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MACROMOLECULAR CHEMISTRY AND POLYMERIC MATERIALS

Modification of Vinylformamide by Michael Addition to Methyl Acrylate and Methyl Vinyl Ketone, and Copolymers Derived from the Resulting Products

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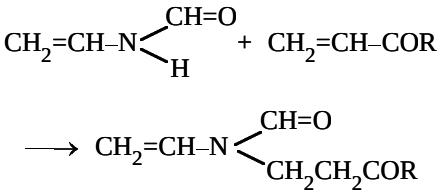
Abstract—Vinylformamide reacts with methyl acrylate and methyl vinyl ketone under conditions of base catalysis, following the Michael addition pattern, to give methyl 3-(vinylformylamino)propionate and previously unknown 4-(vinylformylamino)-2-butanone. Radical copolymerization of these compounds with vinylformamide and *N*-vinylpyrrolidone was studied.

Targeted transport of a physiologically active substance to a definite organ, cell, or tissue of a living body is an important problem in modern pharmacology. Efficient carriers for such transport can be water-soluble copolymers derived from *N*-vinylamides, which show enhanced affinity for proteins owing to the presence of similar amide groups and other functional moieties.

Polymers derived from *N*-vinylpyrrolidone and *N*-vinylacetamide and its *N*-alkyl analogs were studied previously [1–3]. Introduction of hydrophobic alkyl radicals into side chains of such polymers opens up possibilities for control of their conformational state and increases the probability of their binding with hydrophobic sections of cell membranes.

In this work, with the aim to develop new copolymers based on vinylformamide (VF) and containing functional fragments in pendant chains, we studied modification of VF by the reactions with methyl acrylate (MA) and methyl vinyl ketone (MVK) under conditions of base catalysis, following the Michael addition pattern:



Ia, Ib

where R = OCH_3 (**Ia**), CH_3 (**Ib**).

We found that the reaction occurs within 24 h at room temperature without a solvent in the presence of catalytic amounts of an alkali. The products are liquids readily distillable in a vacuum. The physicochemical characteristics of the compounds are listed in Table 1.

The ^1H NMR spectra of **Ia** and **Ib** fully confirm their structure. In particular, the spectra (Fig. 1a) contain a characteristic *ABX* pattern of vinyl protons (4.5 and 6.5 ppm) and two multiplets of methylene protons (2.5 and 4.0 ppm, CH_2CH_2N). Some signals are doubled because of braked rotation of the formyl group about the C–N bond (Table 2).

Thus, Michael addition of vinylformamide to com-

Table 1. Physicochemical characteristics of **Ia** and **Ib**

Compound	bp, °C/*P*, mm Hg	Found, %			Formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
Ia	93–96/2	53.54	6.97	8.87	$C_7H_{11}NO_3$	53.49	7.05	8.91	70
Ib	98–104/1	59.60	7.79	9.88	$C_7H_{11}NO_2$	59.56	7.85	9.92	75

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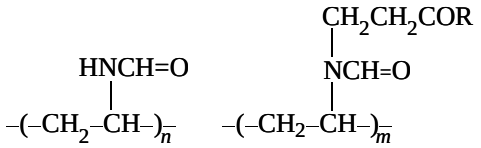
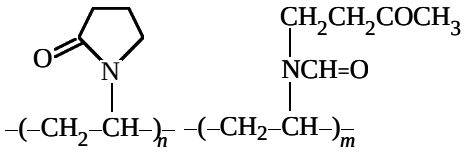
Table 2. ^{1}H NMR spectra of **Ia** and **Ib** in $CDCl_3$

Compound	Conformational composition, %	δ, ppm					
		CH_3, s	CH_2CO, m	CH_2N, m	CH_2=, m	CH=, m	CH=O, s
Ia	*E*, 75	3.62	3.80	4.51	6.51	7.18	8.23
	Z, 25	3.62	3.80	4.51	6.49	6.90	8.18
Ib	*E*, 80	2.07	2.63	4.41	6.50	7.11	8.20
	Z, 20	2.07	2.63	4.41	6.49	6.91	8.18

pounds containing an activated C=C bond (MA, MVK) is a convenient route to modified vinylformamide derivatives, which are of interest as monomeric precursors of water-soluble copolymers containing a functionally substituted vinylamide moiety:



IIa, IIb



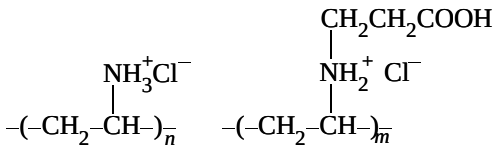
III

where R = OCH_3 (**IIa**), CH_3 (**IIb**).

Copolymerization of VF and VP with modified VF analogs, methyl 3-(vinylformylamino)propionate (VFMA) and 4-(vinylformylamino)-2-butanone (VFVMK) was performed by heating of the monomers dissolved in isopropanol at 60°C in glass ampules under nitrogen, with azobis(isobutyronitrile) initiator (1 wt % relative to comonomers). The conditions for preparing copolymers **IIa**, **IIb**, and **III** and their intrinsic viscosities [η] are listed in Table 3. The procedure allows preparation of random water-soluble copolymers in high yields.

The compositions of the copolymers were determined from the integral intensities of the characteristic ^{1}H NMR signals, namely, of those of H–C=O (8 ppm) and CH_2 (2.8 ppm) groups in the case of **IIa** and **IIb** (Fig. 1b, Table 4) and of H–C=O group (8 ppm) and H^5 atom in the pyrrolidone ring in the case of copolymer **III** derived from VP. The measurement error was ±3–5%.

