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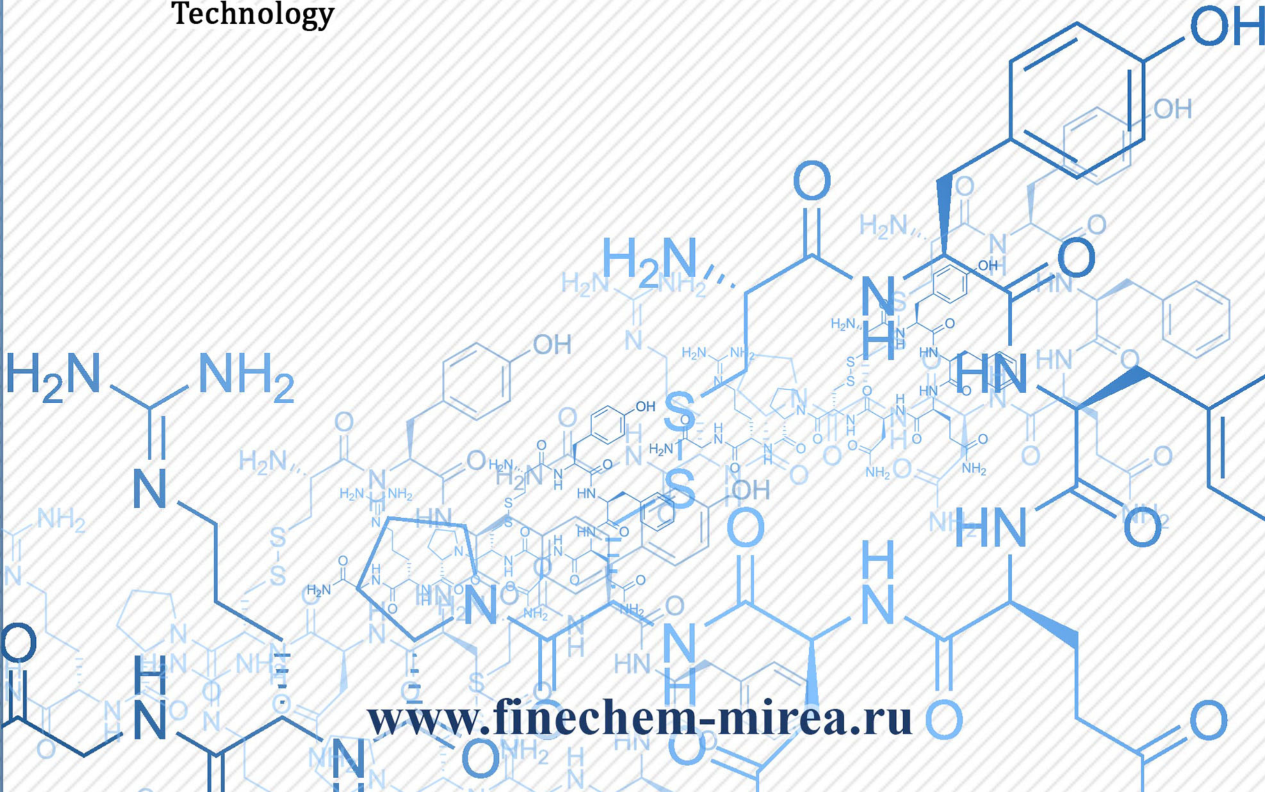
МИТХТ

ТОНКИЕ ХИМИЧЕСКИЕ ТЕХНОЛОГИИ

Fine Chemical Technologies

- Theoretical Bases of Chemical Technology
- Chemistry and Technology of Organic Substances
- Chemistry and Technology of Medicinal Compounds and Biologically Active Substances
- Synthesis and Processing of Polymers and Polymeric Composites
- Chemistry and Technology of Inorganic Materials
- Analytical Methods in Chemistry and Chemical Technology
- Mathematical Methods and Information Systems in Chemical Technology



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ТОНКИЕ
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FROM THE EDITOR-IN-CHIEF

To the true benefit and glory of the Fatherland

On the 120th anniversary
of the M.V. Lomonosov Institute of Fine Chemical Technologies

The simple words of the great Russian scientist, Mikhail V. Lomonosov, in the title appropriately describe the 120-year history of the M.V. Lomonosov Moscow State Institute of Fine Chemical Technology (MITHT in Russian abbreviation). The anniversary date, the award of the Order of the Red Banner of Labor for achievements in training specialists (1970), and the name of M.V. Lomonosov given to MITHT and Moscow State University by a single decree in 1940 are glorious milestones in the life of our wonderful University.

Just as the whole world is reflected in a drop of water, the past years form an amazing mosaic of the history of MITHT. Remembering all those with whom fate brought me together for almost 50 years of study and work here, I would like to share what the Institute means to me with kind words.

Going down the memory lane, I recall the directors and rectors of Moscow Higher Women's Courses, 2nd MSU, MITHT—V.I. Guerrier, S.A. Chaplygin, S.S. Nametkin, A.P. Pinkevich, S.Ya. Plotkin, G.D. Vovchenko, P.I. Zubov, N.A. Myshko, K.A. Bolshakov, V.I. Ksenzenko, S.S. Kiparisov, and V.S. Timofeev. When I entered MITHT in 1971, could I have imagined that I would belong to this outstanding cohort? I am proud of it!

Outstanding scientists and teachers who were the pride of Soviet, Russian, and worldwide science have worked at MITHT, among whom I would like to mention, V.I. Vernadsky, N.D. Zelinsky, A.N. Nesmeyanov, V.M. Rodionov, G.G. Urazov, S.S. Medvedev, I.P. Alimarin, I.N. Nazarov, Ya.K. Syrkin, K.A. Andrianov, I.L. Knunyants, I.V. Tananaev, N.P. Fedorenko, N.N. Nekrasov, V.I. Goldansky, K.A. Bolshakov, A.N. Bashkirov, O.N. Tsuberbiller, N.A. Preobrazhensky, A.N. Pravednikov, S.S. Voyutsky, N.I. Gelperin, B.V. Unkovsky, S.V. Lvov, R.P. Evstigneeva, V.I. Shvets, V.S. Timofeev, and L.A. Serafimov. Madlen Grigor'evna Shirmazan, who worked as the Scientific Secretary of the Institute for many years, is remembered especially with love and gratitude.

Graduates of MITHT are a great army of engineers, masters, candidates, and doctors of science who have successfully worked and are currently working for the development of Russia in academic and industrial institutions, large firms and engineering companies, and industrial enterprises in the fields of organic and inorganic technologies, biotechnology, materials science, polymer synthesis and processing, economics, standardization, technosphere security, and information technology. Among them, I would like to recall graduates with an unusual professional fate, Ekaterina A. Furtseva, a party and statesman; Doctor of Science, Professor Varvara Chichagova-Chernaya known as Mother Serafima, the abbess of the Novodevichy Monastery; and composer Vladimir Dashkevich.

Of the many different events—joyful and difficult—that we have experienced together in our Fatherland, we must remember the Great Patriotic War. In 1942, MITHT announced recruitment for the first year and continued to work. Scientists of the Institute received seven Stalin prizes for scientific developments in the subjects of defense and civil. I would also like to mention Nison Ilyich Gelperin, who created a powerful air bomb (NG-5); and a graduate of MITHT, the skier Lyubov' Korotaeva, who was the only woman in the team that hoisted the Soviet flag on Elbrus again.

In the postwar years, MITHT continued to train specialists for the expedited restoration of the national economy and the country's chemization. In 1956, MITHT was awarded the medal, "For the Development of Virgin Lands," and in 1970, an award of the Order of the Red Banner of Labor was received. The movement of student construction teams was widely developed; MITHT was famous for its tourist section, submariners' club, and "kapustniki" (in Russian).

In the 1960s and 1970s, industry laboratories played a significant role in the development of research and the simultaneous transformation of MITHT into an educational and research institute. Since then, the unity between education and science remains our priority for improving the quality of training.

Expanding the educational, scientific, and technical base is an integral part of the development of MITHT. Among the main achievements, I will list the following: the building of the Physical and Chemical Department of the Moscow Higher Women's Courses at Malaya Pirogovskaya, designed by A.A. Eichenwald (1908), with the famous "hole" ("dyrka" in Russian); the construction of a dormitory at Vernadsky Prospect, where the judges of the Olympic Games lived in 1980; an academic–scientific building in the southwest (phase 1, 1985, and the commissioning of the whole complex in 2004); a sports complex with a climbing wall; and participation in investment projects for the construction of dwelling houses, which provided housing for many faculty and staff.

MITHT is a leader among Russian universities in the field of multilevel training, which constantly adapts to the requirements of the economy and employers and the changeable educational needs of students. For their contribution to the development of a multilevel education system, three author teams in MITHT received Russian Federation Presidential awards. Since 1997, the training of personnel at MITHT has been fully conducted according to the bachelor/master (specialist) level system. Training has been conducted in 23 master's programs. The share of masters in the annual commencement of young specialists from MITHT was about 40%. According to the results of state attestations, MITHT received the status of an Academy in 1993, University in 2011, and the name M.V. Lomonosov Moscow State University of Fine Chemical Technologies, from which the short name MITHT has been preserved. Since November 2015, MITHT has been part of the MIREA – Russian Technological University (RTU MIREA) as the M.V. Lomonosov Institute of Fine Chemical Technologies (ITHT in Russian abbreviation). In its new capacity, ITHT remains faithful to its history, honoring and developing University traditions. The teaching staff of ITHT is noticeably younger. This stems from special support programs for young doctoral students and postgraduates who are preparing for teaching at the University. The contribution of ITHT scientists to the indicators of scientific activity of RTU MIREA is high; teams win prestigious grants on a competitive basis; research results are published in Russian and international journals with a high impact factor; dissertation councils work successfully on a regular basis. Student science, cultural initiatives, and competitions have a significant support from the University management. Much has been done to recreate the historical appearance of the large A-61 and A-63 auditoriums at Malaya Pirogovskaya. At the campus at Vernadsky Prospect, build. 86, classrooms, departments, and student chemical laboratories have been renovated and decorated; the instrument park has been updated; and computer classes have been equipped. Specialized mega laboratories and training and research centers equipped with modern equipment as well as the Altair Technopark have been created.

Today, I want to remember many anniversaries: the 100th, 110th, 115th anniversary of MITHT, the 300th anniversary of M.V. Lomonosov, the 100th anniversary of the 2nd MSU, the 110th anniversary of the MITHT scientific library (1909), and 15 years of the MITHT Museum and Chamber Choir—a winner of many Russian and international competitions. The 20th anniversary of the MITHT scientific journal (Scientific Proceedings of MITHT, Vestnik MITHT, Fine Chemical Technologies) holds a special place among these memories. The celebration of such events unites the team, causes pride in our University, and builds a careful attitude toward the traditions and memory of our predecessors.

I would like to extend to the teachers and staff, students and postgraduates, and veterans and graduates of M.V. Lomonosov MITHT, the most sincere and kind wishes of success, health, wellbeing, preservation, and multiplication of our achievements.

Alla K. Frolkova

CHEMISTRY AND TECHNOLOGY OF ORGANIC SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ОРГАНИЧЕСКИХ ВЕЩЕСТВ

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RESEARCH ARTICLE

Synthesis of alkyl-*gem*-dichlorocyclopropanes based on isoamylene fraction

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Objectives. *The study aims to analyze the dichlorocarbenation of the isoamylene fraction, which is a mixture of 2-methyl-butene-1 and 2-methyl-butene-2, in order to obtain the corresponding alkyl-gem-dichlorocyclopropanes in quantitative yield, and also to determine their structure.*
Methods. *In order to determine the qualitative and quantitative composition of the reaction masses, the following analysis methods were used: gas-liquid chromatography (using the Crystal 2000 hardware complex), mass spectrometry (using a Chromatec-Crystal 5000M device with NIST 2012 database), and nuclear magnetic resonance (NMR) spectroscopy (using a Bruker AM-500 device at operating frequencies of 500 and 125 MHz).*
Results. *Alkyl-gem-dichlorocyclopropanes were synthesized from an isoamylene fraction in the presence of catamine AB as a catalyst. Alternatively, isomeric alkenyl-gem-dichlorocyclopropanes were obtained on the basis of isoprene, and by reduction, the corresponding alkyl-gem-dichlorocyclopropanes were synthesized. The synthesized substances were analyzed by gas-liquid chromatography, mass spectrometry, and NMR spectroscopy, as previously mentioned above.*
Conclusions. *The results show that the dichlorocyclopropanation of the isoamylene fraction proceeds quantitatively with the formation of a mixture of 2-methyl-2-ethyl-1,1-dichlorocyclopropane and 2,3,3-trimethyl-1,1-dichlorocyclopropane. Using isoprene, counter-synthesis through successive dichlorocarbenation and hydrogenation was used to synthesize 2-methyl-2-ethyl-1,1-dichlorocyclopropane, one of the products of dichlorocarbenation of the isoamylene fraction.*

Keywords: *alkenyl-gem-dichlorocyclopropane, isoamylene fraction, hydrogenation, Pd/C*

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НАУЧНАЯ СТАТЬЯ

Синтез алкил-*гем*-дихлорциклопропанов на основе изоамиленовой фракции

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Цели. *Изучить дихлоркарбенирование изоамиленовой фракции, представляющей собой смесь 2-метил-бутена-1 и 2-метил-бутена-2, получить соответствующие алкил-гем-дихлорциклопропаны с количественным выходом и установить их строение.*
Методы. *Для определения качественного и количественного состава реакционных масс были использованы газожидкостная хроматография (на аппаратно-программном комплексе «Кристалл 2000»), хроматомасс-спектрометрия (на приборе «Хроматэк-Кристалл 5000М» с базой NIST 2012), и спектроскопия ядерного магнитного резонанса (ЯМР-спектроскопия) (на приборе «Bruker AM-500» с рабочими частотами 500 и 125 МГц).*
Результаты. *Алкил-гем-дихлорциклопропаны синтезированы из изоамиленовой фракции в присутствии катализатора катамина АВ. Альтернативным путем на основе изопрена получены изомерные алкенил-гем-дихлорциклопропаны, восстановлением которых синтезированы соответствующие алкил-гем-дихлорциклопропаны. Вещества проанализированы и доказаны методами газожидкостной хроматографии, хроматомасс-спектрометрии и ЯМР-спектроскопии.*
Выводы. *Установлено, что дихлорциклопропанирование изоамиленовой фракции протекает количественно с образованием смеси 2-метил-2-этил-1,1-дихлорциклопропана и 2,3,3-триметил-1,1-дихлорциклопропана. С использованием изопрена встречным синтезом через последовательное дихлоркарбенирование и гидрирование был синтезирован 2-метил-2-этил-1,1-дихлорциклопропан – один из продуктов дихлоркарбенирования изоамиленовой фракции.*

Ключевые слова: *алкенил-гем-дихлорциклопропаны, изоамиленовая фракция, гидрирование, Pd/C*

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INTRODUCTION

In the industrial production of isoprene by dehydrogenation of pentanes (at the first stage), pentenes (isoamylene fraction) with a total volume of 2-methylbut-1-ene **1** and 2-methylbut-2-ene **2** (of at least 80%) are formed. This mixture, along with the formation of isoprene, is used in the alkylation, the epoxidation of the Prince reaction, and others as well [1–4].

