ISSN 1070-3632, Russian Journal of General Chemistry, 2018, Vol. 88, No. 3, pp. 514–519. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © M.V. Solovskii, M.S. Borisenko, E.B. Tarabukina, A.I. Amirova, 2018, published in Zhurnal Obshchei Khimii, 2018, Vol. 88, No. 3, pp. 487–492.

Synthesis of Copolymers of *N*-Vinylpyrrolidone with Crotonic Acid Modified with 4-Oxybenzaldehyde

M. V. Solovskii, M. S. Borisenko*, E. B. Tarabukina, and A. I. Amirova

Institute of Macromolecular Compounds, Russian Academy of Sciences, Bol'shoi pr. V. O. 31, St. Petersburg, 199004 Russia
**e-mail: aarghm@mail.ru*

Received September 28, 2017

Abstract—Radical copolymerization of *N*-vinylpyrrolidone with crotonic acid in 2-propanol has afforded water-soluble products, which have been characterized in terms of composition as well as molecular and hydrodynamic parameters. The obtained copolymers have been modified with 4-oxybenzaldehyde. Structures of the products of the polymer analogous reaction, potential carriers of several bioactive substances, have been confirmed using elemental and functional analysis and spectroscopic data.

Keywords: *N*-vinylpyrrolidone, crotonic acid, copolymer, 4-crotonoyloxybenzaldehyde, *N,N'*-dicyclohexylcarbodiimide

DOI: 10.1134/S1070363218030192

Tertiary copolymers of *N*-vinylpyrrolidone are of great interest in scope of the general issue of preparation of copolymer carriers of biological active substances based on *N*-vinylpyrrolidone, on top of its binary copolymers. The presence of two types of units bearing different functional groups in these terpolymers allows binding of two or more bioactive substances with different mechanisms of biological action at the terpolymer, to obtain *N*-vinylpyrrolidone copolymers with polyfunctional biological activity.

Terpolymers of *N*-vinylpyrrolidone are usually obtained via tertiary polymerization of the comonomers, for example, *N*-vinylpyrrolidone, crotonic acid, and 2-oxyethyl methacrylate [2]. At the same time, reactive terpolymers of *N*-vinylpyrrolidone can be synthesized using polymer analogous reactions of binary copolymers with a modifying agent, for example, of carboxyl-containing copolymers *N*-vinylpyrrolidone–crotonic acid **1** with *p*-nitrophenol [3]. These copolymers of *N*-vinylpyrrolidone with crotonic acid are of special interest since the carboxyl groups in the macromolecule are separated by blocks of *N*-vinylpyrrolidone units. This feature may facilitate the interaction of copolymers **1** with modifying agents and bioactive substances. The block structure of the copolymers is related to the copolymerization rate constants (for crotonic acid, r_2 equals 0). In this regard, copolymers of *N*-vinylpyrrolidone with other crotonic and allyl monomers, for example, vinyl acetic acid, are of interest. These copolymers are biocompatible because of high fraction of *N*-vinylpyrrolidone units.

Copolymers of *N*-vinylpyrrolidone with crotonic acid obtained via bulk radical polymerization of the comonomers initiated by 2,2'-azo-bis(isobutyronitrile) (AIBN) have been described [4]. However, this process can be hardly scaled because of strong exothermic effect and the related problem of heat removal. Hence, the polymerization preferably should be carried out in a solution. Radiation-induced copolymerization of *N*-vinylpyrrolidone with crotonic acid in ethanol using an MPX-γ-20 device (γ-source ^{60}Co) has been described [5]. The copolymerization of *N*-vinylpyrrolidone with crotonic acid a solution under the action of radical initiators has remained poorly studied. Molecular and hydrodynamic characteristics of the copolymers of *N*-vinylpyrrolidone with crotonic acid have not been investigated.

