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Fluorine-containing polyamphiphiles constructed from synthetic and biopolymer blocks

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Aim. Synthesis of polymeric surfactants combininghydrophobic fluorine-containing and hydrophilic synthetic and natural blocks via radical and non-radical reactions using peroxide, epoxide and/or amino-terminal groups of the polymeric elementary blocks. **Methods.** Radical and non-radical condensation reactions, polymerization, spectral (NMR- and luminescence spectroscopy), gel-permeation chromatography and other analytical techniques. **Results.** Primary poly(F-MA)-MP oligomers were synthesized via radical polymerization of fluorine-alkyl methacrylate (F-MA) in the presence of peroxide-containing telogen (MP). This allows to control the oligomer chain length and architecture as well as insert a terminal peroxide group in the macromolecules. Radical polymerization of vinylpyrrolidone (NVP) initiated by poly(F-MA)-MP as the macroinitiator in the presence of epoxide-containing derivative of cumene (CGE) was used to obtain water soluble poly(F-MA)-*block*-poly(NVP)-CGE. Finally, oligonucleotide (ONC) was attached by condensation reaction of ONC primary amino group with the terminal epoxide group of the poly(F-MA)-*block*-poly(NVP)-CGE. **Conclusions.** A series of novel block/comb-like copolymers with synthetic and natural parts was synthesized. Obtained tri-block copolymers can be used as markers for labelling bacteria and pathological cells including cancer cells.

K e y w o r d s: fluorinated polyamphiphiles, oligonucleotide, radical and coupling reactions, hybrid block-copolymer, bacteria labeling.

Introduction

Among functional surfactants used for biomedical purposes the water soluble polymers of comb-like and block structures assume ever greater importance as carriers of the drugs and nucleic acids due to their ability to bind bioactive substances including water insoluble drugs, to form highly stable systems providing their addressed delivery to organ-target, to protect drugs from damage during transportation, prolong therapeutic efficiency, and reduce their toxicity [1].

Such drug delivery systems are widely used for immobilization of hydrophilic or hydrophobic drugs, peptides, vaccines, oligonucleotides via various mechanisms, solubilization [2], and formation of hydrogen bonds [3], electrostatic interactions [4] or covalent binding [5] with polymeric carriers.

Unique properties of fluorine-containing polymers caused the rapid growth of their studies in various areas. Fluorinated fragments and chains of polymeric surfactants are more hydrophobic in comparison with their hydrocarbon counterparts [6]. Amphiphilic copolymers containing fluorine-alkyl chains were tested successfully as carriers for nucleic acid delivery as well as for labeling cells and microorganisms [7, 8]. Amphiphilic fluorine-containing copolymers are perspective as carriers for drug delivery systems [9] or contrast agents for magnetic resonance imaging [8, 9].

Purposeful application of functional polymeric surfactants demands controlling their structural, molecular-weight characteristics and functionality that define their efficiency for drug and nucleic acid delivery and release, overcoming blood-brain barrier and acquired resistance to drug action. Thus, the tasks of tailored architecture copolymers conscious synthesis are still topical.

Novel route of the synthesis and properties of fluorinated polyamphiphils of comb-like/block structures including blocks of natural origin via combination of radical and non-radical condensation reactions of polymer functional terminal groups are considered in the paper.

Materials and Methods

Monomers. N-vinyl-2-pyrrolidone (NVP) (Merck) was purified by vacuum distillation or glass column rectification and its characteristics coincided with the referred in [10]. 2,2,3,3,4,4,5,5-octafluoropentylmethacrylate (F8-MA) (Aldrich) was synthesized in the Institute of Organic Chemistry of NAS of Ukraine and used without further purification**.**

Initiator: 2,2′-Azobis(2-methylpropionitrile) (AIBN) (Aldrich) was purified by recrystallization from methanol. The melting point T_m after recrystallization was 378-379 K.