At an earlier point in time [5–8], it was shown that alkenyl- and alkyl-*gem*-dichlorocyclopropanes are used as solvents, plasticizers, and intermediate products in organic synthesis. In this regard, it was of interest to study the preparation of substituted alkyl-*gem*-dichlorocyclopropanes by dichlorocarbenation of an industrial isoamylene fraction.

MATERIALS AND METHODS

The analysis of the reaction masses was carried out using gas-liquid chromatography (on a Crystal 2000 hardware-software complex, *NPF Meta-khrom*, Russia). Mass spectra were obtained using a Chromatec-Cristall 5000M instrument (*Chromatec*, Russia) with the NIST 2012 database (*National Institute of Standards and Technology*, USA). Nuclear magnetic resonance (NMR) spectra of ^{1}H and ^{13}C were recorded on a Bruker AM-500 spectrometer (*Bruker Corporation*, USA) with operating frequencies of 500 and 125 MHz, respectively, in a $CDCl_3$ solvent. Chemical shifts are reported on a δ (ppm) scale relative to tetramethylsilane as the internal standard. Spin-spin coupling constants (*J*) are given in Hz.

We used substituted vinyl-*gem*-dichlorocyclopropanes obtained by the known method [9] using chloroform, a 50% alkali solution, and a catamine AB phase transfer catalyst (*NPK Isomer*, Russia).

Using the same technique, we obtained the following:

2-methyl-2-ethyl-1,1-dichlorocyclopropane 3. Yield (**3** + **4**) 95%, T_{boil} = 52°C (35 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm. (*J*, Hz): 1.07 t (3H, CH_3, $J = 7.9$), 1.23 d (1H, 1 CH_a, $J = 7.1$), 1.28 d (1H, CH_b, $J = 7$), 1.36 d (3H, CH_3), 1.59–1.73 m (2H, CH_2). ^{13}C NMR, δC, ppm: 10.74 (CH_3), 19.65 (CH_3), 29.75 (C), 31.56 (CH_2), 33.03 (CH_2), 68.03 (C). Mass spectrum, *m/e* (I_{rel}, %): 152/154/156 (≤3) $[M]^+$, (137/139/141)/(22/10/3), (123/125)/(30/15), (117/119)/(50/20), (101/103)/(10/3), (79/77)/(30/22), 56/100.

2,3,3-trimethyl-1,1-dichlorocyclopropane 4. Yield (**3** + **4**) 95%, T_{boil} = 52°C (35 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm. (*J*, Hz): 1.16 t (6H, 2 CH_3, $J = 3.9$, 4.0), 1.36 t (3H, CH_3, $J = 6.6$), 1.16 t (1H, CH, $J = 7.2$). ^{13}C NMR, δC, ppm: 9.55 (CH_3), 16.86 (CH_3), 24.73 (CH_3), 28.06 (C), 32.64 (CH), 71.46 (C). Mass spectrum, *m/e* (I_{rel}, %): 152/154/156 (≤3) $[M]^+$, (137/139/141)/(50/25/5), (123/125)/(≤5), (117/119)/(100/30), (101/103)/(22/8), (79/77)/(50/30), 56/(≤5).

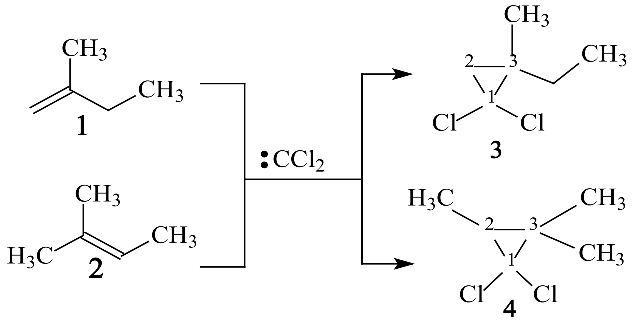
The hydrogenation procedure for unsaturated compounds **6a**, **6b** is similar to that previously published [10].

The catalyst is palladium-carbon, Pd/C granular[1], TU 2170-300-29131036-97. Before use, it was ground in a mortar, sieved, and stored in a desiccator.

By this method, a mixture of substances **3**, **3a** was obtained. The physicochemical constants of compound **3** are presented above. For compound **3a** they correspond to the literature data [11].

RESULTS AND DISCUSSION

As a result of our studies, we found that dichlorocarbenation by the Makoshi method [12, 13] of an isoamylene fraction containing olefins **1**, **2** in a ratio of 1 : 5 gives a mixture (T_{boil} = 156–158°C) 2-methyl-2-ethyl-1,1-dichlorocyclopropane **3** and 2,3,3-trimethyl-1,1-dichlorocyclopropane **4** in the same ratio (Scheme 1, Fig. 1).



Scheme 1. Carbenation of the amylene fraction **1**, **2**.

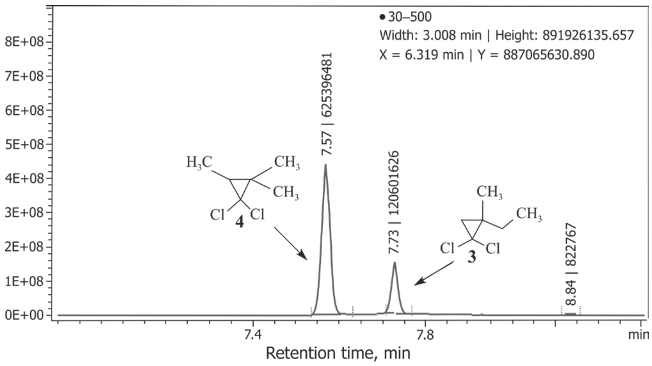
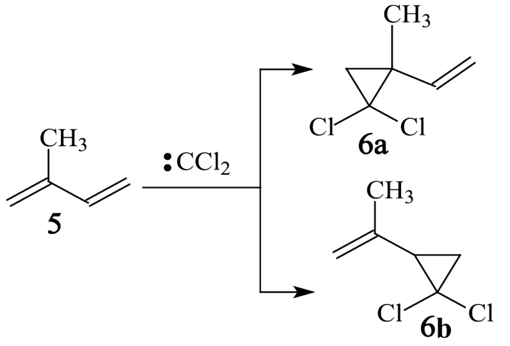


Fig. 1. Chromatogram of a mixture of alkyl-*gem*-dichlorocyclopropanes **3**, **4**.

Earlier [9], we carried out selective monocarbenation of isoprene **5** to vinyl- and isopropenyl-*gem*-dichlorocyclopropanes **6a,b** (Scheme 2), which are formed in a ratio of 95 : 5 (Fig. 2).



Scheme 2. Carbenation of 2-methyl-2-vinyl-butadiene-1,3 **5**.

Hydrogenation (Scheme 3) of a mixture of alkenyl-*gem*-dichlorocyclopropanes **6a,b**, according to the known method [14, 15], was carried out on an industrial catalyst Pd/C [14, 15] at a temperature of 22–24°C and atmospheric pressure for 4–5 h. A mixture of products **3**, **7** was obtained in a quantitative yield, in which their ratio corresponded to the content of olefins **6a,b** (Fig. 3).

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[1] Information about the catalyst is available on the manufacturer's website https://www.kazanorgsintez.ru.

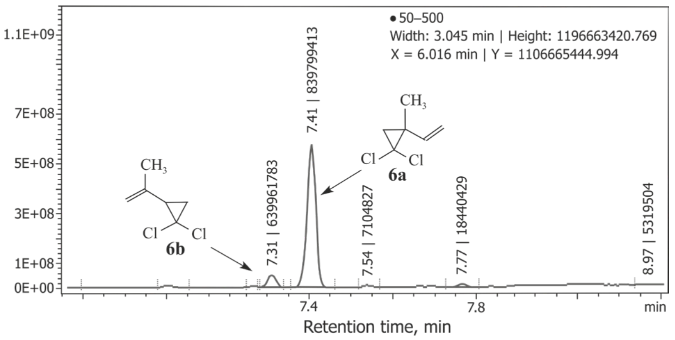


Fig. 2. Chromatogram of a mixture of alkenyl-*gem*-dichlorocyclopropanes **6a,b**.

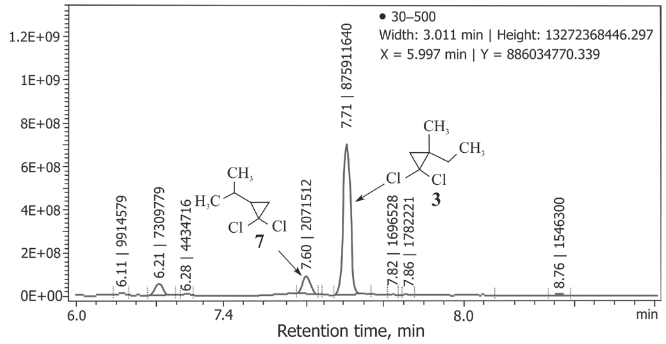
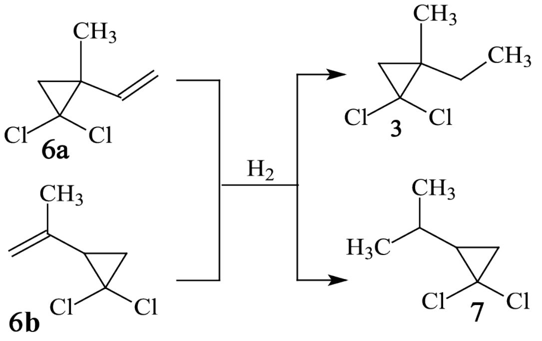


Fig. 3. Chromatogram of a mixture of hydrogenation products **3**, **7**.



Scheme 3. Hydrogenation of a mixture of alkenyl-*gem*-dichlorocyclopropanes **6a,b**.

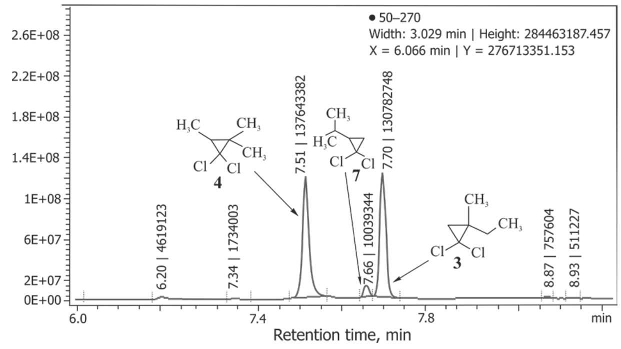


Fig. 4. Chromatogram of an artificial mixture of alkenyl-*gem*-dichlorocyclopanes hydrogenation products **3**, **7** and a mixture of dichlorocarbenation products of the amylene fraction **3**, **4**.

The chromatogram of an artificial mixture of the carbeneation products of the isoamylene fraction **3**, **4**, and the hydrogenation products of alkenyl-*gem*-dichlorocyclopane **3**, **7** indicates the identity of 2-methyl-2-ethyl-*gem*-dichlorocyclopropane **3**, which is obtained by different methods (Fig. 4).

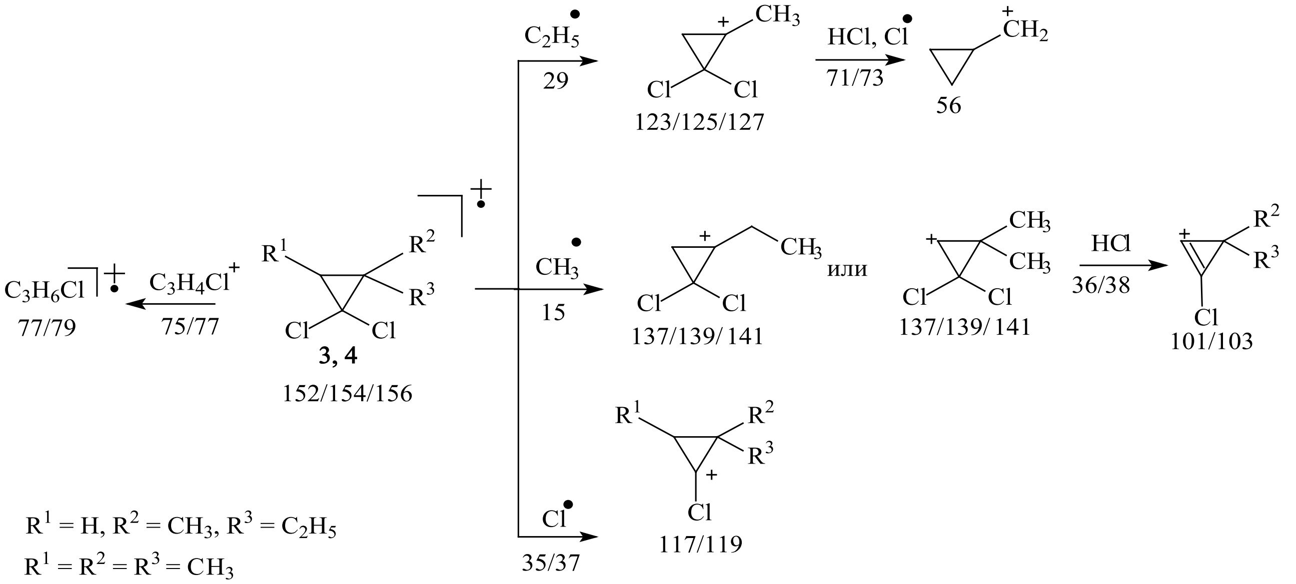
The NMR spectrum of the obtained mixture of alkenyl-*gem*-dichlorocyclopanes **3**, **4** contains signals of protons of the cyclopropane ring at δ C^2 and $C^{2''}$ carbon atoms. For molecule **3**, protons at δ C^2 carbon atom appear as two doublets at 1.23 ppm ($^2J = 7.1$ Hz) and 1.28 ppm ($^2J = 7$ Hz), while for molecule **4** the proton at δ $C^{2''}$ carbon atom is a triplet in the region of 1.16 ppm ($^3J = 7.2$ Hz). Methyl groups are registered with a triplet for 2-methyl-2-ethyl-1,1-dichlorocyclopropane **3** at 1.07 ppm ($^3J = 7.9$ Hz) and a doublet at 1.36 ppm ($^2J = 6.2$ Hz), for 2,3,3-trimethyl-1,1-dichlorocyclopropane **4**—at 1.16 ppm ($^3J = 6.6$ Hz) triplet and 1.36 ppm ($^2J = 3.9$ Hz) doublet.