This work aimed to synthesize the *N*-vinylpyrrolidone–crotonic acid copolymers via copolymerization of the monomers in a solution with AIBN as the initiator, determination of their composition, molecular and hydrodynamic parameters, and investigation of their reaction with *p*-oxybenzaldehyde to obtain the *N*-vinylpyrrolidone terpolymers containing car-

Table 1. Copolymerization of *N*-vinylpyrrolidone with crotonic acid in 2-propanol at 65°C

Exp. no.	Initial mixture of monomers			Copolymers of *N*-vinylpyrrolidone with crotonic acid				
	$[M_2]_0$, mol %	$[M_1]_0 + [M_2]_0$, wt %	[AIBN], wt %	Comp. no.	Yield after 48 h, %	m_2, Mol %	$[\eta]^{25^\circ}_{0.1\ M\ AcONa}$, cm^3/g	M_η, (M_{SD}), M_w[b]
1	15	10	1	**1a**	80.2	12.5	11	15000
2	15	20	1	**1b**	83.8	13.4	17	27000
3	15	30	1	**1c**[a]	94.5	12.7	20	34000
4	15	30	3	**1d**[a]	94.2	13.7	17	27000
5	20	30	3	**1e**[a]	82.4	18.3	13	19000
6	20	30	1	**1f**[a]	81.3	16.4	20	34000
7	25	30	1	**1g**	68.1	24.7	15	(22000)
8	30	30	1	**1h**	55.7	24.2	13	(14000)
9	35	40	1	**1i**	39.8	31.8	17	34800[b]

[a] $\overline{M}_w/\overline{M}_n = 1.7$ (**1c**), 1.8 (**1d**), 1.8 (**1e**), 1.6 (**1f**). [b] Determined using static light scattering method.

boxyl and aromatic aldehyde groups, as potential carriers of several bioactive substances.

The copolymerization of *N*-vinylpyrrolidone with crotonic acid was carried out in 2-propanol in the presence of AIBN, varying the composition of the initial mixture as well as concentrations of the monomers and the initiator. The experimental results are given in Table 1. The increase in the content of crotonic acid in the initial mixture (other copolymerization conditions being the same) led to the decrease in the copolymer yield and its molecular weight (Exp. 4–8). This feature is general for radical copolymerization with crotonic acid monomer which is prone to degradative chain transfer [6]. In accordance with the basic dependencies of radical polymerization, the increase in total concentration of the monomers in the initial mixture ($[M_1]_0 + [M_2]_0$) led to the increase in the molecular mass of the formed copolymers (Exp. 1–3), and the increase in the concentration of initiator decreased the copolymer molecular mass (Exp. 3 and 4, 6 and 5). Hence, we determined the conditions allowing the control of the composition and molecular weight of copolymers **1**. Copolymers **1** had low molecular mass (19000–34000 Da) and can be excreted after parenteral administration without accumula-tion in a body to achieve the therapeutic effect of the immobilized biologically active substances. The amount of COOH groups in copolymers **1a**–**i** is enough (≥10 mol %) for their usage in further modification reactions.

Polydispersity index ($\overline{M}_w/\overline{M}_n$ ratio) of those copolymers was below 2.0 (Table 1).

Structure and composition of the copolymers **1a–1i** were confirmed using IR spectroscopy and titration of carboxylic groups. The IR spectra of the copolymers contained the absorption bands at 1718 cm^{-1} (characteristic of stretching the carboxylic group C=O) and 1677 cm^{-1} (the C=O group of *N*-vinylpyrrolidone unit).