Chain transfer agents: 1- isopropyl-3(4)-[1-(*tert*-butyl peroxy)-1-methylethyl] benzene (MP) was synthesized from *tert*-butyl hydroperoxide and 2-(4-isopropylphenyl)-2-propanol in acetic acid medium as described earlier [11]. 2-{[(4-isopropyl benzyl)oxy]methyl} oxirane (CGE) was synthesized from cumene alcohol and described earlier (Fig. 1) [12].

Oligonucleotide C6-EUB338-Fam-6. Universal bacterial probe Eub338 FITC, green fluorescence, sequence - 5'- GCT GCC TCC CGT AGG AGT -3' (molecular mass-6000 Da) was given from Biomers Pte Ltd. Probe EUB 338, which is complementary to a portion of the 16S rRNA gene conserved in the domain

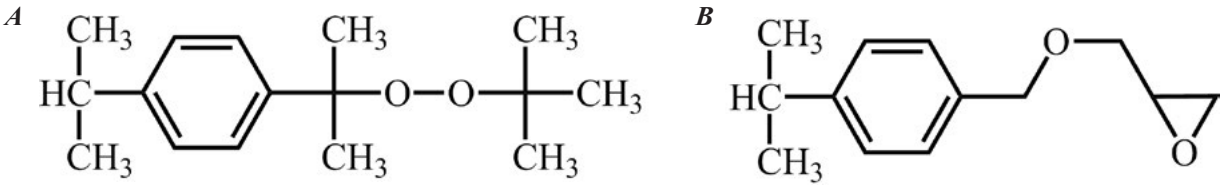

Fig. 1. The structures of MP (*A*) and CGE (*B*)

Bacteria, was used to visualize the entire bacterial population in the specimens [13]. With the universal bacterial probe EUB 338-FITC, bacteria could be detected by FISH technique (Fluorescence In Situ Hybridization) [14].

Solvents were used after purifications according to the techniques described [15].

Block/comb-like poly(F8-MA)-block-poly(NVP)-CGE copolymers were synthesized via three-stage polymerization, namely:

1) Telechelic oligoperoxide macroinitiators poly(F-MA)-MP were obtained by polymerization of macromer ([F-MA] = 1.5 mol/l) using AIBN ([AIBN] = 0.03–0,1 mol/l) as initiator and MP ([MP] = 0.15–0,62 mol/l) as chain transfer agent in dry dioxane at 343K. Macromer conversion was measured using dilatometric and gravimetric techniques [16]. After being cooled to room temperature, the mixture was concentrated, dissolved in acetone and several times purified by precipitation into hexane. The polymer was dried under vacuum at 323 K till a constant weight. After polymerization the resulting polymer samples were fractionated via dialysis technique using semi-penetrating membranes MILLIPORE (GSWP, 0.22mm) possessing capability 12 000 Da or via technique of fractional precipitation.

2) For the synthesis of poly(F-MA)-*block*-poly(NVP)-CGE macroinitiator poly(F-MA)-MP ([-O:O-] = 1.6–7.8 mol/l) was dissolved in dry dioxane, NVP ([NVP] = 1.5 mol/l) and CGE ([CGE] = 0.18 mol/l) were added to the solution. The reaction mixtures were charged into calibrated dilatometers; dilatometers were cooled, vacuumed, purged with argon and heated for 6–8 h at 363K. Monomer conversion was determined using dilatometric techniques. After polymerization [the] reaction mixtures were cooled, dried, dissolved in acetone, multiply purified by precipitation into hexane and dried again under the vacuum till constant weight. Then [the] resulting block/comb-like copolymers were purified from the macroinitiator poly(F-MA)-MP.