In the ^{13}C NMR spectra of the mixture of alkyl-*gem*-dichlorocyclopropanes **3**, **4**, the common signal is the C^1 signal of the carbon atom at 68.03 ppm and 71.46 ppm, respectively. For isomer **3** δ C^2 and C^3, the carbon atoms of cyclopropane are recorded in the region of 33.03 ppm and 29.75 ppm, respectively, and for isomer **4** δ $C^{2''}$ and $C^{3''}$ carbon atoms—at 32.64 ppm and 28.06 ppm, respectively. The presence of high-field signals of carbons for molecule **3** in the region of 10.74 ppm and 19.65 ppm corresponds to methyl groups, for molecule **4** the same groups appear at 9.55 ppm and 24.76 ppm.

Mass spectra of a mixture of *gem*-dichlorocyclopropanes **3**, **4** contain peaks of molecular ions $m = 152/154/156$ of low intensity (≤3%). Dissociative ionization of *gem*-dichlorocyclopropanes **3**, **4** can proceed in different ways. The molecule decomposes into a dichlorocyclopropane fragment and a substituent R, or the molecule loses chlorine atoms, but the main carbon skeleton is retained (Scheme 4).

The table shows the values of fission ion mass *m* and the relative intensity of the ion peaks *e* (% of the maximum) for compounds **3**, **4**.

Therefore, based on the frequency of occurrence and intensity of the peaks (see table), the most stable fragment in the molecule is the cyclopropane fragment, which forms a fragmented ion upon the decomposition of all compounds **3**, **4** with a *gem*-dichlorocyclopropane substituent.



Scheme 4. Dissociative ionization of *gem*-dichlorocyclopropanes **3**, **4**.

Values of fission ion mass *m* and relative intensity of ion peaks *e* (% of maximum) for compounds **3** and **4**

Compounds	***m/e* (%)**						
	M^+ 152/154/156	**56**	**77/79**	**101/103**	**117/119**	**123/125**	**137/139/141**
3	≤3	100	30/22	10/3	50/20	30/15	22/10/3
4	≤3	≤3	55/30	22/8	100/30	≤5	50/25/5

CONCLUSIONS

It was found that dichlorocarbenation of the isoamylene fraction, by the Makoshi method, proceeds with the formation of isomeric alkyl-*gem*-dichlorocyclopropanes: 2-methyl-2-ethyl-1,1-dichlorocyclopropane and 2,3,3-trimethyl-1,1-dichlorocyclopropane. Using isoprene, counter-synthesis through sequential dichlorocarbenation and hydrogenation was used to synthesize 2-methyl-2-ethyl-1,1-dichlorocyclopropane, one of the products of dichlorocarbenation of the isoamylene fraction.

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Authors' contribution

A.I. Musin – conducting research, literature analysis;

Yu.G. Borisova – collection and processing of the material, writing the text of the article;

G.Z. Raskil'dina – collection and processing of the material, statistical processing;

R.R. Daminev – consultation on planning, methodology and implementation of the study;

R.U. Rabaev – consultation on conducting individual stages of the study;

S.S. Zlotskii – development of the concept of scientific work, critical revision with the introduction of valuable intellectual content.

The authors declare no conflicts of interest.

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CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Dedicated to Professor A.F. Mironov on the occasion of his 85th birthday

Amino acid derivatives of natural chlorins as a platform for the creation of targeted photosensitizers in oncology

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Objectives. *This study aims to obtain the amino acid derivatives of chlorophyll a and bacteriochlorophyll a for the targeted delivery of pigments to tumor foci. This will increase biocompatibility and, as a result, reduce toxic side effects. In addition to photodynamic efficiency, an additional cytotoxic effect is expected for the obtained conjugates of photosensitizers (PSs) with amino acids. This is owing to the participation of the latter in intracellular biochemical processes, including interaction with the components of the glutathione antioxidant system, leading to the vulnerability of tumor cells to oxidative stress.*

Methods. *In this work, we have implemented the optimization of the structure of a highly efficient infrared PS based on O-propyloxim-N-propoxybacteriopurpurinimide (DPBP), absorbing at 800 nm and showing photodynamic efficacy for the treatment of deep-seated and pigmented tumors, by introducing L-lysine, L-arginine, methionine sulfoximine (MSO), and buthionine sulfoximine (BSO) methyl esters. The structure of the obtained compounds was proved by mass spectrometry and nuclear magnetic resonance spectroscopy, and the photoinduced cytotoxicity was studied in vitro on the HeLa cell line.*

Results. *Conjugates of DPBP with amino acids and their derivatives, such as lysine, arginine, MSO, and BSO have been prepared. The chelating ability of DPBP conjugate with lysine was shown, and its Sn(IV) complex was obtained.*

Conclusions. *Biological testing of DPBP with MSO and BSO showed a 5–6-fold increase in photoinduced cytotoxicity compared to the parent DPBP PS. Additionally, a high internalization of pigments by tumor cells was found, and the dark cytotoxicity (in the absence of irradiation) of DPBP-MSO and DPBP-BSO increased fourfold compared to the initial DPBP compound. This can be explained by the participation of methionine derivatives in the biochemical processes of the tumor cell.*

Keywords: *chlorins, amino acids, bacteriochlorins, photosensitizers, photodynamic therapy, photo-induced cytotoxicity*

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НАУЧНАЯ СТАТЬЯ

К 85-летию со дня рождения профессора А.Ф. Миронова

Аминокислотные производные природных хлоринов как платформа для создания таргетных фотосенсибилизаторов в онкологии

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Цели. *Целью настоящей работы является получение аминокислотных производных хлорофилла а и бактериохлорофилла а для направленной доставки пигментов в опухолевые очаги, увеличения биосовместимости и, как следствие, уменьшения побочного токсического действия. Кроме фотодинамической эффективности для полученных конъюгатов фотосенсибилизаторов с аминокислотами ожидается дополнительный цитотоксический эффект, вызванный участием последних во внутриклеточных биохимических процессах, включая взаимодействие с компонентами глутатионовой антиоксидантной системы, приводящее к уязвимости опухолевых клеток к окислительному стрессу.*

Методы. *В настоящей работе реализована оптимизация структуры высокоэффективного ИК-фотосенсибилизатора на основе О-пропилоксим-N-пропоксибактериопурпуринимида (DPBP), поглощающего при 800 нм и показавшего фотодинамическую эффективность для лечения глубокозалегающих и пигментированных опухолей, путем введения на периферию макроцикла метиловых эфиров L-лизина, L-аргинина, метионинсульфоксимина (MSO) и бутионинсульфоксимина (BSO). Структура полученных соединений доказана методами масс-спектрометрии и ЯМР-спектроскопии, а фотоиндуцированная цитотоксичность исследована in vitro на линии клеток HeLa.*

Результаты. *Были получены конъюгаты О-пропилоксим-N-пропоксибактериопурпуринимида с аминокислотами и их производными, такими как, лизин, аргинин, метионинсульфоксимин и бутионинсульфоксимин. Показана хелатирующая способность конъюгата DPBP с лизином и получен его Sn(IV)-комплекс.*

Выводы. *Биологические испытания DPBP с метионинсульфоксимином и бутионинсульфоксимином показали 5–6 кратное увеличение фотоиндуцированной цитотоксичности по сравнению с исходным фотосенсибилизатором DPBP. При этом обнаружена высокая интернализация пигментов опухолевыми клетками, а темновая цитотоксичность (при отсутствии облучения) DPBP-MSO и DPBP-BSO увеличилась в 4 раза по сравнению с исходным соединением DPBP, что может быть объяснено участием производных метионина в биохимических процессах опухолевой клетки.*

Ключевые слова: *хлорины, аминокислоты, бактериохлорины, фотосенсибилизаторы, фотодинамическая терапия, фотоиндуцированная цитотоксичность*

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INTRODUCTION

The addition of amino acids into photosensitizer (PS) molecules, on the one hand, increases the hydrophilicity of pigments, and on the other hand, improves the selectivity of their accumulation in tumor tissues, since amino acids are involved in numerous intracellular processes, including the accelerated proliferation of tumor cells [1, 2]. In addition, some amino acids, including non-proteinogenic ones, can affect various processes inside the cell, weakening its defenses, for example, against oxidative stress. Due to the structural features of some amino acids, they can be used as complexing agents for metal cations and organometallic complexes, which have their antitumor activity [3].

In clinical practice, derivatives of natural chlorins with amino acids are already being used, and their efficiency for the therapy of tumors of various origins has been proven [4, 5]. The relay race of such studies was continued at the N.A. Preobrazhensky Department of Chemistry and Technology of Biologically Active Compounds, Medical and Organic Chemistry in the group of Professor M.A. Grin and Professor A.F. Mironov, where bacteriochlorin derivatives with methyl esters of L-lysine, L-arginine, methionine sulfoximine (MSO), and buthionine sulfoximine (BSO), as well as the structural isomers of some of the earlier mentioned conjugates were first obtained. The publication of this work is timed to the anniversary of the outstanding scientist working in the field of creating new PSs, and the creator of the first Russian drug, Photogem, Professor A.F. Mironov.

The development of new highly specific anticancer drugs is an urgent task for medical and pharmaceutical chemistry [6]. First, the need to develop targeted anticancer drugs is dictated by numerous side effects and the general systemic toxicity of chemotherapeutic drugs used in clinical oncology [7].

The strategy of attaching fragments of other biomolecules to the leader molecule, such as amino acids [1, 2], peptides [8, 9], and carbohydrates [10–12], is employed for the targeted delivery of drugs to tumor foci; biocompatibility is increased, and thus, toxic side effects are reduced.

Of particular interest is the addition of amino acids, because the hydrophilicity and bioavailability of anticancer drugs increase, and their side effects decrease simultaneously. Several endogenous carriers of amino acids are concentrated in tumor cells and contribute to the internalization of the amino acid derivatives of various pharmacologically active substances [13]. For example, the histidine transport system in the body consists of 50% of the SLC15A4 (PHT1) transporter protein, 30% of other amino acid transporters, and only 20% of all histidine is delivered to cells using passive transport and other transport systems. The main carrier protein, PHT1, transports histidine and oligopeptides from lysosomes to the cytosol of eukaryotic cells. It is known to overexpress the arginine transporters, CAT-1, in rectal cancer cells. An in vitro study has shown that disabling CAT-1 in tumor cells induces apoptosis and death, and the carrier protein itself is a unique molecular biomarker and therapeutic target in tumor cells. Studies show that the intracellular transport of certain amino acids is a common feature of most neoplastic cells [14]. A classic example of the use of amino acids in the chemical design of alkylating agents is the creation of the antitumor drug, Melphalan (Fig. 1) (trade name Sarcolysin), which is a derivative of bis-β-chloroethylamine and the amino acid, L-phenylalanine. Melphalan is less toxic than the original chlormethine (embichinum). The resistance of tumor cells to melphalan also develops more slowly than that to chlormethine [15], which is primarily due to the presence of an amino acid residue in the preparation structure [16].

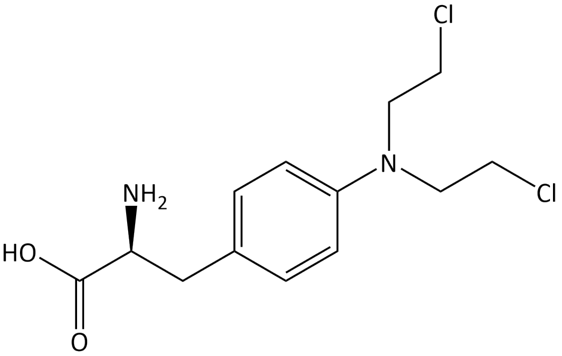


Fig. 1. Structure of Melphalan.

A similar strategy for the inclusion of amino acids in the composition of targeted drugs is implemented for PSs. The main cytotoxic agent in photodynamic therapy (PDT) is singlet oxygen ($^1O_2$); the action of which is not specific, since reactive oxygen species interact and destroy various biomolecules, such as lipids, proteins, and nucleic acids. The lifetime of the biochemically active singlet oxygen form in cells is 250 ns [17]. The diffusion of the $^1O_2$ molecule calculated based on this value is in good agreement with the experimental data on the radius of action of $^1O_2$ in cells and tissues, which does not exceed 50 nm [18]. Since the size of human tissue cells is relatively large (about 100 μm), $^1O_2$ is consumed close to the place of its formation. In this regard, the effectiveness of the cytotoxic action of a PS directly depends on its location in the tumor cell. This is confirmed by the fact that no direct correlation was found between the quantum yield of $^1O_2$ and PS cytotoxicity.

The accumulation of our scientific group's work with PSs of the chlorin and bacteriochlorin series shows that, most often, the intracellular accumulation of pigments occurs nonspecifically (diffusely or granularly in the cytoplasm) [19, 20] and does not affect the vital cell compartments, which together with a small radius of action of $^1O_2$ limits the effectiveness of PSs.

Currently, the priorities of scientists who create anticancer drugs have shifted toward the development of subcellular-oriented drugs [21], in particular, mitochondria-targeted drugs [22]. Damage to the mitochondria, which are the energy depots of the cell, disrupts protein biosynthesis and can lead to the launch of the tumor apoptosis [23].

It is known that molecules containing positively charged groups have membranotropic properties with respect to mitochondria [24]. One of the known cationic domains in mitochondria-oriented preparations is a guanidine residue [25], which, due to a delocalized positive charge, binds to carboxyl and phosphate groups on membranes, providing an efficient transmembrane transfer of PSs.

Amino acids have been repeatedly used to modify PSs based on porphyrins and chlorins. The purpose of this modification was to increase the hydrophilicity of pigments, as well as mitochondrial targeting of drugs. An example of the successful use of amino acids to increase the hydrophilicity of pigments is the enzymatic transesterification of chlorophyll a with various amino acids, peptides, and proteins, implemented in an Israeli scientific group. The use of the enzyme, chlorophyllase, as a catalyst for transesterification, allowed the authors to obtain esters of chlorophyll *a* under mild conditions; for example, with methyl ester of serine (chlorophyllideserine) (Fig. 2). The latter showed a 100-fold increase in photocytotoxicity in the culture of M2R melanoma cells in comparison with the official drug, Photosan [26].

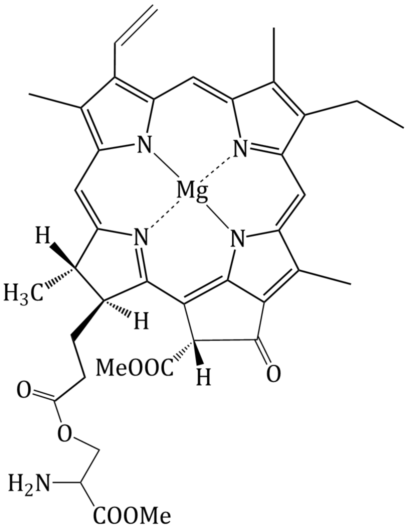


Fig. 2. Structure of chlorophyllideserine.

In *in vivo* experiments, water-soluble chlorophyllideserine was removed from normal tissue within 72 h and predominantly accumulated in the tumor, with low skin toxicity. This PS exhibited high photodynamic activity on M2R melanoma in mice [27].