Copolymers **1g–1i** were studied using molecular hydrodynamics and optical methods in an aqueous solution of CH_3COONa. The samples for the study were chosen in view of the high content of crotonic acid units ($m_2 > 20$ mol %) which made the assessment of molecular weight from the intrinsic viscosity incorrect. The values of the Huggins constant (K'), sedimentation constant (S_0), diffusion coefficient (D_0), and molecular weight (M_{SD}) of the investigated copolymers determined using a combination of diffusion and sedimentation methods are given in Tables 1 and 2, along with some other molecular parameters. As follows from the data in Table 2, the values of partial specific volume V of the copolymers were 0.77 cm^3/g, close to that of poly-*N*-vinylpyrrolidone (0.78 cm^3/g). The values of the Huggins constant K' (0.3–0.7) corresponded to the usual range for polymers in a good solvent. Copolymers **1g** and **1i** with higher molecular weight showed lower value of the diffusion coefficient (D_0) as compared with copolymer **1h**. Positive and high values of the second virial coefficient A_2 indicated the good

Table 2. Molecular and hydrodynamic parameters of copolymers of *N*-vinylpyrrolidone with crotonic acid in 0.1 M. solution of sodium acetate

Comp. no.	V, cm^3/g	K'	S_0, S	$D_0\times10^7$, cm^2/s	M_w[a]	R_h^D, nm	R_h^f, nm[b]	R_h^s, nm[b]	$A_2\times10^3$, $cm^3\ mol\ g^{-2}$ [b]
1g	0.77	0.3	1.3	7.0	28600	3.5	2.8	90	1.11
1h	0.77	0.3	1.1	9.4	19500	2.6	2.2	104	0.23
1i	0.77	0.7	–	5.4[a]	34800	–	4.0	75	0.32

[a] Determined using static light scattering method. [b] Determined using dynamic light scattering method.

Table 3. Condensation of *p*-oxybenzaldehyde with copolymers of *N*-vinylpyrrolidone and crotonic acid[a]

Initial copolymer	Molar ration of reacting groups		Reaction product **2**				Q, %
	COOH/DCC	COOH/*p*-oxybenzaldehyde	Symbol	Yield, %	l, mol %	k, mol %	
1d	1 : 1	1 : 1	**2a**	53.4	7.7	6.1	56.3
1e	1 : 1	1 : 1	**2b**	73.2	10.2	8.1	55.7
1g	1 : 1.5	1 : 1.5	**2c**	52.5	17.0	7.7	68.7
1h	1 : 1.3	1 : 1.3	**2d**	55.8	14.1	10.1	58.3
1i	1 : 1.5	1 : 1.5	**2e**	61.1	21.0	10.8	62.0

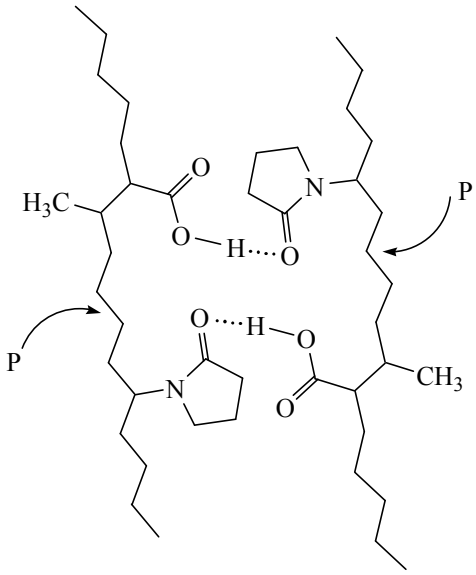
[a] Q—degree of condensation of *p*-oxybenzaldehyde with copolymers **1**, l—content of aldehyde groups in terpolymer, k—content of carboxylic groups in terpolymer.

thermodynamic property of the solvent. Two modes were registered for copolymers **1g–1i** using dynamic light scattering method. The same has been earlier observed for the solutions of copolymers of *N*-vinylpyrrolidone with 2-aminoethyl methacrylate hydrochloride [7]. The fast mode, characterized by hydrodynamic radius R_h^f of 2.2–4.0 nm, corresponded to the diffusion of individual macromolecules. It should be noted that the R_h^f values were close to the hydrodynamic radius R_h^D obtained from translational diffusion measurements (2.6–3.5 nm). The slow mode of dynamic light scattering was caused by the diffusion of supramolecular structures. It was characterized by hydrodynamic radii R_h^s (extrapolated to infinite dilution) of 75–104 nm. The formation of supramolecular structures (associates) was probably caused by the H-bonds involving carboxylic groups of different macromolecules (Scheme 1).