3) The synthesis of poly(F-MA)-block-poly(NVP)-CGE-block-oligonucleotide was carried out in water at 293 K. 0.0025 g of poly(F8-MA)-block-poly(NVP)-CGE copolymer was dissolved in 0.5 ml of water. Then 0.05 ml of aqueous solution of oligonucleotide C6-EUB338-Fam-6 ([C6-EUB338-Fam-6] = 0.00015 mol/l) was added dropwise to the polymer solution under constant stirring. The system was kept for 48 h at 293 K for condensation reaction. The obtained poly(F8-MA)-block-poly(NVP)-CGE/C6-EUB338-Fam-6 conjugate was purified from unreacted oligonucleotide by dialysis method. Aqueous solution of [the] reaction product was loaded to cellulose membrane (pore size — 14 kDa) and dialyzed for 48 h at 293 K. Experiment was conducted without light access. The molar ratio of epoxy-containing compounds to substances with amino group was 10:1.

Conversion of the monomers (*S*) was measured using dilatometric method [16]: S = ·(DV/(V×k))×100 %, where V — initial monomer volume at the defined temperature, ml; DV — a volume change after the defined period, ml; k — an average contraction constant for the monomer at the defined temperature [17], and controlled using [of] gravimetric technique. The rate of polymerization R_p (mol/(l·s)) was determined on [the] stationary section of kinetic curve of total change of monomer conversion in time [16] in coordinates S — τ. Effective rate constant of polymerization (K_{pol}) was calculated from the equation: $R_p = K_{pol}[I]^a[M]^b$, where [I] is the concentration of MP fragments, [M] — the monomer concentration [17].

The determination of relative constants of chain transfer to telogen (Tn), MP (C_{MP}), was carried out using equation $1/P_n = 1/(P_n)_0 + C_{Tg}\cdot([Tn]/[M])$ described in ref. [18], where P_n is polymerization degree at definite content of Tn, $(P_n)_0$ is polymerization degree of polymer synthesized without Tn. Thus C_{Tn} can be determined from inclination of the linear dependence $1/P_n$ on [Tn]/[M]. The constants of chain transfer to telogen (k_{tTn}) are calculated using equation $k_{tTn} = k_p \cdot C_{Tn}$, where k_p is a constant of the propagation rate.

Analytical techniques

The content of terminal MP fragments in copolymer molecules was calculated from the results of gas-liquid chromatography determination of the acetone and *tert*-butyl alcohol – final products of the peroxide group decomposition in isokinetic point at 473K [19]. The content of terminal CGE fragments in copolymer molecules was calculated from the results of determination of epoxide groups via back titration of residual HCl with KOH.

Content of NVP links (A,%) was calculated using equation $A = (a \cdot m_1)/4$ from results of Nitrogen content determination by elementary analysis [16], where *a* is Nitrogen content (%), m_1 — molecular weight of NVP.

The determination of copolymer molecular weights

Molecular weights of copolymers were determined by gel-penetration chromatography [20] using „Waters GPC/HPLC" equipped with Styragel columns, tetrahydrofuran (TGF) was used as eluent; elution rate was 0.5 ml/min.

IR-spectra of the copolymers were recorded on the device Specord –M80 in tablets with KBr, in petrolatum dispersions or in the films deposited from THF solution [21]. NMR spectra were recorded on spectrometer ^1H and ^{13}C Varian-VXR-300 with working frequency 299,943 MHz in the solutions of deuterated solvents.

Surface tension of the solutions was measured using device PPNL-1 (Ukraine) by the measurement of maximum bubble pressure [22].

Measurement of particle size

The hydrodynamic radii of the micelles were studied by dynamic light scattering (DLS) on DynaProNanoStar (Wyatt Technology, Santa Barbara, USA) at 298 K.

Results and Discussion

The developed approach to the synthesis of block-copolymers consists of consequent stages of radical and condensation reactions of

terminal functional groups according to the presented scheme (Fig. 2).