The group of Professor K. Smith carried out the chemical synthesis of various amino acid derivatives of chlorin e_6. The leader compound obtained in the course of the study is mono L-aspartylchlorin e_6 (Fig. 3). This drug, called Talaporfin, belongs to the second-generation PS and is used in the treatment of various forms of cancer [4, 5]. In its pharmacodynamic parameters, the inhibition of tumor growth, increase in life expectancy, and rate of elimination from the body, the drug is superior to the drug, Photofrin, which is widely used in cancer PDT.

The scheme for the synthesis of Talaporfin includes the preparation of methylpheophorbide *a*, opening of the exocycle in the latter with sodium methoxide, and esterification of the product with

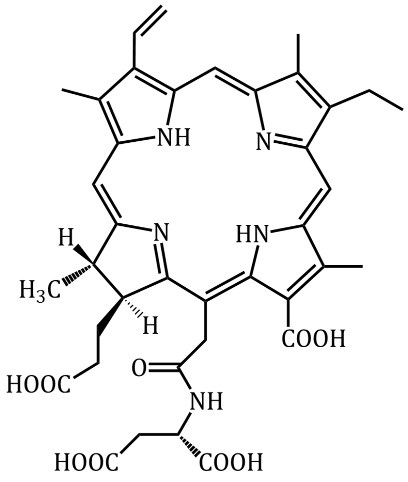


Fig. 3. Structure of Talaporfin.

diazomethane to obtain the trimethyl ester of chlorin e_6. Alkaline hydrolysis of ester groups and the interaction of chlorin e_6 with dimethyl aspartic acid after the removal of the protective groups results in mono L-aspartylchlorin e_6 [28].

The amidation of chlorin e_6 can take place at one of three carboxyl groups; therefore, it was believed for a long time that aspartic acid was attached at the 17^3-position. However, later, the structure of mono L-aspartylchlorin e_6, which is the pharmaceutical substance of the drug, was finally clarified using regioselective chemical synthesis [29].

The presence of the guanidine group alone or in the composition of arginine attached to the chlorin-series PS, Verteporfin (Vizudin drug), ensures the accumulation of the latter in the mitochondria of tumor cells. This fact was discovered during the study of the intracellular distribution of the modified drug by fluorescence microscopy on the line of human carcinoma cells resistant to the action of cisplatin [30]. Other amino acids, including lysine, serine, and tyrosine, orient 5-(4-carboxyphenyl)-10,15,20-tris(3-methoxyphenyl) porphyrin into the lysosomes of HeLa tumor cells [31].

The ability of the guanidine group to be protonated in physiological fluids ensures the participation of arginine in many metabolic processes. Therefore, the inclusion of the latter in the structure of drugs, including PSs, largely determines their pharmacokinetic and pharmacodynamic properties. There is a research project in which the derivatives of zinc phthalocyanine and arginine with a free and esterified carboxyl group of amino acids were obtained. The two drugs were compared by different biological tests, and it was shown that both PSs differ insignificantly in photophysical parameters, while the results of biological tests revealed significant differences in their properties. For the conjugate of the Zn-complex of phthalocyanine with ethyl arginine ether, a twofold increase in the accumulation in tumor cells and a fivefold increase in photoinduced cytotoxicity were found [32].

In addition to antitumor PDT, antimicrobial PDT is currently being actively developed. The tropism of PSs to gram-negative bacteria is significantly increased in the presence of positively charged groups in their structure. The inclusion of lysine into the tetraphenylporphyrin molecule enhances the antimicrobial activity of the latter against antibiotic-resistant strains of *Staphylococcus aureus*, *E. coli*, and *P. Aeruginosa*, with tetra-substituted tetraphenylporphyrin being the most promising [33].

The well-known ability of amino acids to chelate metal cations due to the presence of carboxyl, amino, thiol, hydroxyl, and other groups in their molecules is actively used in the creation of the metal complexes of porphyrins and related compounds containing a metal at the periphery of the macrocycle.

Another important intracellular target for targeted therapy is the thiol-containing tripeptide—glutathione. It is a key molecule that plays an important role in the regulation of redox status, drug detoxification, and cell protection from damage by free radicals, peroxides, and toxins [34]. Currently, active research is being carried out on therapeutic agents acting on the glutathione antioxidant system. Some of them are already at the stage of *in vitro* and *in vivo* preclinical trials. [35]. Sulfur-containing amino acids—cysteine, methionine, and its derivatives: MSO and BSO—are targeted molecules that target components of the antioxidant system of tumor cells, making the latter vulnerable to photodynamic effects.

All of the above motivated us to research the synthesis and biological properties of the conjugates of natural chlorins with amino acids to obtain targeted PSs with optimal amphiphilicity, improved bioavailability, and high photodynamic efficiency.

MATERIALS AND METHODS

All solvents used in this work were prepared according to standard procedures. Column chromatography was performed on silica gel 60 (0.040–0.063 mm, *Merck*, Germany). For preparative thin-layer chromatography (TLC), glass plates with silica gel 60 (*Merck*) were used; for analytical TLC, aluminum plates with Kieselgel 60 F_{245} silica gel (*Merck*) were used.

Electronic absorption spectra were obtained on a Shimadzu UV1800 UV/VIS spectrophotometer (*Shimadzu*, Japan) in 10 mm thick cuvettes; dichloromethane was used as a solvent. Nuclear magnetic resonance (NMR) ^{1}H spectra were recorded using a Bruker DPX 300 spectrometer (*Bruker Daltonics*, Germany) in $CDCl_3$.

Mass spectra were obtained using a Bruker Ultraflex TOF/TOF spectrometer (*Bruker Daltonics*) by the MALDI method with 2,5-dihydroxybenzoic acid as a matrix.

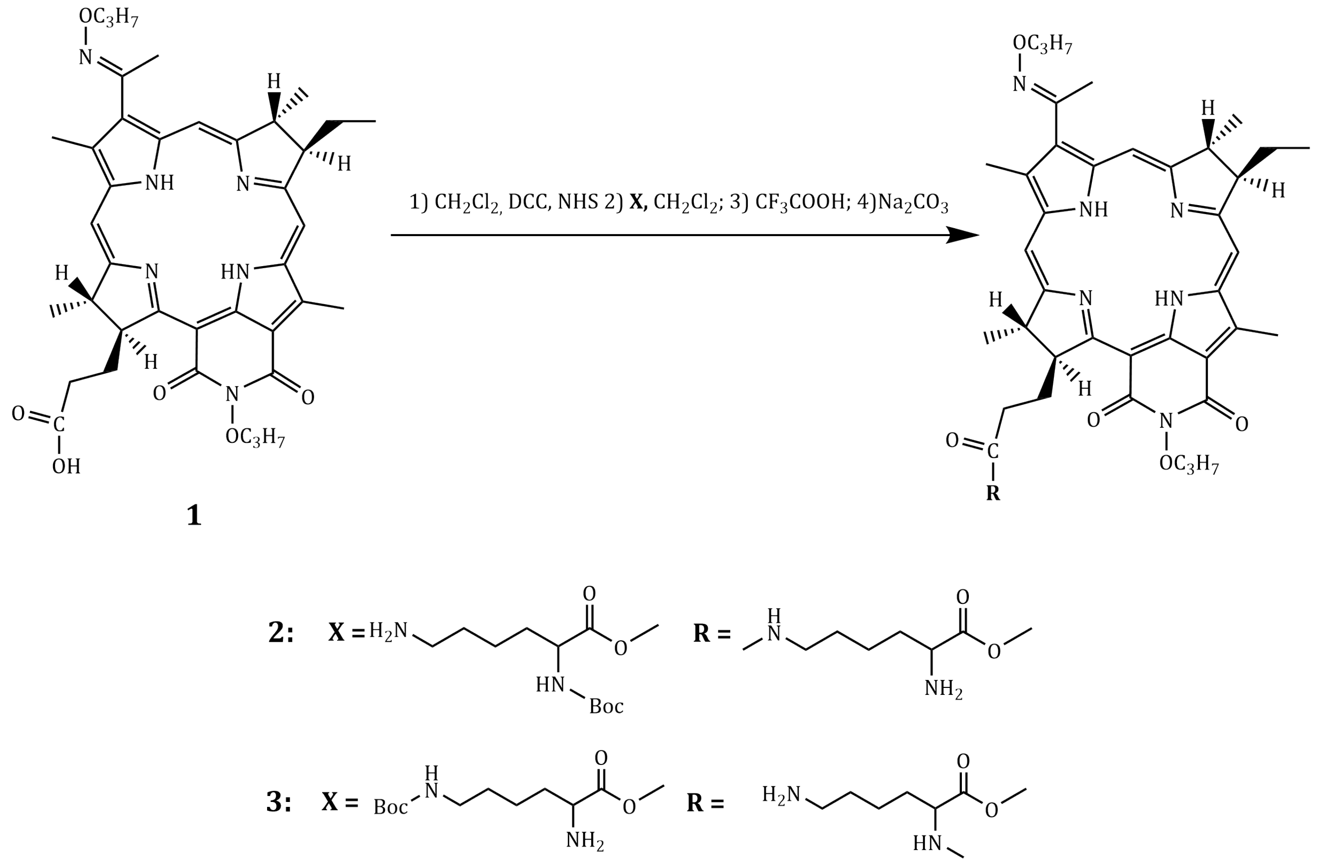
RESULTS AND DISCUSSION

The purpose of the first stage of the work was to obtain a lysine-containing derivative of bacteriopurpurinimide and the structural isomers of this conjugate, in which the amino acid is attached at both the α- and ε-amino groups.

Lysine is an essential amino acid and is involved in several metabolic processes within the cell. This is largely due to the presence of an amino group in the side chain, which is capable of protonation under physiological conditions. The resulting positive charge ensures the binding of the amino acid to the tumor and bacterial cell membranes. The electron-donating nitrogen atom of the ε-amino group of lysine, as well as the presence of α-NH_2– and α-COOH– groups in the molecule, allows the amino acid to create stable complexes with various metals, which increases the therapeutic and diagnostic potential of lysine-containing PSs. *O*-propyloxime-*N*-propoxybacteriopurpurinimide **1**, which is a derivative of natural bacteriochlorophyll *a*, whose synthesis was described by us earlier, was chosen as the lead compound in this work [34]. The pigment modification was carried out at the propionic acid residue in the 17th position of the macrocycle. In this work, based on the limited solubility of amino acid derivatives in organic solvents and the low solubility of bacteriochlorins in water, a synthesis strategy was chosen that included the initial preparation of an activated *O*-propyloxime-*N*-propoxybacteriopurpurinimide ester and the subsequent addition of amino acid derivatives.

For the activation of *O*-propyloxime-*N*-propoxybacteriopurpurinimide, we obtained a succinimide ester, which is stable both in aqueous media and in organic solvents. Dicyclohexylcarbodiimide was used as a condensing reagent (Scheme 1).

For the addition of lysine at the ε-amino group, the methyl ester of α-*N*-*tert*-butyloxycarbonyllysine was used, followed by the deprotection of the α-amino group of the attached amino acid by the action of trifluoroacetic acid (Scheme 1).



Scheme 1. Preparation of *O*-propyloxime-*N*-propoxybacteriopurpurinimide conjugates with lysine methyl ester.

The structure of compound **2** after isolation and chromatographic purification was confirmed by mass spectrometry (Fig. 4) and NMR spectroscopy (Fig. 5).

The mass spectrum contained the signal of the molecular ion ($[M]^+$ 837.58), as well as fragmentation typical of this bacteriopurpurinimide with the elimination of one ($M^+ – OC_3H_7$) or two oxypropyl groups ($M^+ –2–OC_3H_7$) (Fig. 4).

In turn, the NMR spectrum contained signals of the protons of both bacteriochlorin and amino acid residue, including the signals of the protons of the hydrocarbon side chain of lysine in the form of a multiplet in the region of 1.8–2.3 ppm and the amide proton signal at 8.25 ppm (Fig. 5).

The preparation of structural isomer **3**, in which the amide was formed due to the α-amino group of lysine, was carried out similarly to that of compound **2**; however, ε-*N*-*tert*-butyloxycarbonyl lysine methyl ester was used as the amino acid component (Scheme 1). The structure of lysine-bacteriopurpurinimide **3** was confirmed by mass spectrometry and NMR spectroscopy.

Since tin complexes are currently considered as an alternative to platinum-containing preparations, it was interesting to study the complexation of lysine with tin to then reproduce the metallation reaction on conjugate **2** [36–39]. For this purpose, the interaction of Boc-protected at the ε-amino group of lysine with trimethyltin chloride Me_3SnCl was realized. The reaction was carried out in the presence of triethylamine Et_3N (Scheme 2).

In the mass spectrum of metal complex **5**, isotopic splitting of the molecular ion signal was observed, confirming the presence of a tin atom in the molecule (Fig. 6).

The reaction of α-*N*-Boc-Lys with diphenyltin dichloride Ph_2SnCl_2 was carried out similarly under basic conditions. To confirm the structure, the matrix-assisted laser desorption/ionization (MALDI) mass spectrum of compound **6** was obtained, in which there was a molecular ion corresponding to the required mass, *m/z*: 568 $[M]^+$, with characteristic signals of tin isotopes (Fig. 7).

After the conditions of complexation for lysine derivatives were selected, we obtained an organotin complex based on the conjugate of dipropoxybacteriopurpurin-imide with lysine attached to the ε-amino group of the latter (ε-*N*-Lys-DPBP) **2** (Scheme 3).

For compound **7**, a mass spectrum was obtained (Fig. 8), where the expected signal of a molecular ion with an *m/z* value of 1001 $[M]^+$ and characteristic signals of tin isotopes was present.