Copolymers **IIa** were hydrolyzed to vinylamine–3-(vinylamino)propionic acid copolymers (in the form of hydrochlorides, **IV**) by heating in 10% HCl at 120°C for 24 h; the products were isolated by precipitation into acetone.



IV

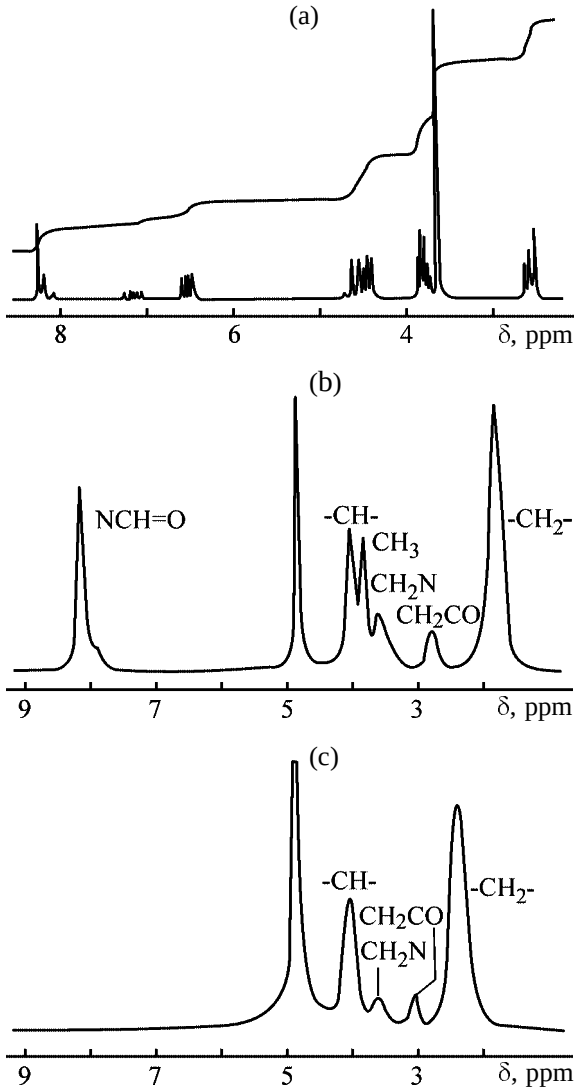


Fig. 1. ^{1}H NMR spectra of (a) **Ia** in $CDCl_3$, (b) **IIa** in D_2O, and (c) **IV** in D_2O. (δ) Chemical shift.

Table 3. Copolymerization conditions and characteristics of copolymers

Compound	Content of initial monomers, mol %		Yield, %	Copolymer composition, mol %		[η], dl g^{-1}
	VF or VP	VFMA or VFVMK		VF or VP	VFMA or VFVMK	
IIa	85	15	90	85	15	0.27
	50	50	60	60	40	0.18
	25	75	50	35	65	0.17
IIb	80	20	95	84	16	0.40
	65	35	70	62	38	0.18
III	80	20	98	82	18	0.21
	70	30	75	75	25	0.13
IV	85	15	65	85	15	0.15
	50	50	75	60	40	0.12
	25	75	70	35	65	0.10

Table 4. ^{1}H NMR spectra of copolymers in D_2O

Compound	δ, ppm					
	$-CH_2-$	–CH–	H–C=O or H^3, H^4, H^5	CH_2CO	CH_2N	CH_3
IIa	1.97	4.02	8.12 (H–C=O)	2.76	3.56	3.78
IIb	1.98	4.12	8.20 (H–C=O)	3.08	3.61	2.46
III	2.03	3.97	2.24 (H^4), 2.48 (H^3), 3.53 (H^5)	3.13	3.44	2.41
IV	2.21	4.04	–	3.13	3.64	–

The degree of hydrolysis was evaluated from the Cl^- content, determined by conductometric titration with 0.01 M $AgNO_3$, and also from the ^{1}H NMR spectra (disappearance of the formyl proton signal at 8.0 ppm and of the methoxy group signal at 2.8 ppm; Fig. 1c). The conditions for synthesis of copolymers **IV** and their intrinsic viscosities are given in Table 3.

Thus, Michael addition of vinylformamide to compounds containing an activated double bond is a convenient route to modified derivatives of this monomer. The procedure allows introduction into pendant chains of ester and carbonyl groups for subsequent modification by functional binding of physiologically active substances.

EXPERIMENTAL

Elemental (C, H, N) analysis was performed with a Hewlett–Packard 185B analyzer. The ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer. Titration was performed with a TV-6L-1 conductometer. The intrinsic viscosity was measured with an Ubbelohde viscometer in water at 25°C. Compound **Ia** was prepared as described in [4].

4-(Vinylformylamino)-2-butanone Ib. A 35-g (0.5-mol) portion of VF was added dropwise with cooling (the temperature was maintained within 20–25°C) to a mixture of 40 g (0.55 mol) of freshly distilled MVK, 0.56 g of KOH, and 0.01 g of hydroquinone in 10 ml of methanol. The mixture was left overnight at room temperature and, after addition of 0.5 g of sodium acetate, distilled in a vacuum.

CONCLUSIONS

(1) Michael addition of vinylformamide to methyl acrylate and methyl vinyl ketone, yielding new monomers, methyl 3-(vinylformylamino)propionate and 4-(vinylformylamino)-2-butanone, was studied.

(2) Copolymers of these monomers with vinylformamide and *N*-vinylpyrrolidone were prepared, and their acid hydrolysis was studied. The *N*-formyl and ester groups can be quantitatively removed with the

formation of vinylamine–3-(vinylamino)propionic acid copolymers in the form of hydrochlorides.

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