As evident from the scheme (Fig. 2) the polymerization of F-MA macromers in the presence of MP provides the formation of comb-like polymers containing side fluorinealkyl chains and terminal peroxide fragment as it was shown earlier [23]. The polymerization is obeyed to reverse dependences of the polymerization rate and molecular weight of resulting polymers on MP concentration (Table 1) due to the transfer and linear termination of growing chains due to the interaction with MP molecules. The values of polymerization orders rates in respect of initiator concentration (0.8-0.9) and high value of the chain

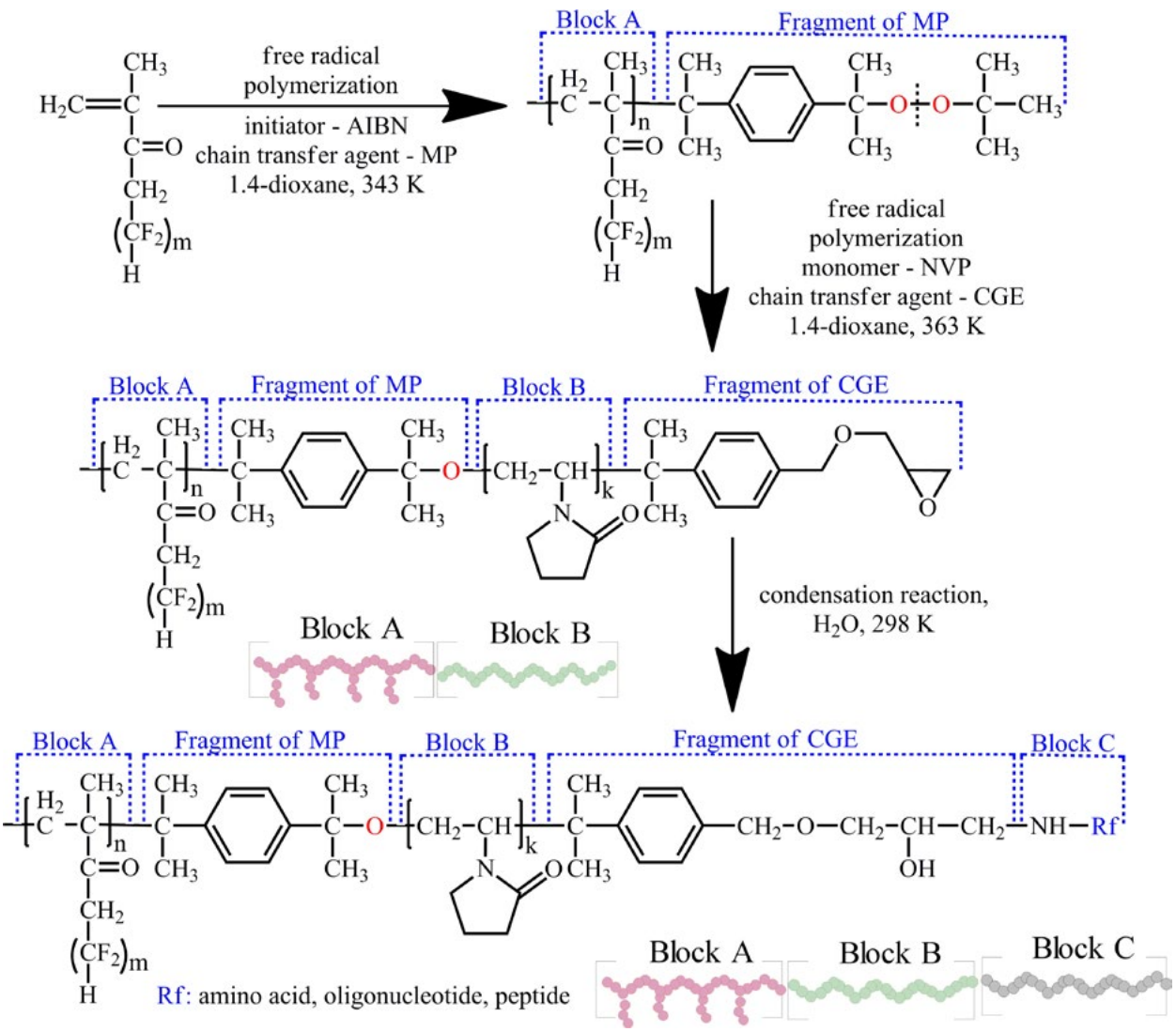

Fig. 2. General scheme of the synthesis of block amphiphilic copolymers based on poly(fluoroalkyl methacrylate)s