As noted earlier, arginine, like lysine, is a positively charged amino acid under physiological conditions, since the guanidine group of the side chain is capable of protonation. Some works describe the

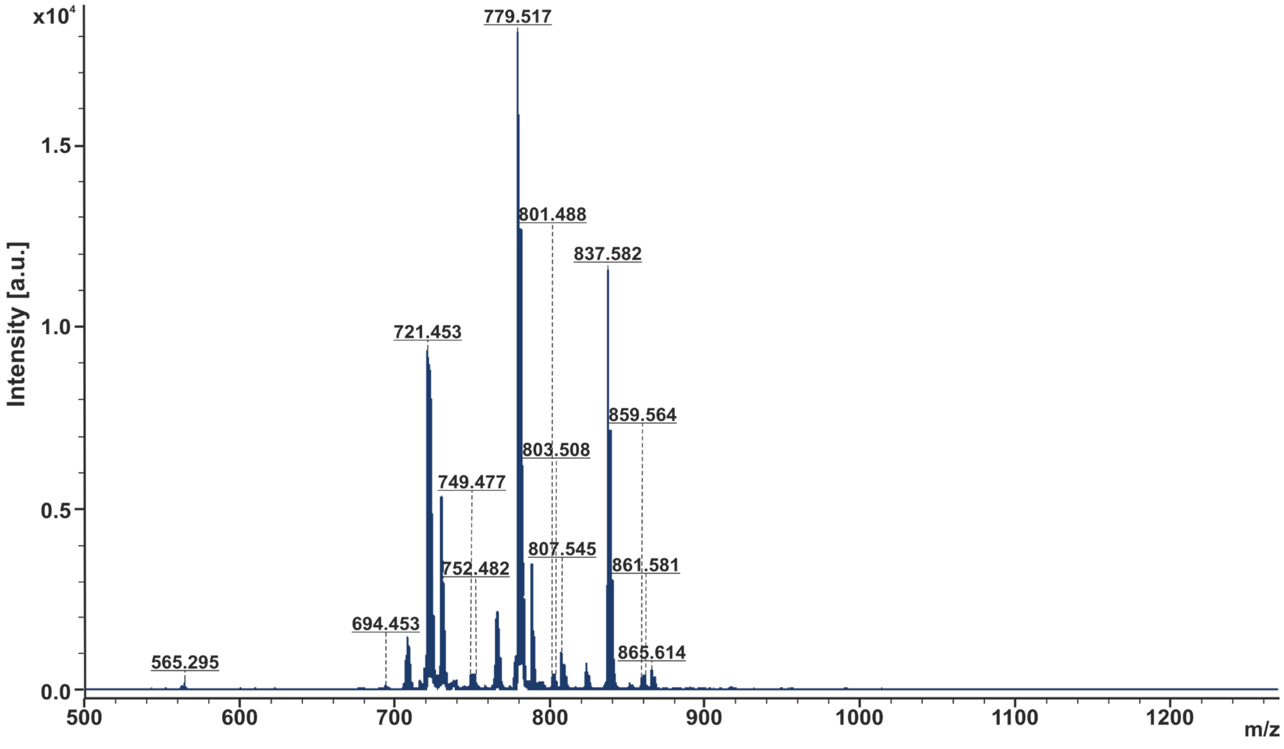


Fig. 4. MALDI TOF mass spectrum of compound **2**.

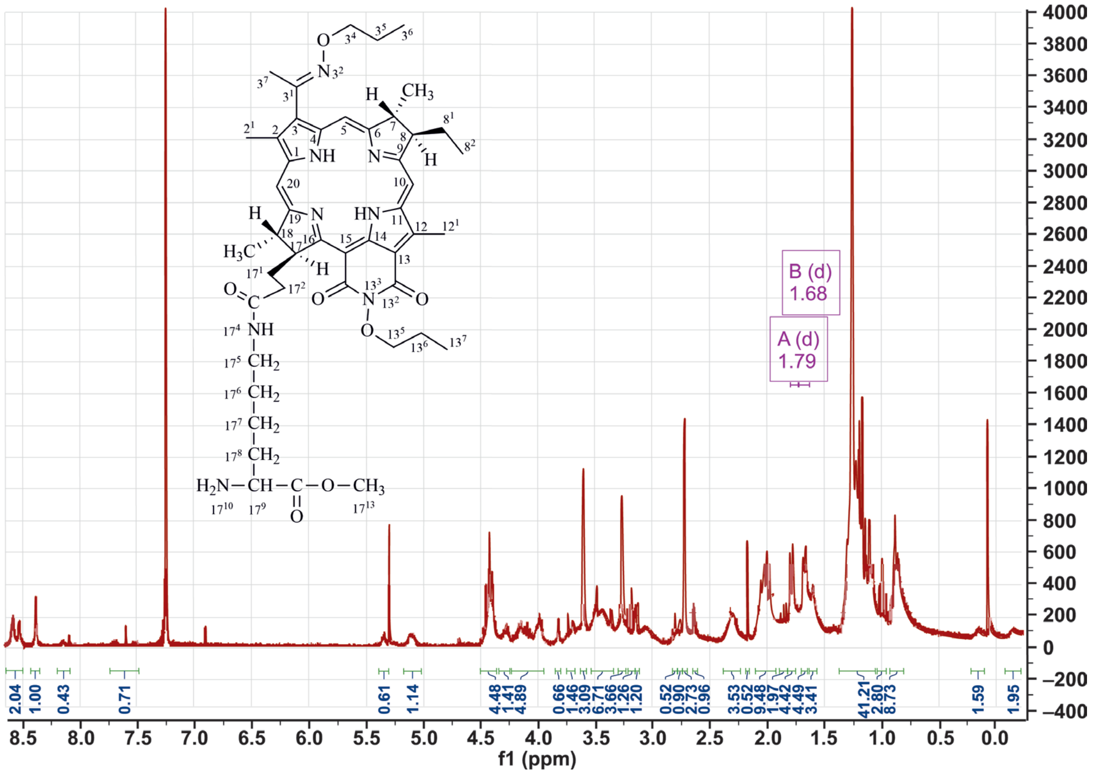
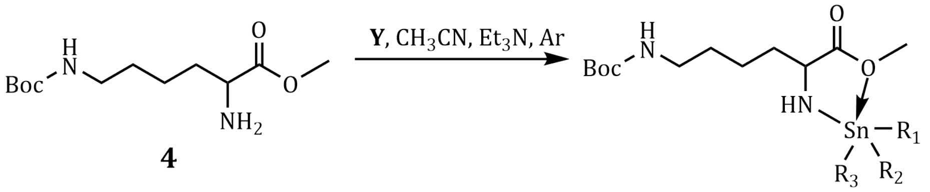


Fig. 5. ^{1}H NMR spectrum of compound **2**.



4

5: Y = $(CH_3)_3SnCl$ $R_1=R_2=R_3=CH_3$

6: Y = $(Ph)_2SnCl_2$ $R_1=R_2=Ph$ $R_3=Cl$

Scheme 2. Preparation of tin complexes with Boc-derivative of lysine (**5** and **6**).

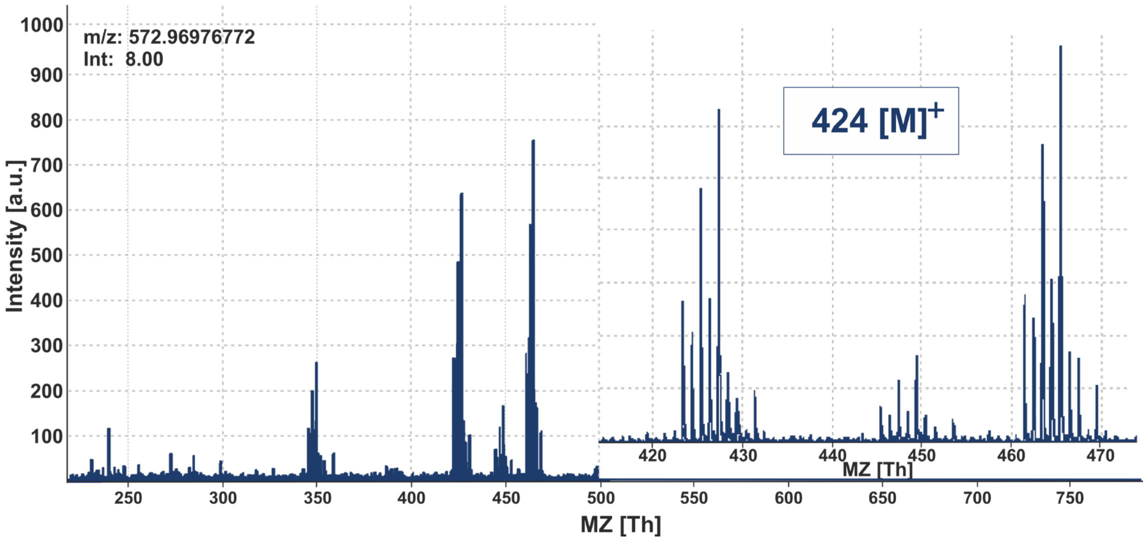


Fig. 6. MALDI TOF mass spectrum of metal complex **5.**

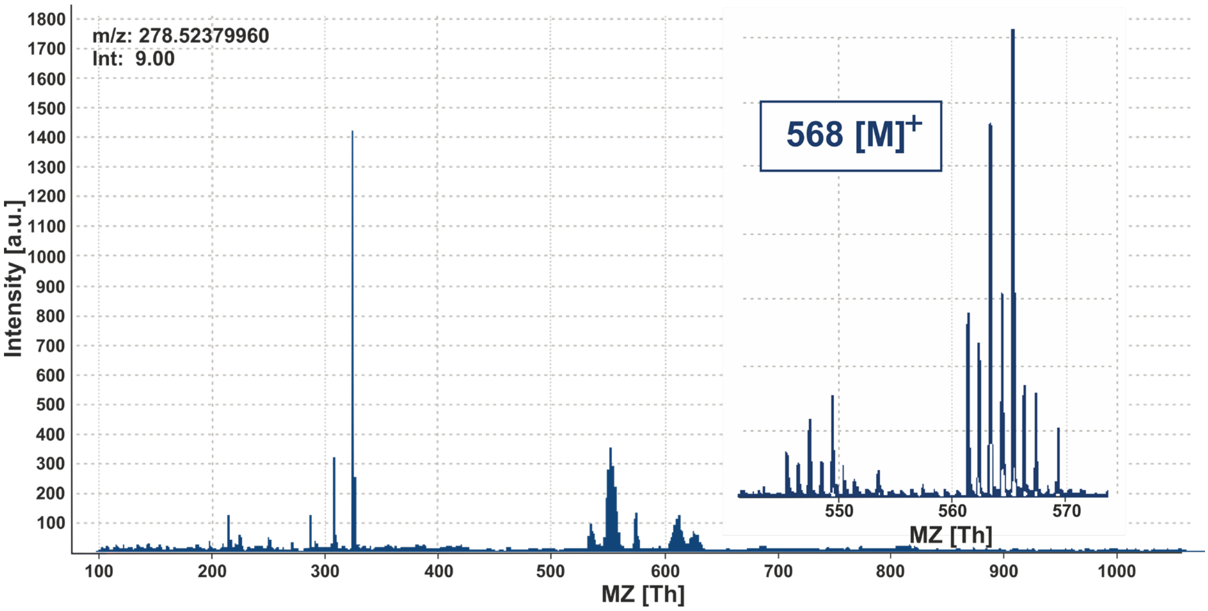
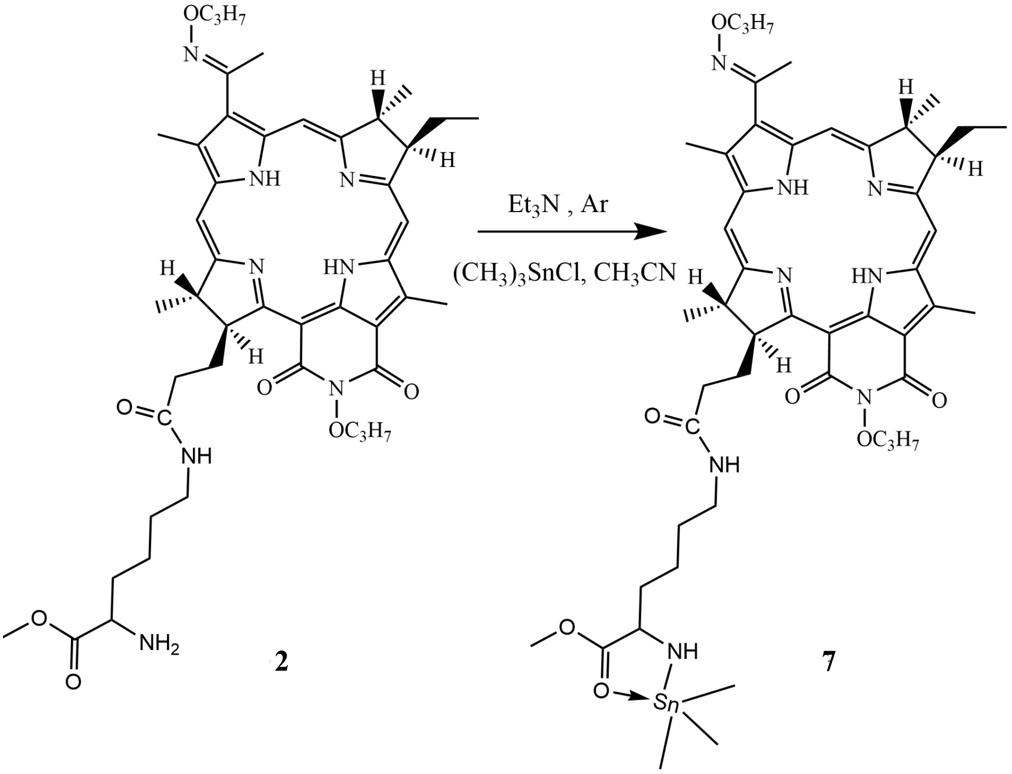


Fig. 7. MALDI TOF mass spectrum of compound **6.**



Scheme 3. Preparation of tin complex ε-*N*-Lys-DPBP **7**.

accumulation of PSs containing a guanidine group in mitochondria, which increases the photoinduced cytotoxicity of such pigments. In our work, arginine was the second amino acid introduced into the PS molecule according to the method described above for lysyl-DPBP (Scheme 4).

The ^{1}H NMR spectrum of the obtained conjugate **8** contains a broadened signal of the protons of the amino and imino groups of the guanidine fragment of arginine at 8.26 ppm (Fig. 9).