The presence of supramolecular structures in the solution led to overestimation of the weight-average molecular mass M_w as compared with the hydrodynamic M_{SD} (Tables 1 and 2). At the same time, the lability of the supramolecular structures (their destruction during motion in the hydrodynamic fields of ultracentrifuge and viscometer) cannot be ruled out. It should be noted that the fraction of the supramolecular structures is small [7].

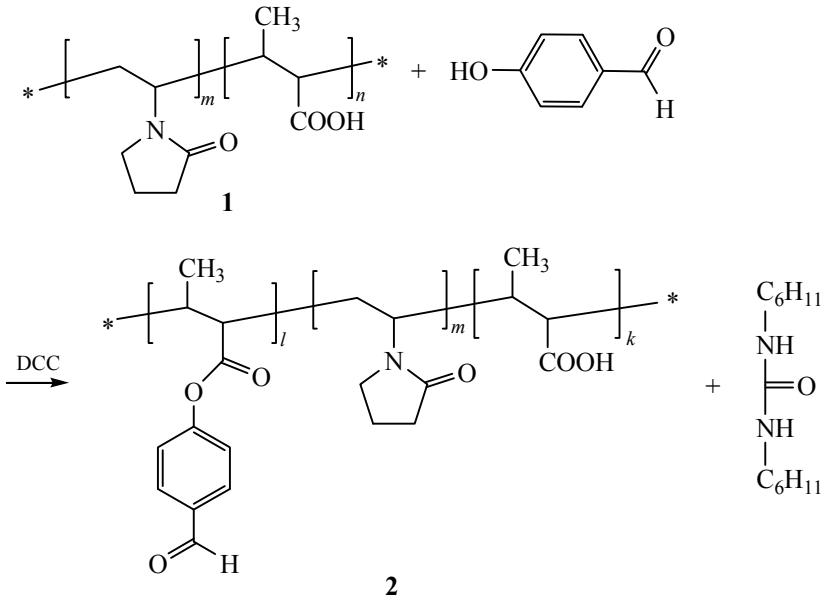
The reaction of *p*-oxybenzaldehyde condensation with copolymers **1d**, **1e**, **1g–1i** (Scheme 2) was carried out in DMF at 0°C in the presence of *N*,*N*'-dicyclo-

Scheme 1.



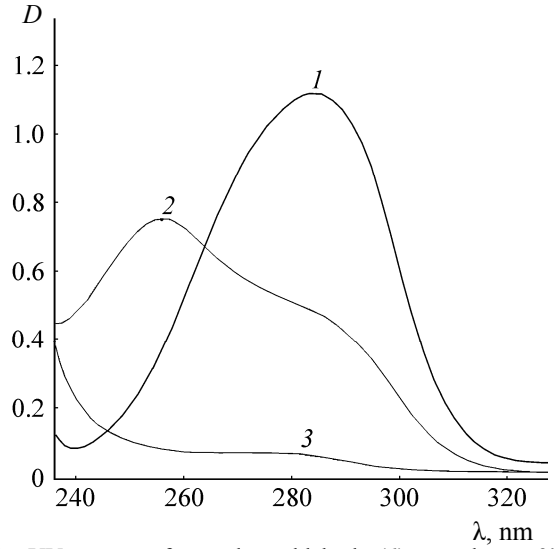
P—polymeric chains.

Scheme 2.



