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CHEMISTRY

β-Oxalylamino-Substituted *O*-Ethyl *N*-Arylcarbamates and *N*-Ethyl-*N*′-arylureas Encapsulated into Micelles of Vinylimidazole–Vinylcaprolactam Copolymer

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Abstract—Low-molecular-weight compounds—β-oxalylamino-substituted *O*-ethyl carbamates and unsymmetrical ureas showing biological activity—have been synthesized and encapsulated into micelles of vinylimidazole–vinylcaprolactam copolymers. Solubilization in micelles has provided a preparation of water-soluble colloidal formulation of these compounds suitable for practical application.

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Physiological functions of phytohormonal cytokinins deal with stimulation of plant cell division, intensification of nutrients transport into cells, inhibition of root meristem, retardation of leaf ageing [1], and other regulatory effects. Up to date, cytokinin activity of synthetic analogs of natural phytohormones was mainly used to obtain compounds with herbicide properties (Phenmedipham) and defoliants (Thidiazuron, Cytodef), as well as antistress-type plant growth regulators that protect plants from water lack and frost [2, 3]. The methods of preparation of synthetic analogues of cytokinins with defoliant activity are based mainly on the reaction of amino-substituted heterocycles with aryl isocyanates [4]. The resultant unsymmetrical ureas show definite structural resemblance with natural cytokinins, one of which is diphenylurea [1].

β-Oxalylamino-substituted *O*-ethyl *N*-arylcarbamates and *N*-ethyl-*N*′-arylureas are a new class of phytoactive compounds showing growth regulatory activity [5]. These carbamates and unsymmetrical ureas are structural analogs of herbicidal and growth-regulatory biscarbamates, including well-known Phenmedipham and Kartolin 2 [1]. The obtained β-oxalylamino-substituted *O*-ethyl carbamates and ureas are stable crystalline compounds poorly soluble in water and organic solvents, which considerably hampers their transformation in formulations. At the same time, it is known that micellar media increase considerably the solubility of hydrophobic compounds, this fact can be used to design transport systems for the delivery of physiologically active compounds [6].

In this work, we report the results of study on the encapsulation of the prepared low-molecular-weight compounds—beta-oxalylamino-substituted *O*-ethyl carbamate and unsymmetrical ureas with potential biological activity—into micelles of vinylimidazole–vinylcaprolactam copolymers with the aim to obtain water-soluble colloidal formulations suitable for the practical application of these compounds in agriculture.

Carbamate **I** was obtained by Scheme 1. Diethyl oxalate was prepared by esterification by azeotropically removing water with carbon tetrachloride. The amidation of diethyl oxalate with ethanolamine was carried out using fourfold excess of the initial ester to reduce the yield of byproduct, *N*,*N*′-bis(2-hydroxyethyl)oxamide. Target carbamate **I** was obtained by the reaction of β-hydroxyethyloxamate with the appropriate isocyanate.

Urea **II** was synthesized by the aminolysis of diethyl oxalate with β-aminoethyl-(*p*-chlorophenyl)urea according to Scheme 2. Initial β-aminoethyl-(*p*-chlorophenyl)urea was prepared by the reaction of

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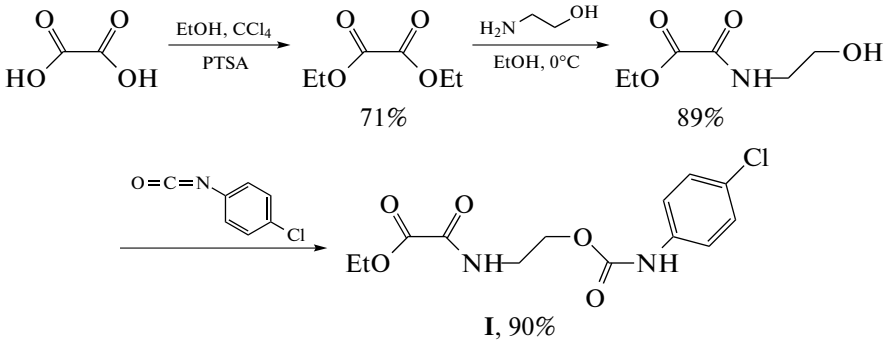
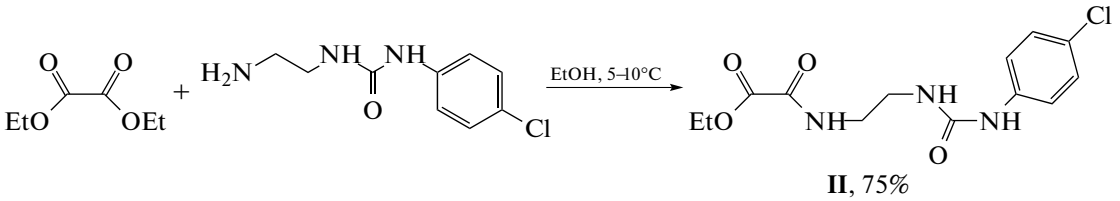