It is known from the literature that the target molecules for interacting with the components of

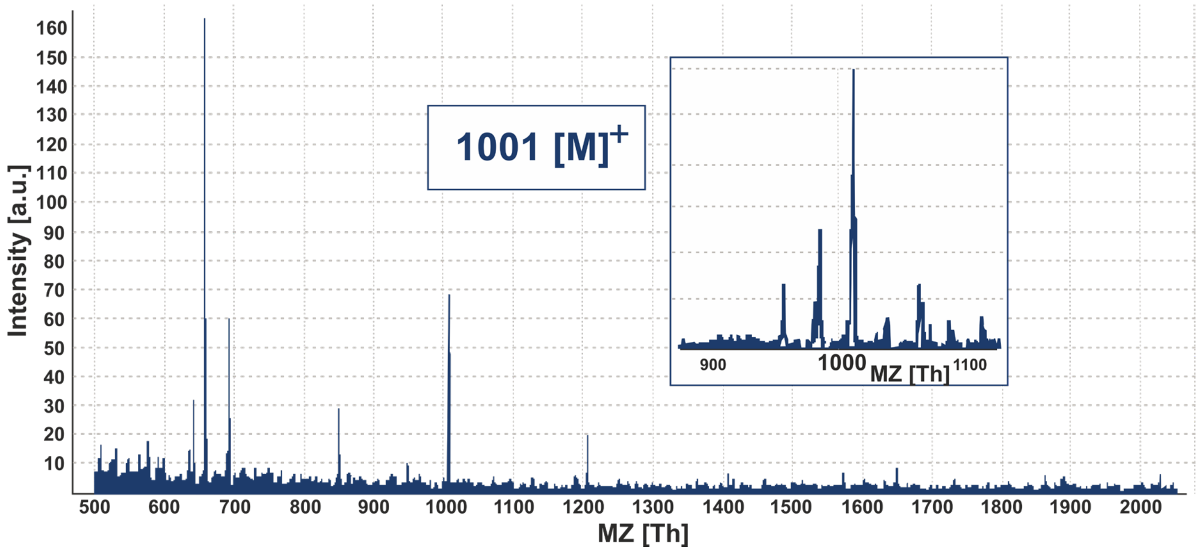
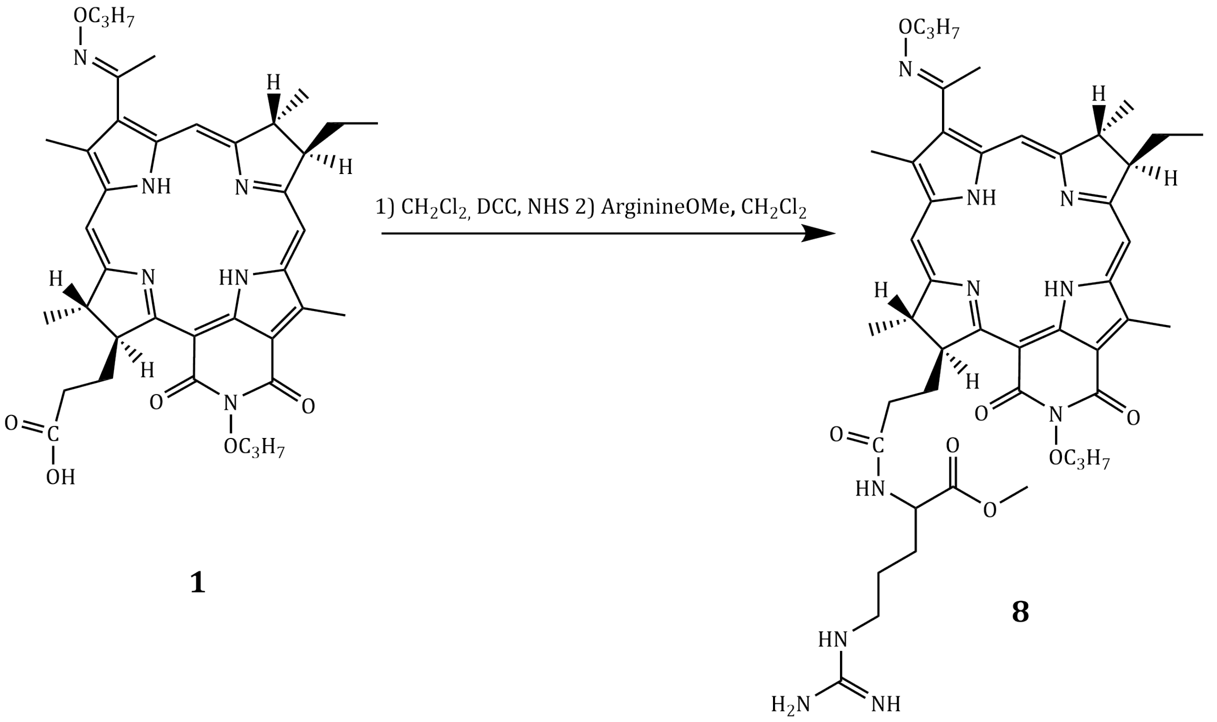


Fig. 8. MALDI TOF mass spectrum of compound **7.**



Scheme 4. Synthesis of *O*-propyloxime-*N*-propoxybacteriopurpurinimide with arginine methyl ester.

the glutathione antioxidant system are methionine derivatives: MSO and BSO, the addition of which into the leader *O*-propyloxime-*N*-propoxybacteriopurpurinimide was implemented in this work (Scheme 5). The amidation of the propionic acid residue at position 17^3 of the macrocycle was carried out according to the traditional procedure in the presence of the activating agent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (Scheme 5).

To assess the photoinduced activity of DPBP derivatives with the methyl esters of MSO (DPBP-MSO) **9** and BSO (DPBP-BSO) **10**, the HeLa cellline was chosen [40]. *O*-propyloxime-*N*-propoxybacteriopurpurinimide was taken as a reference drug, and the survival of tumor cells was assessed visually using an inverted microscope and the MTT test; the results of which are shown in the table[1].

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[1] Biological tests were performed at the P.A. Herzen Moscow Oncological Research Institute, Branch of the Federal State Budgetary Institution of the National Medical Research Center of Radiology of the Ministry of Health of Russia under the leadership of the Head of the Department, Cand. Sci. A.A. Pankratov.

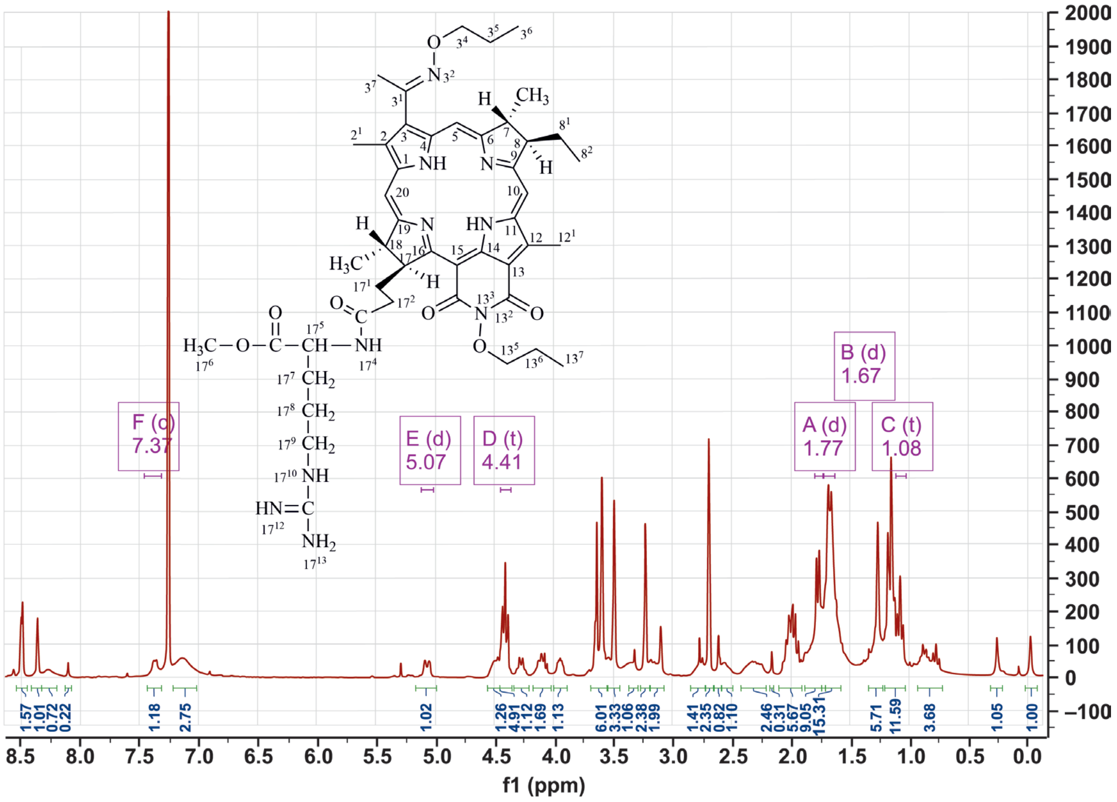
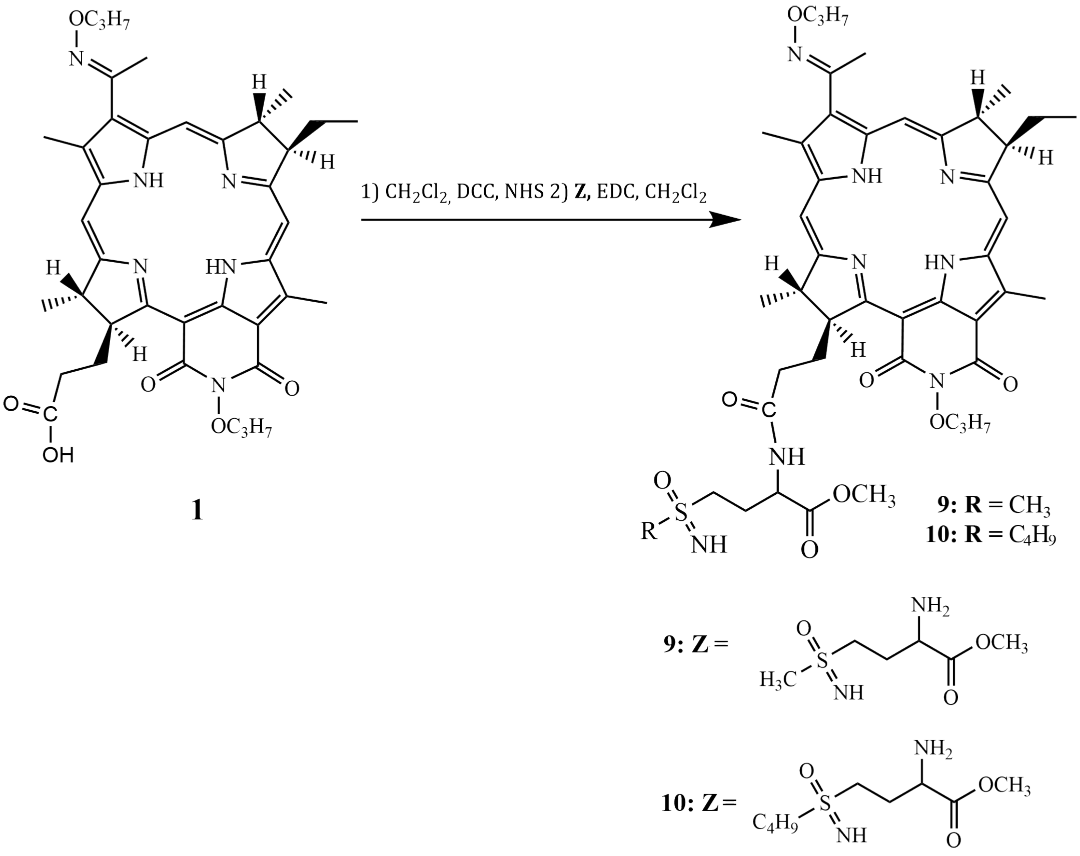


Fig. 9. ^{1}H NMR spectrum of compound **8**.



Scheme 5. Synthesis of the conjugate of *O*-propyloxime-*N*-propoxybacteriopurpurinimide with methyl ester of L-MSO and L-(S,R)-BSO.

The presented results show a 5- and 6-fold increase in the photoinduced cytotoxicity of the DPBP-MSO and DPBP-BSO derivatives compared to the parent compound DPBP. The half-maximal inhibitory concentration, IC_{50}, changed insignificantly upon irradiation in the presence of PS in the incubation medium and after washing the cells from PS, which indicates a high internalization of the pigment by tumor cells. Additionally, dark cytotoxicity increased fourfold in DPBP-MSO and DPBP-BSO compared to the initial compound DPBP.

EXPERIMENTAL

Conjugate of *O*-propyloxime-*N*-propoxybacteriopurpurinimide with lysine methyl ester (2). Compound **1** (1 equiv, 28.7 µmol, 20 mg) was dissolved in 2 mL of methylene chloride, 1,3-dicyclohexylcarbodiimide (1.5 equiv, 43.1 µmol, 9 mg) was added and stirred at 0°C for 30 min. Afterward, *N*-hydroxysuccinimide (1.5 equiv, 43.1 µmol, 8 mg) was added to the reaction mixture and stirred for 24 h, after which the solvent was removed in a vacuum. The residue was dissolved in ethyl acetate, the resulting precipitate was collected by filtration on a Schott filter, and the solvent was removed in vacuo. The obtained activated ester of *O*-propyloxime-*N*-propoxybacteriopurpurinimide (1 equiv, 25.2 µmol, 20 mg) was dissolved in 2 mL of methylene chloride, and the methyl ester of α-*N*-*tert*-butyloxycarbonyl lysine (2 equiv, 50.4 µmol, 13.8 mg) was added, after which the reaction mixture was stirred for 24 h. Subsequently, trifluoroacetic acid (2 equiv, 8.5 µL) was added, and the mixture was stirred for another 24 h at room temperature. The progress of the reaction was monitored chromatographically (R_f = 0.55, CH_2Cl_2/CH_3OH, 40/1, v/v). The solvent was removed in vacuo and compound **2** was purified by preparative TLC (CH_2Cl_2/CH_3OH, 40/1, v/v). The product yield was 11 mg (55%).

Mass spectrum, *m/z*: calculated for $C_{46}H_{62}N_8O_7$ $[M]^+$: 838.47, found: 837.48.

^1H NMR spectrum (δ, ppm): 8.6 (H, s, 10-H), 8.54 (H, s, 5-H), 8.4 (H, s, 20-H), 8.25 (H, m, 17^4-NH), 5.10 (H, m, 17-H), 4.47 (2H, m, 17^9-CH_2), 4.45 (4H, t, *J* = 6.7 Hz, 3^4-CH_2, 13^5-CH_2), 4.28 (H, m, 18-H), 4.15 (2H, m, 7-H), 3.99 (H, m, 8-H), 3.63 (3H, s, 17^{13}-CH_3), 3.61 (3H, s, 12-CH_3), 3.43 (2H, m, 17^5-CH_2), 3.27 (3H, s, 2-CH_3), 2.72 (3H, s, 3^1-CH_3), 2.30 (4H, m, 17^2-CH_2^a, 17^1-CH_2^a, 17^2-CH_2^b, 17^1-CH_2^b), 2.05 (2H, m, 17^6-CH_2), 2.01 (6H, m, 3^5-CH_2, 13^6-CH_2, 8^{1a}, 8^{1b}-H), 1.86 (2H, m, 17^8-CH_2), 1.79 (3H, d, *J* = 7.2 Hz, 7-CH_3), 1.68 (3H, d, *J* = 6.2 Hz, 18-CH_3), 1.6 (2H, m, 17^7-CH_2), 1.17 (6H, m, 13^7-CH_3, 3^6-CH_3), 1.11 (3H, m, 8^2-CH_3), and 0.16 (s, NH), −0.13 (s, NH).

Conjugate of *O*-propyloxime-*N*-propoxybacteriopurpurinimide with lysine methyl ester (3). The activated *O*-propyloxime-*N*-propoxybacteriopurpurinimide ester (1 equiv, 25.2 µmol, 20 mg) was dissolved in 2 mL of methylene chloride, and ε-*N*-*tert*-butyloxycarbonyl lysine (2 equiv, 50.4 µmol, 13.8 mg) was added. The reaction mixture was stirred for 24 h, after which a twofold excess of trifluoroacetic acid was added, and the reaction was left for another 24 h. The progress of the reaction was monitored chromatographically (R_f = 0.6, CH_2Cl_2/CH_3OH, 35/1, v/v). The solvent was removed in vacuo and compound **3** was purified by preparative TLC (CH_2Cl_2/CH_3OH, 35/1, v/v). The product yield was 10 mg (50%).

Mass spectrum, *m/z*: calculated for $C_{46}H_{62}N_8O_7$ $[M]^+$: 838.47, found: 837.58.