$m + n = 100$ mol %; $l + k = n$ mol %.

hexylcarbodiimide (DCC) as the condensing agent. The degree of condensation of *p*-oxybenzaldehyde with copolymers **1** was tuned by changing the composition of the initial copolymer and the molar ratio of the DCC-activated reactive carboxylic hydroxyl groups. The data on the condensation of *p*-oxybenzaldehyde with copolymers **1d**, **1e**, **1g–1i** are given in Table 3. Quite high (*Q* 55.7–68.7%) degree of addition of *p*-oxybenzaldehyde to carboxyl-containing units of copolymer **1** were achieved in the experiments. The terpolymers **2** were transformed into the ionic form to obtain water-soluble polymers.



The UV spectra of *p*-oxybenzaldehyde (*1*), terpolymer **2i** (*2*), and co-polymer **1i** (*3*) in ethanol.

Composition and structure of terpolymers **2** were confirmed using the data on carbon content, titration of carboxylic groups, and UV and NMR spectroscopy. After addition of *p*-oxybenzaldehyde to copolymer **1**, the content of carbon in the reaction product was increased by 4.3–6.8% compared to that in the initial copolymer of *N*-vinylpyrrolidone with crotonic acid.

A strong absorption band with λ_{max} 284 nm was observed in the UV spectrum of ethanolic solution of *p*-oxybenzaldehyde (see the figure). Another absorption band with λ_{max} 255 nm appeared in the UV spectra of ethanolic solution of the obtained terpolymers **2**; furthermore, an absorption band at 284 nm was found, absent in the spectra of initial copolymers **1**. These observations confirm the presence of *p*-oxybenzaldehyde units in the prepared terpolymers **2** (after purification from the unreacted *p*-oxybenzaldehyde via precipitation of the polymerizate with a mixture of diethyl ether and acetone, *p*-oxybenzaldehyde being soluble in that mixture).

The signals of protons of aldehyde groups at 9.77 ppm were observed in the ^{1}H NMR spectra of terpolymers **2**. Furthermore, there were signals of benzene rings protons at the typical 7.46–8.00 ppm region. Those signals were absent in the ^{1}H NMR

spectra of copolymers **1**, evidencing the presence of *p*-crotonoyloxybenzaldehyde units in terpolymers **2**.

The synthesized terpolymers **2** contained 7.7–10.8 mol % of carboxylic groups and 10.2–21.0 mol % of aldehyde groups. This is enough for binding of several bioactive substances. Sample **2a** containing <10 mol % of carboxylic groups can be used as the targeted delivery system after introduction of the vector groups.

EXPERIMENTAL

The composition of copolymers **1** and **2** were determined by potentiometric titration of carboxylic groups with 0.1 M. solution of NaOH using a HJ 2210 pH-meter. The determination of hydrodynamic (M_{SD}) and weight-average (M_w) molecular masses was performed as described in [8] and [7], respectively. Hydrodynamic radius of the scattering objects was determined using the regularization method [9]. The A_2 parameter was calculated using the Debye equation [9] from the data on static light scattering of the copolymers solutions. Partial specific volume was determined by pycnometry. Polydispersity index of the copolymers of *N*-vinylpyrrolidone with crotonic acid was determined from the GPC data. The GPC experiments were performed using a system of microstyrogel chromatography columns (Waters/Millipore) with porosity of 10^2, 10^3, and 10^5 nm; with DMF as the solvent. The chromatograph was calibrated using narrow fractions of polystyrene references. The calibration for poly-*N*-vinylpyrrolidone was calculated from the universal Benoit's calibration.

Electronic absorption spectra were recorded using an SF-256 spectrophotometer. NMR spectra (DMSO-d_6) were registered using a Bruker Avance II-400 spectrometer [400.1 (^{1}H) and 100.6 MHz (^{13}C)]. IR spectra were registered using a Bruker JFC 88 FTIR spectrometer in KBr pellets. Viscometry measurements were performed using an Ubbelohde viscometer in 0.1 M aqueous solution of sodium acetate at 25°C; the solvent flow time was 142.3 s.

