–15] Polymer-analogous transformations of this polymer (introduction of the groups containing chelating sites into polymer chains) make it possible to prepare polymers capable of selective and strong metal ion binding.[16] The resulting coordination compounds can be used as selective sorbents, biomarkers,[17,18] bioimaging agents, radiopharmaceutical preparations for positron-emission tomography,[18–20] and complexes with antitumor activity.[21]

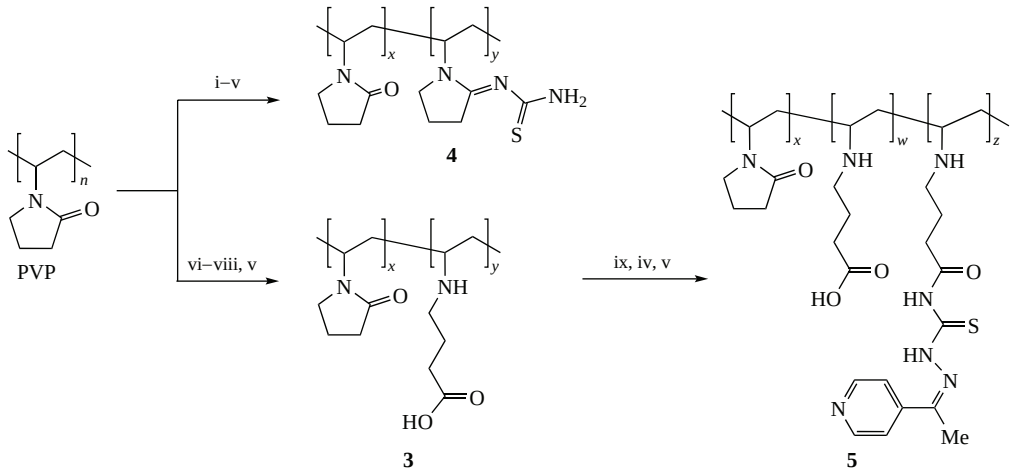
One of the methods used for polymer-analogous transformations of PVP is partial hydrolysis of γ-lactam rings[22] with further possible introduction of various modifying groups into secondary amino or carboxylic groups.[23,24] Another direction in polymer-analogous transformations is the introduction of various substituents into amide groups of γ-lactam rings in the course of condensation reactions; before this reaction, amide fragments in γ-lactam rings are activated.[25,26]

The present paper describes a new technique for polymer-analogous transformations of PVP; the goal of the work was to prepare new complex-forming macromolecular systems containing thiourea and thiosemicarbazone sites. Since both thiourea and thiosemicarbazide demonstrate weak nucleophilic properties, it is difficult to perform modification of the pyrrolidone fragment directly by these compounds. The *in situ* activation of the reaction centre (carbon atom of the carbamide group present in γ-lactam ring) should provide a different way of obtaining materials that contain the above-mentioned coordination sites.

Two versions of this method were realized, namely, preparation of the polymer containing amidine fragments using thiourea and addition of coordination sites to carboxylic groups of partially hydrolyzed PVP by amide coupling. Because the number of research papers devoted to modification of PVP by reactions at amide groups of γ-lactam rings is relatively small,[25,26] it was decided to first perform modification of a model compound, *N*-methyl-2-pyrrolidone (NMP), that contains a γ-lactam ring similar to that in PVP (Scheme 1). The synthesis of the NMP derivative containing thiourea fragment was based on



Scheme 1 *Reagents and conditions*: i, Me_2SO_4, 80 °C, 2 h; ii, NaOMe, <15 °C, 5 min; iii, $(NH_2)_2CS$, room temperature, 12 h; iv, $H_2NC(S)NHNH_2$, AcOH (cat.), BuOH, reflux, 3 h.