Table 1. **Kinetics of F8-MA polymerization ([mon]=1.5 mol/l, initiator – AIBN, 343 K, dioxane) and poly(F8-MA)-MP characteristics**

[MP], mol/l in reaction system	[AIBN], mol/l in reaction system	R_p10^4, mol/l·s	$K_{pol}\cdot10^3$, l/(mol·s)	α*	M^{**}_n, kDa	MP content in polymer molecules, %	*f* an average functionality in respect of MP end fragment	k_t, l/mole×s chain transfer to MP constant***
0.15	0.03	3.83	6.20	0.81	7.1	4.2	–	49.8
	0.06	5.81			6.7	4.5	1.12	
	0.08	7.55			–	–	–	
	0.10	10.7			–	–		
0.38	0.03	1.25	3.24	0.93	7.4	4.03	–	
	0.06	2.31			5.9	5.1	1.18	
	0.08	3.00			5.4	5.55	–	
	0.10	3.92			4.7	6.27		
0.62	0.06	2.07	–	–	4.3	6.9	1.18	

α — reaction order by initiator **GPC results; *k_p= 809 for butyl acrylate at 343K used for calculation*

transfer constant (Table 1) confirm the transfer of growing chains to MP. It is evident that the amount of oligomer molecules containing terminal peroxide group increases with an increase in concentration of MP. An average functionality in respect of MP fragments of the polymers after fractioning confirms entering one terminal peroxide group in accordance with the scheme (Fig. 2).

On the second stage poly(F-MA)-MPs were used for initiation of polymerization of NVP to provide the formation of water soluble polyamphiphils of comb-like/block structures consisting of hydrophobic poly(F-MA) and hy-

Table 2. **Kinetic characteristics of NVP polymerization initiated by poly(F-MA)-MP ([NVP]=1.75 mol/l, [CGE]=0.18 mol/l, 363K, dioxane) and poly(F-MA)-MP-block-poly(NVP)-CGE characteristics**

M_n of poly(F-MA)-MP, kDa	[CGE] in reaction system, mole/l	Content of peroxide groups, 10^3, mol/l	$R_p\cdot10^4$, mole/(l·s)	α	Composition of the block-copolymers, % mole			M_n, kDa*
					Block A	*Block B* poly(NVP)	Content of [CGE] in block-copolymers	
5,5	0.18	5.01	3.47	0.9	22.0	77.82	0.18	25.0
		3.34	2.37		24.7	75.1	0.20	22.3
		1.67	1.44		19.4	80.44	0.16	28.4
4,3		6.76	4.18	0.8	14.7	85.15	0.15	29.3
		4.51	2.12		12.1	87.78	0.12	35.4
		2.25	1.36		11.6	88.28	0.12	37.1
	0.35	4.51	1.84	–	14.7	85.11	0.19	29.3
	0.53		1.70		19.2	80.6	0.20	22.4
	0.88		1.20		22.7	77.07	0.23	18.9

**calculated from GPC data*

drophilic nonionic polymer blocks. The polymerization carried out in the presence of CGE causes entering terminal epoxide-containing fragment (Tables 2).

It is evident (Table 2) that the results of polymerization of NVP initiated by peroxide-terminated poly(F-MA)-MP correspond to the known regularities of radical polymerization, an increase of the polymerization rate at increased concentration of initiating terminal peroxide groups. The concentrations of initiating MP fragments and chain transfer agent are the main factors defining the rate and degree of the polymerization (Table 2). High value of the constant of transfer of growing NVP chains to CGE molecules (26.7 l/moles) causes their predominant termination via growing chain transfer reaction. Polymerization carried out in the presence of chain transfer agent provides the controlling rate and degree of the polymerization and amount of copolymer molecules containing terminal CGE fragments (Table 2). The values of orders of polymerization rates in respect of concentration of initiating peroxide groups as well as reverse dependences of molecular weights of hydrophilic poly(NVP) blocks on CGE concentration witness to the termination of the growing chains due to their transfer to telogen molecules.