^1H NMR spectrum (δ, ppm): 8.62 (H, s, 10-H), 8.52 (H, s, 5-H), 8.42 (H, s, 20-H), 8.17 (H, m, 17^4-NH), 5.13 (H, m, 17-H), 4.44 (4H, t, *J* = 6.5 Hz, 3^4-CH_2, 13^5-CH_2), 4.30 (H, m, 18-H), 4.17 (2H, m, 7-H), 4.00 (H, m, 8-H), 3.75 (2H, m, 17^5-CH_2), 3.66 (3H, s, 17^{13}-CH_3), 3.62 (3H, s, 12-CH_3), 3.15 (2H, m, 17^9-CH_2), 3.28 (3H, s, 2-CH_3), 2.73 (3H, s, 3^1-CH_3), 2.28 (4H, m, 17^2-CH_2^a, 17^1-CH_2^a, 17^2-CH_2^b, 17^1-CH_2^b), 2.06 (2H, m, 17^8-CH_2), 2.00 (6H,

Photoinduced cytotoxicity of compounds **1**, **9** and **10** in HeLa cells *in vitro*

No.	PS	Experiment options		
		Exposure in the presence of PS in the incubation medium	Exposure without PS in the incubation medium	Dark cytotoxicity
		IC_{50} value, nM		
1	**DPBP**	111 ± 8	129 ± 24	2141 ± 763
2	**DPBP-BSO**	20 ± 0.7	21 ± 2	485 ± 63
3	**DPBP-MSO**	16 ± 1	20 ± 5	563 ± 258

m, 3^5-CH_2, 13^6-CH_2, 8^{1a}, 8^{1b}-H), 1.86 (2H, m, 17^6-CH_2), 1.8 (3H, d, *J* = 6.9 Hz, 7-CH_3), 1.68 (3H, d, *J* = 5.9 Hz, 18-CH_3), 1.61 (2H, m, 17^7-CH_2), 1.18 (6H, m, 13^7-CH_3, 3^6-CH_3), 1.11 (3H, m, 8^2-CH_3), 0.08 (s, NH), and −0.22 (s, NH).

The complex of trimethyltin (IV) with ε-*N*-Boc-lysine (5). Methyl ester of ε-*N*-Boc-lysine **4** (1 equiv, 1 mmol, 260 mg) was dissolved in 4 mL of acetonitrile, and 100 µL of triethylamine was added. After 30 min, trimethyltin chloride (1 equiv, 1 mmol, 200 mg) was added and stirred for a day. The progress of the reaction was monitored chromatographically. Afterward, the reaction mixture was extracted in the H_2O/CH_2Cl_2 system to remove excess triethylamine, and the resulting organic extract was chromatographed using preparative TLC in the dichloromethane–methanol system (20/1, v/v). The yield was 130 mg (50%).

Mass spectrum, *m/z*: calculated for $C_{15}H_{32}N_2O_4{}^{118}Sn$ $[M]^+$: 424.14 (100.0%), 422.14 (74.8%), 420.14 (42.2%), 423.14 (36.8%), 421.14 (29.3%), 428.14 (16.9%), 425.14 (16.7%), 426.14 (14.3%), 429.14 (2.8%), 416.14 (2.8%), 427.14 (2.3%), 418.14 (1.9%), 419.14 (1.3%); found: 424.14 $[M]^+$ (100%), 422.14 (74.1%), 420.14 (40.2%), 423.14 (32.1%), 421.14 (28.3%), 428.14 (15.9%), 425.14 (14.0%), 426.14 (14.3%), 429.14 (2.8%), 416.14 (2.8%), 427.14 (2.6%), 418.14 (1.9%), and 432.14 (1.3%).

Diphenyltin (IV) complex with ε-*N*-Boc-lysine (6). ε-*N*-Boc-lysine methyl ester (1 equiv, 1 mmol, 260 mg) was dissolved in 4 mL of acetonitrile, and 100 µL of triethylamine was added; after 30 min, diphenyltin dichloride (1 eq, 1 mmol, 343 mg) was added and stirred for a day. The progress of the reaction was monitored chromatographically.

Next, the reaction mixture was extracted in the H_2O–CH_2Cl_2 system to remove excess triethylamine, and the resulting organic extract was chromatographed using preparative TLC in the dichloromethane–methanol system (30/1, v/v). The yield was 57 mg (22%).

Mass spectrum, *m/z*: calculated for $C_{24}H_{33}ClN_2O_4{}^{118}Sn$ $[M]^+$: 568.12 (100.0%), 566.11 (78.7%), 567.12 (45.3%), 564.11 (40.2%), 565.12 (31.6%), 570.11 (28.4%), 569.12 (25.3%), 568.11 (21.4%), 570.12 (19.5%), 572.12 (17.5%), 569.11 (13.8%), 571.12 (11.5%), 566.12 (7.4%); found: 566.32 (100%), 568.11 (70.7%), 567.12 (42.3%), 564.11 (36.2%), 565.12 (31.6%), 570.11 (28.4%), 569.12 (25.3%), 568.11 (21.4%), 570.12 (19.5%), 572.12 (17.5%), 569.11 (13.8%), and 571.12 (1.5%).

Synthesis of the tin (IV)-complex of ε-Lys-DPBP conjugate (7). Compound **2** (1 equiv, 0.01 mmol, 10 mg) was dissolved in 4 mL of acetonitrile, and 50 µL of triethylamine was added; after 30 min, trimethyltin chloride (2.5 equiv, 0.025 mmol, 5 mg) was added and stirred for a day. The progress of the reaction was monitored chromatographically. Afterward, the reaction mixture was extracted in the H_2O–CH_2Cl_2 system to remove excess triethylamine, and the resulting extract was chromatographed using preparative TLC in the dichloromethane–methanol system (30/1, v/v). The yield was 2 mg (20%).

Mass spectrum, *m/z*: calculated for $C_{49}H_{70}N_8O_7{}^{118}Sn$ 1002.44 (100.0%), 1000.44 (75.9%), 1001.44 (59.5%), 1003.44 (49.0%), 999.44 (41.9%), 998.44 (38.6%), 1006.44 (15.6%), 1004.44 (14.8%), 1004.45 (13.3%), 1002.45 (10.2%), 1007.45 (8.6%), 1005.44 (7.2%), 1003.45 (6.1%); found: 1001.44 (100%), 1000.44 (70.1%), 1002.44 (58.5%), 1003.44 (48.0%), 999.44 (41.9%), 998.44 (38.6%), 1006.44 (13.1%), 1004.44 (14.8%), 1004.45 (7.3%), and 1002.45 (5.2%).

Conjugate of *O*-propyloxime-*N*-propoxybacteriopurpurinimide with arginine (8). Conjugate **8** was prepared from 20 mg of compound **1** by a procedure similar to the preparation of dipropoxybacteriopurpurinimide conjugates with lysine **2** and **3** to obtain activated DPBP succinimide ester. The yield of the target compound **8** was 14.6 mg (73%).

Electronic spectrum, λ_{max}, nm (relative peak intensity): 368, 420, 544, 798 (1 : 0.50 : 0.37 : 0.44).

Mass spectrum, *m/z*: calculated for $C_{46}H_{62}N_{10}O_7$ $[M]^+$: 867.01, found: 867.6.

^1H NMR spectrum (δ, ppm): 8.50 (H, s, 10-H), 8.49 (H, s, 5-H), 8.36 (H, s, 20-H), 8.26 (3H, br.s, 17^{12}-NH, 17^{13}-NH_2), 7.37 (H, d, *J* = 8.5 Hz, 17^4-NH), 7.14 (br.s, 17^{10}-NH), 5.07 (H, d, *J* = 9.5 Hz, 17-H), 4.49 (H, m, 17^5-H), 4.41 (4H, t, *J* = 6.6 Hz, 3^4-CH_2, 13^5-CH_2), 4.28 (H, m, 18-H), 4.14 (2H, m, 7-H), 3.99 (H, m, 8-H), 3.64 (3H, s, 17^6-CH_3), 3.60 (3H, s, 12-CH_3), 3.35 (2H, m, 17^7-H) 3.23 (3H, s, 2-CH_3), 3.13 (2H, m, 17^8-H), 2.69 (3H, s, 3^1-CH_3), 2.57 (2H, m, 17^9-H), 2.31 (4H, m, 17^2-CH_2^a, 17^1-CH_2^a, 17_2-CH_2^b, 17^1-CH_2^b), 1.99 (6H, m, 3^5-CH_2, 13^6-CH_2, 8^{1a}, 8^{1b}-H), 1.77 (3H, d, *J* = 7.1 Hz, 7-CH_3), 1.67 (3H, d, *J* = 6.8 Hz, 1^8-CH_3) 1.16 (6H, m, 13^7-CH_3, 3^6-CH_3), 1.08 (3H, t, *J* = 7.28 Hz, 8^2-CH_3), and 0.26 (s, NH), −0.02 (s, NH).

Conjugate of *O*-propyloxime-*N*-propoxybacteriopurpurinimide with L-MSO methyl ester (9). Compound **1** (1 equiv, 35.9 µmol, 20 mg) was dissolved in 1 mL of methylene chloride, and EDC HCl (1.5 equiv, 53.8 µmol, 11 mg) was added, after which the reaction mixture was stirred for 15 min at 0°C. Next, a solution of L-MSO methyl ester (4 equiv, 143.6 µmol, 33 mg) in 1 mL of methylene chloride was added, and the reaction mixture was stirred for another 48 h in an inert argon atmosphere without access to light. The product was extracted with a 4% aqueous hydrochloric acid–chloroform mixture (250/25, v/v), then the extract was purified by preparative TLC in dichloromethane–methanol (45/1, v/v). The yield was 8 mg (40%).

Mass spectrum, *m/z*: calculated for $C_{45}H_{60}N_8O_8S$ $[M]^+$: 872.43, found: 872.38.

Electronic spectrum, λ_{max}, nm: (relative peak intensity): 368, 419, 543, 798 (1 : 0.50 : 0.39 : 0.42).

^{1}H NMR spectrum (δ, ppm): 8.51 (s, H, 5-H), 8.44 (s, H, 10-H), 8.41 (s, H, 20-H), 5.04 (d, *J* = 8.7 Hz, H, 17-H), 4.35 (m, 4H, $-OCH_2CH_2CH_3$), 4.07 (m, 2H, 18-H, 7-H), 3.92 (m, H, 8-H), 3.58 (s, 3H, OCH_3), 3.53 (s, 3H, 12-CH_3), 3.2 (s, 3H, 2-CH_3), 3.07 (s, H, CH_3–S–CH_2–CH_2–CH–), 2.72 (m, 2H, CH_3–S–CH_2–), 2.64 (s, 3H, CH_3–S), 1.97 (m, 2H, CH_3–S–CH_2–CH_2–), 1.71 (d, *J* = 7.1 Hz, 3H, 7-CH_3), 1.63 (d, *J* = 7.0 Hz, 9H, $-OCH_2CH_2CH_3$, 18-CH_3), 1.0 (t, *J* = 7.2 Hz, 3H, 8^2-CH_3), 0.1 (s, H, NH), and −0.2 (s, H, NH).

Conjugate of *O*-propyloxime-*N*-propoxybacteriopurpurinimide with L-(S,R)-BSO methyl ester (10).The preparation of conjugate 10 from 25 mg of compound **1** was carried out similarly to the preparation of compound **9**. The yield was **9** mg (36%).

Mass spectrum, *m/z*: calculated for $C_{48}H_{66}N_8O_8S$ $[M]^+$: 914.47, found: 914.69.

Electronic spectrum, λ_{max}, nm (relative peak intensity): 368, 420, 545, 799 (1 : 0.47 : 0.34 : 0.46).

^{1}H NMR spectrum (δ, ppm): 9.06 (s, H, S=NH), 8.60 (s, H, 5-H), 8.53 (s, H, 10-H), 8.45 (s, H, 20-H), 5.12 (d, *J* = 8.5 Hz, H, 17-H), 4.44 (m, 4H, O–CH_2–CH_2–CH_3), 4.33 (m, 3H, 13^1-CH_3), 4.17 (m, 2H, 18-H, 7-H), 4.00 (m, H, 8-H), 3.88 (m, 2H, O–CH_2–CH_2–CH_3), 3.66 (s, 3H, O–CH_3), 3.62 (s, 3H, 12-CH_3), 3.29 (s, 3H, 2-CH_3), 3.24 (t, *J* = 7.4 Hz, H, NH–CH), 2.73 (d, *J* = 7.6 Hz, 7H, CH_2–S–CH_2, 3^1-CH_3), 2.71 (m, 2H, 17^2-CH_2), 2.33 (m, 2H, 8^1-CH_2), 2.04 (m, 2H, NH–CH–CH_2), 1.79 (d, *J* = 7.3 Hz, 3H, 7-CH_3), 1.70 (d, *J* = 6.8 Hz, 9H, O–CH_2–CH_2–CH_3), 1.26 (s, 2H, S–CH_2–CH_2–CH_2–CH_3), 1.18 (m, 2H, S–CH_2–CH_2–CH_2–CH_3), 1.09 (t, *J* = 7.3 Hz, 3H, 8^2–CH_3), 0.89 (s, 3H, $(CH_2)_3$–CH_3), 0.15 (s, H, NH), and −0.14 (s, H, NH).

Investigation of the photoinduced activity of compounds (9) and (10) *in vitro*.

Cytotoxicity was assessed using the standard MTT test. The cells were cultured under standard conditions at 37°C in a humidified atmosphere with 5% CO_2 in DMEM medium supplemented with L-glutamine (2 mM) and fetal calf serum (10%, *PanEko*, Russia). Photoinduced efficacy was assessed as follows: HeLa cells were seeded in a 96-well flat-bottomed microtiter plate (*Costar*, USA). Test compounds were added 24 h after inoculation. The concentration varied in the range of 0.05–28.00 μM. Subsequently, the cells were irradiated with a halogen lamp through a KS-19 broadband filter that transmits light with a wavelength of more than 720 nm. The power density was 21.0 ± 1.0 mW/cm^2, and the calculated light dose was 10 J/cm^2. Irradiation was performed with and without the removal of PS from the medium. After irradiation, the cells were incubated under standard conditions for 24 h. To analyze the PS cytotoxicity, the cells were placed in darkened conditions for 24 h. The survival rate was assessed by visual inspection and colorimetry using the MTT test. Inhibition of cell growth by more than 50% was considered biologically significant. This value was calculated as the mean of three independent tests.

CONCLUSIONS

In the present work, several conjugates of *O*-propyloxim-*N*-propoxybacteriopurpurinimide with amino acids and their derivatives, such as lysine, arginine, MSO, and BSO were prepared. The structure of all the obtained compounds was reliably confirmed by a complex of physicochemical methods of analysis. The chelating ability of the DPBP conjugate with lysine was shown, and the Sn(IV) complex was obtained. Biological tests were carried out, and the high photoinduced cytotoxicity of DPBP derivatives with MSO and BSO was shown.