Scheme 1.

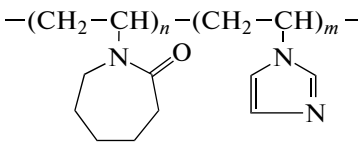


Scheme 2.

p-chlorophenyl isocyanate with excess of ethylenediamine at 0–5°C.

We used micelles of copolymers of *N*-vinylcaprolactam (NVCL) with *N*-vinylimidazole (NVI) in water (Scheme 3). The synthesis of the corresponding NVCL–NVI copolymers was carried out in a solution at temperature above phase separation point of the reaction system, which, as was shown previously in theoretical [7] and experimental works [8–10], provides coil–globule conformational transition for oligo(NVCL) blocks of resulting macromolecules and formation of heteroblock protein-like sequence of the corresponding polymer chains.

These copolymers at concentrations above critical micelle concentration were used to reveal the features of encapsulation of the prepared low-molecular-weight *O*-ethyl carbamate **I** and urea **II** with oxamate functional groups. To control solubilization in micelles, we used fluorescent spectroscopy (excitation at 280 nm). The addition of separate portions of the copolymer into aqueous solutions of compounds **I** and **II** that sequentially increased their concentration by 0.15 wt % led to decrease in the fluorescence of the



Scheme 3. Vinylcaprolactame–vinylimidazole copolymers.

studied compounds outside of micelles (Fig. 1, peak A) and the growth of their fluorescence inside micelles (Fig. 1, peak B). The obtained spectra display an isosbestic point (about 340 nm), which facilitates the determination of component concentration from fluorescence spectra. Thus, the solubilization in micelles provides a possibility to prepare water-soluble colloidal formulation of these compounds suitable for practical application.

EXPERIMENTAL

NVCL–NVI copolymers as a soluble fraction NVCL/NVI-S [8] were provides by the laboratory by Professor V.I. Lozinsky (Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE™ 400 spectrometer using $CDCl_3$ and DMSO-d_6 as internal references. IR spectra were registered on a Nicolet 380 IR Fourier-transform spectrophotometer coupled with ATR add-on unit (ThermoFisher Scientific Inc.). Fluorescence spectra were obtained with the use of a Perkin Elmer LS55 luminescent spectrometer. Excitation wavelength was 280 nm, slits were 10 and 5 nm. Fluorescence was monitored continuously in the range from 295 to 495 nm at scanning rate 150 nm/min. Titration conditions were as follows: a freshly prepared solution of 1.5 mg of carbamate in 1 mL of acetonitrile was diluted with 24 mL of water and 2 mL of this solution was placed into a cuvette (1-cm path length) of the luminescent spectrometer. This solution was used for

encapsulation by the sequential addition of a solution (30 mg/mL aqueous solution) of the copolymer by portions of 10 μL each (Fig. 1).