Elemental and functional analyses were used also for determination of functional groups in the attached block of poly(NVP) and terminal epoxide fragment of CGE (Table 2).

The ^{19}F (a) and ^{13}C (b) NMR spectra of resulting telechelic polymers contain characteristic peaks confirming the formation of oligomer molecules of poly(F-MA) with terminal fragment of MP (Fig.3) as well as functional structure of di-block-copolymers containing terminal epoxide group.

The epoxide terminal group availability in the molecules of poly(F-MA)-*block*-poly(NVP)-CGE provides easy and convenient route for the synthesis of hybrid block-copolymers combining synthetic block and block of oligonucleotide attached via condensation reaction of terminal epoxide group of di-block-copolymer with amino group of ONC linker (the scheme in Fig. 2).

An excitation and emission bands in luminescent spectra (Fig.4) proper to FITC fragment in the structure of ONC of tri-block-copolymer confirm the successful attachment of ONC via condensation reaction of ONC amino group with terminal epoxide group of di-block-copolymer.

It can be concluded that hybrid tri-block-copolymer is of interest as a marker for labeling bacteria and pathological items including cancer cells.

Conclusions

Polymeric surfactants consisting of branched fluorine-containing and linear hydrophilic poly(NVP) and biopolymer blocks were synthesized via the consequent radical and condensation reactions of polymer terminal peroxide or epoxide groups included in a product of polymerization in the presence of proper functional derivatives of cumene.

The established dependences of polymer chain length and structures as well as content of functional terminal groups in oligomer molecules as a result of polymerizations occurred in the presence of the cumene derivatives as telogens witness to the convenient and simple approach of the controlling structures, colloidal-chemical characteristics and bioactivity of the developed polymeric materials.