N-Vinylpyrrolidone (Lancaster) was purified by double vacuum distillation over KOH; a fraction with bp 60–62°C (2–3 mmHg) was collected, n_D^{20} 1.5110 (n_D^{20} 1.517 [10]). According to GLC data, the purity of the obtained *N*-vinylpyrrolidone was 99.7%. GLC conditions: Hewlett-Packard chromatograph, PEG modified with nitroterephthalic acid as the sorbent, helium as the carrier gas, flame ionization detector, evaporator temperature 300°C, column temperature (final) 220°C, gas flow rate 20 mL/h, sample volume 1 μL. DMF was purified as described elsewhere [11]. DCC (Fluka) and 2-propanol (Vekton) were used as received.

Crotonic acid (Merk) was twice recrystallized from water in the presence of activated carbon, mp 71°C. Found, %: C 55.64; H 6.72. $C_4H_6O_2$. Calculated, %: C 55.81; H 6.98.

AIBN initiator was purified as follows. 46 g of AIBN was heated on a water bath in a mixture of 100 mL of chloroform and 80 mL of ethanol, the temperature not exceeding 40°C. The major fraction of AIBN was dissolved. The insoluble coagulated particles were filtered off on a Buchner funnel. 400 mL of ethanol was added to the transparent filtrate. The obtained solution was kept at –10°C for 20 h. The precipitate was collected on a Buchner funnel and dried under vacuum of a water-jet pump. The obtained product was dissolved in a mixture of 40 mL of chloroform and 30 mL of ethanol. The solution was kept at –10°C for 20 h. The obtained product was collected on a Schott filter and dried under vacuum to constant mass. Yield of the purified AIBN 25.3 g (55%), mp 103°C. Found, %: C 57.97; H 7.27. $C_8H_{12}N_4$. Calculated, %: C 58.53; H 7.31.

***p*-Oxybenzaldehyde.** A mixture of 170 mL of freshly distilled anisaldehyde and 400 g of pyridinium chloride was stirred at 170°C for 3 h. A hot solution was poured into 1.5 L of cold water. The obtained oil was extracted with diethyl ether. The extracts (~600 mL) were dried over anhydrous sodium sulfate for 24 h. Ether was distilled off; the residue was dried under vacuum and twice recrystallized from water with addition of activated carbon. Yield 76.5 g (45.2%), mp 113°C. Found, %: C 68.37; H 4.6. $C_7H_6O_2$. Calculated, %: C 68.85; H 4.95.

Synthesis of co-polymers 1a–1i. AIBN and a solution of a mixture of *N*-vinylpyrrolidone and crotonic acid in propanol-2 were put in an ampoule. The mixture was bubbled with argon; the ampoule was sealed at heated at 65°C for 48 h. The copolymer was isolated from the polymerizate by precipitation in diethyl ether, collected on a Schott filter, dried under vacuum, and reprecipitated from 2-propanol into diethyl ether.

Synthesis of terpolymers 2. A solution of DCC in 5 mL of DMF was added to a solution of co-polymer **1**

in 10 mL of DMF at cooling (0 to –5°C). The obtained solution was stirred for 0.5 h, and then *p*-oxybenzaldehyde was added. The obtained mixture was stirred for 2 h at cooling and for 4 h at room temperature, and then kept at –10°C for 20 h. The precipitate was filtered on a Schott filter. The filtrate was concentrated under vacuum at 40–42°C (5 mmHg). 3 mL of ethanol was added to the viscous residue. The reaction product was isolated via precipitation in a mixture of diethyl ether and acetone (1 : 1 v/v), collected on a Schott filter, and dried under vacuum.

ACKNOWLEDGMENTS

Authors acknowledge S.V. Konova, A.I. Lelyuh, and E.N. Vlasova (Institute of Macromolecular Compounds, Russian Academy of Science) for participating in the work.

This work was performed within the framework of the state assignment of Ministry of Education and Science of the Russian Federation (AAAA-A16-116071450049-0).

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