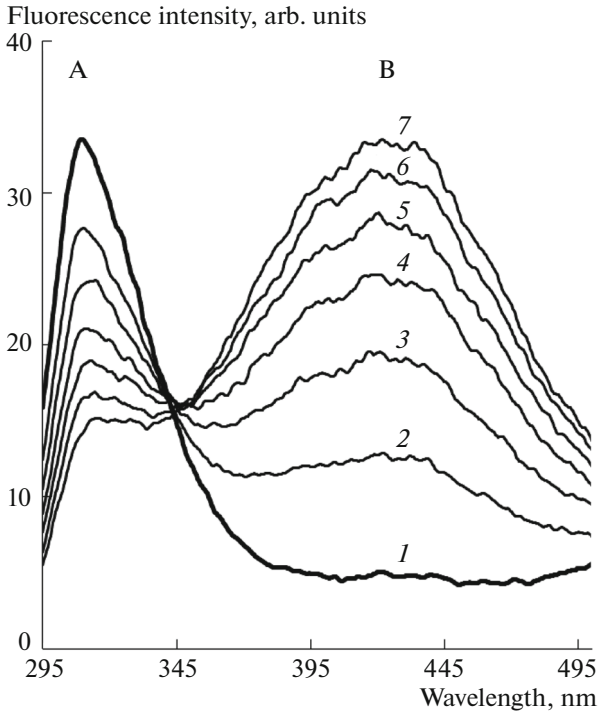
Preparation of *O*-ethyl *N*-2-hydroxyethyloxamate. Diethyl oxalate [11] (11.7 g, 0.08 mol) was placed into a 100-mL round-bottomed flask and 4 mL of ethanol was added. The mixture was cooled in an ice bath, 1.2 mL (0.02 mol) of monoethanolamine in 10 mL of ethanol was added dropwise with stirring, and cooling was terminated after that. According to NMR spectroscopy, the precipitate formed during warming the reaction mixture to ambient temperature was *N*,*N*'-bis(2-hydroxyethyl)oxamide with mp 133–136°C; it was separated by filtration. The filtrate was concentrated by rotary evaporation, the excess ester was removed in a vacuum of water-jet pump. The residue was the oxamate sufficiently pure for further transformations. Yield 89%, mp 133–135°C (lit.: mp 133–134°C [12]).

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 1.38 (t, 3H, CH_3, $J = 7.3$); 3.05 (br s, 1H, –OH); 3.53 (dt, 2H, NH–CH_2, $J_{NH-CH_2} = 4.9$, $J_{CH_2-CH_2} = 5.4$); 3.8 (t, 2H, CH_2–OH, $J = 5.4$); 4.35 (q, 2H, CH_2–CH_3, $J = 7.3$). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 13.9 (CH_3), 42.4 (NH–CH_2), 61.1 (CH_2OH); 63.3 (–CH_2–CH_3), 157.3 (–O–C(O)), 160.5 (–C(O)–NH).

Preparation of *N*-(2-aminoethyl)-*N*'-(4-chlorophenyl)urea. A solution of 39 g (0.25 mol) of 4-chlorophenyl isocyanate in 100 mL of acetonitrile was added dropwise to a solution of 78 g (1.3 mol) of ethylenediamine in 200 mL of dry acetonitrile on cooling in an ice bath with vigorous stirring. The resultant precipitate was separated by filtration on a Schott filter funnel (byproduct, *N*-[(4-chlorophenyl)carbamoyl]ethylenediamine). The mother liquor was concentrated by rotary evaporation. Excess ethylenediamine was removed in vacuum of water-jet pump (bp 114°C at 15–20 mmHg). The crystalline target product was recrystallized from acetonitrile, mp 139–142°C. Yield 90%. (lit.: mp 140–142°C [13]).

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, *J*, Hz): 2.64 (m, 2H, C$\underline{H_2}$NH$_2$); 3.09 (m, 4H, C$\underline{H_2}$NH and N$\underline{H_2}$); 6.64 (t, 1 H, NHCH$_2$, $J = 8$); 7.24 (d, 2H, CH_{arom}, $J = 8$); 7.43 (d, 2H, CH_{arom}, $J = 8$); 9.04 (s, 1H, C(O)NHC). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 41.9 ($NH_2\underline{C}H_2$); 42.3 (NH_2CH_2); 119.5 (HNC$\underline{C}$H); 124.6 (Cl$\underline{C}$); 128.8 (ClC$\underline{C}$H); 140.2 (HN$\underline{C}$CH); 155.8 (NH$\underline{C}$(O)NH).

Preparation of *N*-(*N*-ethoxycarbonylcarbonyl-2-aminoethyl)-*N*'-(4-chlorophenyl)urea (I). *O*-Ethyl-*N*-2-aminoethyloxamide (0.60 g, 3.7 mmol) was placed into a 50-mL round-bottomed flask and dissolved in 5 mL of toluene, a solution of 0.57 g (3.7 mmol) of *p*-chlorophenyl isocyanate in 4 mL of toluene was added to the resultant solution at ambient temperature with stirring. Four drops of triethylamine was added to the resultant mixture with stirring. The reaction mixture



Fluorescence spectra of *O*-alkyl carbamate **I** in the absence (curve *1*) and in the presence (curves *2*–*7*) of NVCL–NVI copolymer micelles. Micelle concentration increases as an aqueous copolymer solution (30 mg/mL) was added in 10-μL portions (from *2* to *7*). (*1*) Spectrum of initial carbamate **I** (0.06 mg/mL).

was stirred at ambient temperature for 1 h. The resultant precipitate was separated by filtration and recrystallized from isopropanol. Yield of the target product is 90%, mp 179–180°C.