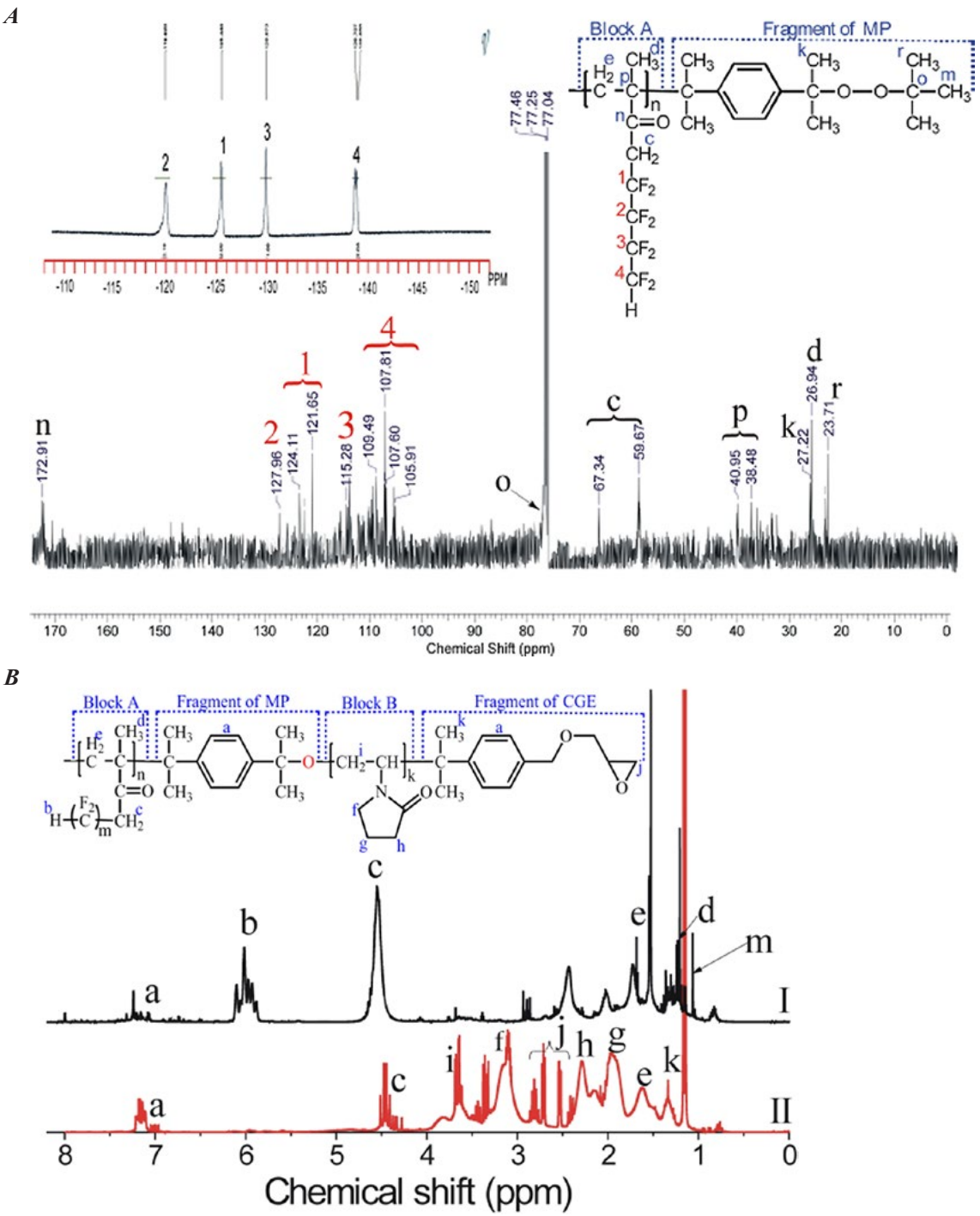

Fig. 3. NMR-spectra of poly(F-MA)-MP (^{19}F and ^{13}C — a, ^{1}H — b, line I) and poly(F-MA)-*block*-poly(NVP)-CGE (^{1}H — b, line II)

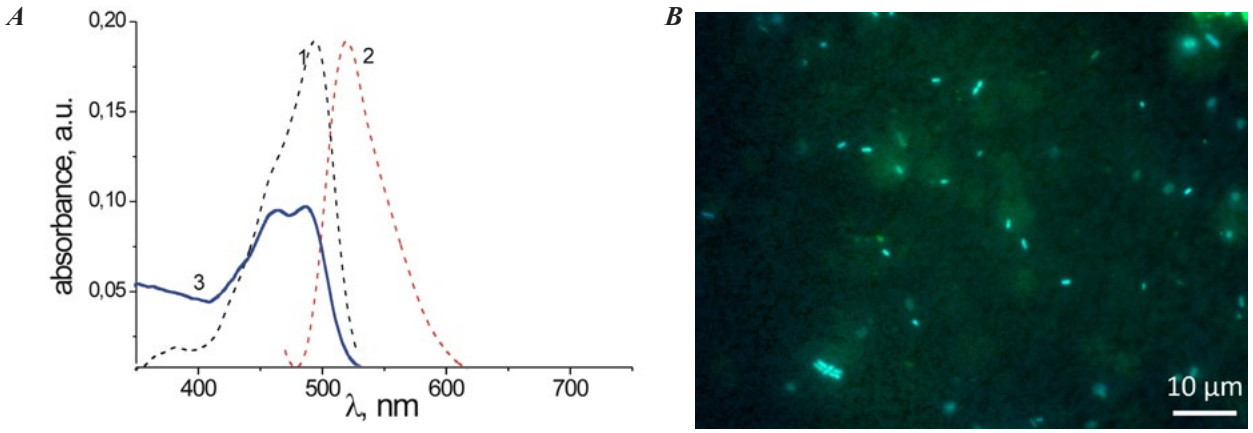

Fig. 4. Fluorescein excitation (440nm) (1) and emission spectra (550nm) (2) of fluorescein and tri-block-copolymer poly(F-MA)-*block*-poly(NVP)-*block*-Eub338FITC (a) and images of bacteria *Pseudomonas putida* labelled with tri-block-copolymer made on luminescent microscope (b)

Finally oligonucleotide (ONC) was attached via the condensation reaction of ONC primary amino group with terminal epoxide group of di-block-copolymer.