Scheme 2 *Reagents and conditions*: i, Me_2SO_4, MeOH, 80 °C, 2 h; ii, NaOMe, 10–15 °C, 5 min; iii, $(NH_2)_2C{=}S$, MeOH, room temperature, 2 h; iv, dialysis in MeOH, 72–96 h; v, freeze drying; vi, 0.1 M NaOH, 140 °C, 48 h; vii, 1 M HCl to pH 2–3, cooling; viii, lyophilization in distilled water, 48 h; ix, DCC, NHS, MeOH, room temperature, 1 h, then thiosemicarbazone **2**, 1 h.

the reported[27] technique for obtaining derivatives of lactams and weak N-nucleophiles. According to this method, the reaction centre in NMP is activated with dimethyl sulfate to produce intermediate dimethyl acetal. Then sodium methoxide is introduced into the reaction system followed by addition of thiourea. The reaction proceeds through the mechanism of nucleophilic addition–elimination[27] involving generation of N,O-stabilized carbocation. In this way, thiourea derivative of NMP **1** was obtained. Scheme 1 also depicts the preparation of auxiliary thiosemicarbazone **2** from 4-acetylpyridine.

Polymer-analogous transformations of PVP were performed according to the technique optimized in the experiments with NMP; some alterations were made taking into account specific aspects of work with macromolecular systems (Scheme 2). Thus, methanol was selected as a solvent, because this enabled[13] us to carry out the reaction in a homogeneous medium. Apparently, post-polymerization modification of PVP is strongly influenced by spatial structure of individual macromolecules, which would acquire coil or globular conformations in water–alcohol solutions.[2,28] This, in turn, determines the number of modified fragments in the resulting product. The obtained modified polymer **4** contains the C=N bond that is easily hydrolyzed in aqueous solutions; therefore, purification of the final product (removal of low molecular weight fractions) was performed by dialysis in methanol. Partially hydrolyzed PVP **3** was used as the starting material for the synthesis of substance **5**. The IR spectra of **3** at high degrees of hydrolysis (10 % and more) show weak stretching vibrations for carboxy groups at 1500 and 1650 cm^{-1}. However, in samples with a low content of carboxy groups (degree of hydrolysis up to 5%), this band cannot be detected.[29] Probably, it can merge with a more intense band for the carbonyl group at 1670 cm^{-1} (see Online Supplementary Materials, Figure S7). The grafted site for material **3** was thiosemicarbazone **2** prepared in a similar fashion.[30] The structures similar to **2** are interesting within the context of complexation with metal ions, *e.g.*, gallium;[31] the preparations based on ^{66}Ga, ^{67}Ga and ^{68}Ga isotopes are used in biovisualization or treatment of tumor tissues.[14,32,33] To avoid degradation of the prepared polymer **5**, dialysis of the reaction mixture was carried out in methanol solution against methanol. All the obtained polymers were isolated by freeze drying.

In the ^1H NMR spectrum of material **4**, the broad doublet (J = 5.1 Hz) in the 4.00–4.20 ppm range appears; this signal can be attributed to NH_2 fragment of thiourea moiety (see Online Supplementary Materials, Figure S8). The ^1H NMR spectrum of modified polymer **5** (which contains the aromatic pyridine ring) includes signals in the region of 7.90–8.01 ppm (Figure S9). The percentages of modified γ-lactam rings calculated from the ratio between integral intensities of signals in ^1H NMR spectra of polymers were equal to ~ 4% for **4** and ~ 3% for **5**.

The obtained modified polymeric material **4** reacted with silver ions in an aqueous solution. Upon addition of various aliquots of silver nitrate solutions to an aqueous solution of **4** (50 mg ml^{-1}), colouring was observed, which varied from light yellow to dark brown. In all cases, the solutions darkened in 24 h, and a fine-dispersed precipitate was formed. Apparently, this indicates complexation between silver ions and thiourea fragments in the modified PVP.[21]

To summarize, the herein developed technique for polymer-analogous transformations of PVP enables one to obtain a modified polymer containing thiourea and thiosemicarbazone sites. The proposed approach makes it possible to obtain a wide range of derivatives based on polymers containing lactam units in order to create complexing macromolecules on their basis. The main specific feature of this method is the preliminary *in situ* activation of the carbon atom of carbamide group in γ-lactam ring, which allows one to carry out further reactions with poor nucleophiles.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.04.021.

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