For $C_{13}H_{15}ClN_2O_5$ anal. calcd. (%): C, 49.61; H, 4.80; Cl, 11.26; N, 8.90; O, 25.42.

Found (%): C, 49.11; H, 5.27; N, 13.40.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, *J*, Hz): 1.27 (t, 3H, CH_3, $J = 4$); 3.45 (dt, 2H, NHC$\underline{H_2}$, $J_{CH_2-NH} = 8$, $J_{CH_2-CH_2} = 4$); 4.19 (t, 2H, C$\underline{H_2}$CH$_2$NH, $J = 4$); 4.24 (q, 2H, C$\underline{H_2}$CH$_3$, $J = 8$); 7.33 (d, 2H, CH_{2arom}, $J = 8$); 7.49 (d, 2H, CH_{2arom}, $J = 8$); 9.05 (t, 1H, CH$_2$CH$_2$N$\underline{H}$, $J = 4$); 9.84 (s, 1H, CHCN$\underline{H}$). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 14.3 ($\underline{C}H_3$); 39.1 (NH$\underline{C}$H$_2$); 62.5 ($CH_3C\underline{H_2}O$–); 62.7 ($CH_2\underline{C}H_2O$–); 120.1 (HN–C–$\underline{C}$H); 126.5 (ClC$\underline{C}$H); 129.1 (Cl$\underline{C}$); 138.6 (HN–$\underline{C}$–CH); 153.7 (O$\underline{C}$(O)C–); 157.7 (O$\underline{C}$(O)NH); 161.0 (C(O)$\underline{C}$(O)NH). IR (ν, cm^{-1}): 1542.77 (0.530) (NH def.; N–C=O, amide); 1696.90 (0.559) (C(O), amide); 1724.68 (0.557) (C(O)–, ester); 3306.92 (0.456) (NH).

Preparation of *N*-ethoxycarbonylcarbonyl)-2-aminoethyl *N*-(4-chlorophenyl)carbamate (II). Diethyl oxalate (4.5 g, 0.05 mol) was dissolved in 5 mL of ethanol in a round-bottomed flask equipped with a ther-

mometer and a dropping funnel, a solution of 0.885 g (0.004 mol) of *N*-[(4-chlorophenyl)carbamoyl]ethylenediamine in 15 mL of ethanol was added to the resultant solution with stirring and cooling on an ice bath. The reaction mixture was allowed to stand at ambient temperature for 1 h, the resultant white precipitate was separated by filtration and recrystallized from isopropanol. Yield of **II** is 75%, mp 192–194°C.

For $C_{13}H_{16}ClN_3O_4$ anal. calcd. (%): C, 49.77; H, 5.14; Cl, 11.30; N, 13.39.

Found (%): C, 49.91; H, 5.07; N, 13.18.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, *J*, Hz): 1.27 (t, 3H, CH_3, J = 8); 3.22–3.24 (m, 4H, C$\underline{H}_2$); 3.35 (s, 1H, N$\underline{H}$); 4.23 (q, 2H, C$\underline{H}_2$–CH_3, J = 4); 7.26 (d, 2H, CH_{arom}, J = 8); 7.42 (d, 2H, CH_{arom}, J = 8); 9.05 (s, 1H, C(O)–NH–); 9.84 (s, 1H, C–NH–C(O)). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 14.3 ($\underline{C}H_3$); 38.7 ($\underline{C}H_2$); 39.1 ($\underline{C}H_2$); 40.0 ($\underline{C}H_2$); 62.5 ($\underline{C}H$); 120.1 (NH–C–C$\underline{H}$); 126.5 (Cl–$\underline{C}$); 129.1 (Cl–C–$\underline{C}$H); 138.6 (NH–$\underline{C}$–); 153.7 (HN–$\underline{C}$(O)–NH); 157.7 (O–$\underline{C}$(O)); 161.0 (C(O)–$\underline{C}$(O)–NH).

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