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Фтор-вмісні поліамфіфіли блочної будови складені з синтетичних та біо- полімерних блоків

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Мета. Цілеспрямоване одержання полімерних поверхнево-активних речовин, які поєднують гідрофобні фторвмісні та гідрофільні синтетичні та натуральні блоки, за допомогою радикальних та нерадикальних конденсаційних реакцій з використанням пероксидних, епоксидних, та/або аміно- кінцевих груп у складі полімерних елементарних блоків. **Методи.** Радикальні та нерадикальні реакції, полімеризація, спектральні (ЯМР- та люмінесцентна спектроскопія), гель-проникна хроматографія та інші аналітичні техніки. **Результати.** Первинні олігомери полі(F-MA)-МП синтезували шляхом радикальної полімеризації фтор-алкіл метакрилату (F-MA) у присутності пероксидвмісного телогену (МП). Використання МП забезпечує контроль довжини та структури олігомерних ланцюгів, а також входження кінцевої пероксидної групи до складу макромолекул. Радикальна полімеризація N-вінілпіролідону (NВП), ініційована полі(F-MA)-МП як макроініціатором, у присутності епоксидвмісної похідної кумолу (КГЕ) була використана для отримання водорозчинного полі(F-MA)-блок-полі(NВП)-КГЕ. В кінцевому результаті, приєднання олігонуклеотиду (ОНК) до полімерного носія було здійснено реакцією конденсації первинної аміногрупи ОНК з кінцевою епоксидною групою полі(F-MA)-блок-полі(NВП) — КГЕ. **Висновки.** Синтезовано серію нових блок-кополімерів, що поєднують синтетичні та біополімери. Отримані

триблок-кополімери можуть бути використані в якості маркерів для мічення бактерій та патологічних, включаючи ракові, клітин.

Ключові слова: фторовані поліамфіфіли, олігонуклеотид, радикальні та конденсаційні реакції, гібридний блок-кополімер, мічення бактерій.

Фтор-содержащие полиамфифилы блочной структуры собранные из синтетических и биополимерных блоков

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Цель. Целенаправленное получение полимерных поверхностно-активных веществ, сочетающих фторированные гидрофобные и гидрофильные синтетические и натуральные блоки, методами радикальных и нерадикальных конденсационных реакций с использованием концевых пероксидных, эпоксидных и/или амино- групп первичных полимерных блоков. **Методы.** Радикальные и нерадикальные реакции, полимеризация, спектральная (ЯМР- и люминесцентная спектроскопия), гель-проникающая хроматография и другие аналитические методы. **Результаты.** Первичные олигомеры поли(F-MA)-МП синтезировали путем радикальной полимеризации фтор-алкилметакрилата (F-MA) в присутствии пероксидсодержащего телогена (МП). Использование МП обеспечивает контроль длины и архитектуры олигомерной цепи, а также введение концевой пероксидной группы в состав макромолекул. Радикальная полимеризация N-винилпирролидона (NВП) в присутствии эпоксидсодержащей производной кумола (КГЭ), инициируемая макроинициатором поли(F-MA)-МП, была применена для получения водорастворимого поли(F-MA)-блок-поли(N-ВП)-КГЭ. Наконец, олигонуклеотид (ОНК) был присоединен к полимерному носителю посредством реакции конденсации первичной аминогруппы ОНК с концевой эпоксидной группой поли(F-MA)-блок-поли(NВП)-КГЭ. **Выводы.** Синтезирован ряд новых блок-сополимеров сочетающих синтетические и биополимеры. Полученные триблок-сополимеры могут быть использованы как маркеры для мечения бактерий и патологических, в том числе раковых, клеток.

Ключевые слова: фторированные полиамфифилы, олигонуклеотид, радикальные и конденсационные реакции, гибридный блок-сополимер, мечение бактерий.

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