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Authors' contributions

A.F. Mironov – scientific consulting at all stages of the work;

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N.S. Kirin – collecting and processing materials on the arginine derivatives of bacteriopurpurinimide;

V.A. Pogorilyy – collecting and processing materials on the synthesis and study of the properties of the conjugates of bacteriopurpurinimide with MSO and BSO;

S.I. Tikhonov – collecting and processing materials on the synthesis and study of the properties of metal complexes of bacteriopurpurinimides with external chelating groups;

A.A. Tsygankov – management of the biotechnological part of the work, including the cultivation of biomass and isolation of bacteriochlorophyll *a*;

O.O. Chudakova – collecting and processing materials to optimize the conditions for cultivating biomass and isolating bacteriochlorophyll *a*;

M.A. Grin – concept and design of the study, collecting and processing materials.

The authors declare no conflicts of interest.

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CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Method of electrochemical biotesting for comparative analysis of probiotic and antibiotic properties of various plant extracts

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Objectives. *The purpose of this study was to develop an objective instrumental method for assessing microbial contamination and expressing the probiotic and antibiotic properties of food, pharmacological, and other products.*
Methods. *The developed method consists of periodic (every 2 h) registration of changes in pH, redox potential, and electrical conductivity of a liquid nutrient medium incubated in the presence and absence of viable test microorganisms and test samples.*
Results. *Using liquefied* CO_2 *from 10 different types of plant materials, we carried out a comparative analysis of probiotic and antibiotic activities against Lactobacillus acidophilus of various concentrations of subcritical whole extracts obtained.*
Conclusions. *Among the studied plant extracts, the most active prolonged antibiotic properties were exhibited by extracts from the leaves of Eucalyptus globulus Labill. and seeds of Illicium verum Hook.f. at a concentration in the test medium (*C_{TE}*) more than 3 vol %, whereas the most active prolonged probiotic properties were exhibited by an extract from the herb of Mentha arvensis L. at* C_{TE} *= 0.2 vol %. In most cases, the initial antibiotic activity of the tested extracts (TEs) was greater than their prolonged activity. Also, the mid-term (in terms of TEs interaction time with test microorganisms) antibiotic activity of TEs was intermediate in value between their initial and prolonged activity. In the test medium, the decreasing concentration of TEs decreases their antibiotic activity monotonically and increases their probiotic activity, suggesting that the biological activity of products, including various plant extracts, is largely determined not only by the raw material and the method of extracting biologically active substances from it but also by the concentration of the extract in the product and by the interaction time of the said product with microbiota and others. In most cases, a significant number of tests could establish the exact nature*

of these dependencies. The proposed method is much more rapid, objective, and informative and less laborious and material-intensive than using standard microbiological methods in assessing the initial microbial contamination and the probiotic and antibiotic properties of various samples of both the new and already approved pharmaceuticals, foods, and other products, as well as the individual ingredients and additives.

Keywords: *microbiological biotesting, antibiotic properties, plant extracts, microbiological contamination, electrochemical methods*

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НАУЧНАЯ СТАТЬЯ

Методика электрохимического биотестирования для сравнительного анализа про- и антибиотических свойств различных экстрактов

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Цели. *Разработать быструю и объективную инструментальную методику оценки микробной обсемененности, а также про- и антибиотических свойств различных образцов пищевой, фармакологической и иной продукции.*
Методы. *Разработанная методика заключается в периодической (через каждые 2 ч) регистрации изменений pH, редокс потенциала и электропроводности жидкой питательной среды, инкубируемой в присутствии и в отсутствие жизнеспособных тестовых микроорганизмов и тестируемых образцов.*
Результаты. *С помощью представленной методики проведён сравнительный анализ про- и антибиотической активности в отношении Lactobacillus acidophilus разных концентраций цельных докритических экстрактов, полученных с помощью сжиженного* CO_2 *из 10 различных видов растительного сырья.*
Выводы. *Проведенные исследования показали, что среди исследованных растительных экстрактов наиболее активные пролонгированные антибиотические свойства проявили экстракты из листьев эвкалипта шаровидного (Eucalyptus globulus Labill.) и семян бадьяна настоящего (Illicium verum Hook.f.) при их концентрации в тестовой среде (*$C_{ТЭ}$*) больше 3 об.%; а наиболее активные пролонгированные пробиотические свойства проявил экстракт из травы мяты луговой (Mentha arvensis L.) при* $C_{ТЭ} = 0.2$ *об.%. Начальная антибиотическая активность тестированных экстрактов (ТЭ) в большинстве случаев была больше их пролонгированной активности. В то время как среднесрочная (по времени взаимодействия ТЭ с тестовыми микроорганизмами) антибиотическая активность ТЭ как правило была промежуточной по величине между их начальной и пролонгированной активностью. При этом с уменьшением концентраций ТЭ в тестовой среде их антибиотическая активность монотонно уменьшалась, а пробиотическая активность увеличивалась. Таким образом очевидно, что биологическая активность продукции, включающей различные растительные экстракты, в значительной степени определяется не только сырьём и способом экстрагирования из него биологически активных веществ, но и концентрацией экстракта в продукции, а также временем взаимодействия упомянутой*

продукции с микробиотой и т.п. Причем точный характер этих зависимостей в большинстве случаев может быть установлен лишь с помощью значительного числа тестовых испытаний. Последние удобно проводить с помощью представленной в этой работе методики, которая позволяет существенно более быстро, объективно и информативно, а также существенно менее трудоёмко и материалоёмко, чем при использовании стандартных микробиологических методов, оценивать исходную микробную обсемененность, а также про- и антибиотические свойства различных образцов как новой, так и уже допущенной к употреблению продукции, а также отдельных ингредиентов и добавок к оной.

Ключевые слова: *биотестирование микробиологическое, антибиотические свойства, экстракты растительные, микробная обсемененность, электрохимические методы*

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INTRODUCTION

The development of objective, fast, and available for a wide range of applications methods for the quantitative assessment of the probiotic and antibiotic properties of a large number of samples of new and approved-to-use products in pharmaceutical, cosmetic, food, feed, and other sectors of the national economy is becoming increasingly important. The abovementioned methods are one of the important components of the product quality and safety monitoring system. In the implementation of the abovementioned methods, both multicellular and unicellular test living organisms are used. Unicellular living organisms are used both because of they are the cheapest, available and statistically reliable model of living organisms, in general, and because they are also the model of useful natural human microbiota and natural microbiota that can cause various infectious diseases, toxicosis, allergic reactions, and contribute toward the spoilage of food and other products.

However, more time, materials, and labor of qualified personnel are required in standard microbiological testing (visual assessment of the overall survival of microorganisms or the size of the zone of growth retardation of their colonies), resulting in incomplete, subjective, and static information on disorders of the vital functions of test organisms [1–3]. Thus, the use of instrumental technologies in microbiological testing seems promising. Among them, optical and electrochemical methods are simple in execution, reliable, and universal.

In products manufactured and consumed by human society, there is an increasing lack of biologically active substances (BAS) of natural origin that contribute to the normal development and functioning of the human body (the human body is only weakened by stresses, presence of various physical and chemical factors of environmental pollution, lack of natural lighting and physical activity, and contacts with numerous extraneous microbiota, etc.) and symbiotically associated beneficial microbiota, or suppress microbiota's vital activity that is harmful to humans.

Because of the complexity of achieving the desired degree of purity, stereospecificity, and other parameters, the production of concentrated synthetic analogs of BAS at the current level of technology development to achieve a sufficiently high degree of biological activity of such compounds is costly and ineffective. In addition, BAS of natural origin has significantly lower side effects in terms of the spectrum width and intensity of action to humans and other living organisms compared with synthetic agents. Main sources of BAS that are used as functional additives to pharmaceuticals, foods, and other products are extracts and essential oils obtained from various plant materials.

Essential oils obtained by distillation or cold or hot pressing of plant raw materials [4] give the opportunity to achieve a significantly greater and stable biological activity of the final product compared with aqueous, alcoholic, and other plant extracts (PEs) obtained without removing extractants. Therefore, essential oils are now widely used as (i) additives to foods, pharmaceuticals, cosmetics, and other products, which have selective or low-specific promicrobial or antimicrobial actions, (ii) additives with various types of normalizing action used, inter alia, in the treatment of various diseases, and (iii) preserving, antioxidant, aromatizing, flavoring, and other types of additives [3, 4–13]. In addition, essential oils are used as antiseptics, environmental-friendly insecticides and pesticides, and additives to various dental, wound-healing, and other medical and packaging materials [5, 14–19].

However, only sufficient volatile and thermostable substances can be extracted from raw materials by distillation, and only a little yield of the final product is achieved by pressing, which is too critical to the raw materials. Therefore, recently the extracts obtained from plant materials via the subsequent removal of the extractant from the final product by increasing temperature and lowering pressure are used instead of using essentials oils. Currently, PEs obtained using liquefied carbon dioxide (CO_2PE) as an extractant are the most common. Liquefied carbon dioxide is then completely removed from the final product by changing the pressure and temperature of the latter [20–26].

Particularly, *Biozevtica* (Dedovsk, Moscow oblast, Russia)[1] not only has developed but also put into production, followed by a fairly widespread sale, a whole line of yogurts, mayonnaise, vegetable and butter oils, spicy mixtures (dry, fat, or water-soluble), juices, lemonades, and other products with additives of various CO_2PEs (which is also produced by *Biozevtica*).

In comparison with essential oils, CO_2PEs have a significantly wider variety of BAS included in their composition. If the extraction is carried out with pressure above 7.6 MPa and a temperature of the carbon dioxide (CO_2) below 31°C, the extracts are called “subcritical.” Otherwise, the extracts are called “supercritical” because the CO_2, being in a supercritical state, exhibits both the liquid and gas properties. Besides, CO_2PEs are categorized into “selective” (obtained at low CO_2 pressures and having a composition closer to essential oils) and “whole” (obtained at high CO_2 pressures). In addition to volatile components common for essential oils, whole subcritical CO_2PEs (the richest in various BAS) contain heavier plant resins, paraffins, pigments, and others and have more viscous pasty consistency compared with “ordinary” essential oils; however, they are easily dissolved by both ethers and vegetable oils (although, in some cases, slight heating is required to dissolve them).

The purpose of this study was to develop a quick and objective instrumental method for assessing the microbial contamination and expressing the probiotic and antibiotic properties of various products, as well as individual ingredients and additives, followed by a comparative analysis using the developed method for the influence of various PEs on the dynamics of the human microbiota.

MATERIALS AND METHODS

We took whole subcritical extracts produced by *Kazanskii zavod ekstraktov* (Kazan, Russia)[2] using liquefied CO_2 at a pressure of 7.3 MPa and a temperature of 20°C from the following types of plant materials: leaves of southern blue gum (*Eucalyptus globulus Labill.*) (No. 1), clove buds (cloves, *Syzygium aromaticum L. Merr. & L.M. Perry*) (No. 2), ginger roots (*Zingiber officinale Roscoe*) (No. 3), shoots of common sage (*Salvia officinalis L.*) (No. 4), creeping thyme herb (thyme, *Thymus serpyllum L.*) (No. 5), oregano herb (*Origanum vulgare L.*) (No. 6), field mint herb (*Mentha arvensis L.*) (No. 7), shoots of rosemary (*Rosmarinus officinalis L.*) (No. 8), star anise seeds (star anise, *Illicium verum Hook.f.*) (No. 9), and cardamom green seeds (*Elettaria cardamomum L. Maton*) (No. 10). This plant was chosen because it is currently the largest producer in Russia of CO_2PEs, which are used as sources of dietary supplements in medicine, veterinary medicine, cosmetic and food products, household chemicals, etc. Raw material No. 1 was obtained from Australia; raw materials Nos. 2, 3, and 8–10 were from India, and raw materials Nos. 4 and 5–7 were from Russia (Krasnodar krai and Kazan precincts, respectively).

On the basis of the existing our developments on various methods of instrumental biotesting [27–33], to analyze the effect of different concentrations of the tested extracts (TEs) on the dynamics of the vital activity of microorganisms, we developed the method, as described in the following.

Four series of measurements were carried out for each batch of TE, and before the beginning of each batch, a nutrient medium was prepared, which was a sterile aqueous solution with pH 7.2 ± 0.2, containing 5-g/L glucose, 20-g/L protein hydrolyzate, and 2-g/L NaCl. The nutrient medium was then inoculated with *Lactobacillus acidophilus* ATCC 4356, which were selected as typical representatives of the microbiota because they are widespread both outside and inside the human body and other living organisms, which are actively participating in the destruction of various biopolymers, and also because they are widely used by humans in many biotechnological processes, including bioconservation, ensiling, and obtaining various fermented milk products. Then, the mentioned culture medium with test microorganisms was incubated at 37.0 ± 0.1°C until the content of viable microorganisms reached approximately 5×10^6 cells/mL, which was verified by a nephelometric method using a bacterial turbidity standard.

The obtained test medium was poured into the test measuring capacities (MCs), in which the amount

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[1] URL: https://biozevtika.ru. Accessed October 06, 2020.

[2] URL: https://extract.market. Accessed October 06, 2020.

of TE required to achieve its specified concentration in the test medium was previously added each (three MCs in parallel). In this case, we used the following as control (which was also placed in the MC in triplicate): a test medium with viable microorganisms without TE (control-1) and a solution with a given concentration of TEs in a sterile nutrient medium (control-2).

Then both the test and all control MCs were incubated at 37.0 ± 0.1°C for another 6 h. The pH, redox potential (E, mV) and specific linear low-frequency electrical conductivity (X, mS/sm) values of the test media contained in each of the MCs were sequentially recorded with an interval of 2 h. In this case, the pH and E values were recorded using an Expert-001 ionomer (*Econix-Expert*, Moscow, Russia)[3] with combined electrodes ESK-10601/7 and ERP-105, whereas the values of X were recorded using an Expert-002 conductometer (*Econix-Expert*) with a sensor UEP-P-S operating at a frequency of 1.6 kHz.

After that, we calculated the total degrees of activation (+) or inhibition (−) of the vital activity of test microorganisms by the given concentrations of the tested samples after k hours of their joint incubation in a liquid test medium ($\varepsilon_{V,k}$, %) by the following Equation (1):

$$\varepsilon_{V,k} = (\varepsilon_{\mathrm{pH},k} + 0.7\varepsilon_{E,k} + 0.7\varepsilon_{X,k})/2.4 \qquad (1)$$

The values of $\varepsilon_{\mathrm{pH},k}$, $\varepsilon_{E,k}$, and $\varepsilon_{X,k}$ were determined separately from pH, E, and X values of the test media in the MC during the incubation of these MC according to the following Equation (2):

$$\varepsilon_{i,k} = 100 \times (\Delta Yt_{i,k} - \Delta Yc_{i,k})/\Delta Yc_{i,k} \qquad (2)$$

The index i shows the measurements for which parameter (pH, E or X) were taken into account in Equation (2): for example, $\varepsilon_{\mathrm{pH},k} = 100 \times (\Delta Yt\mathrm{p}_{\mathrm{H},k} - \Delta Yc_{\mathrm{pH},k})/\Delta Yc_{\mathrm{pH},k}$.

The values of $\Delta Yt_{i,k}$ and $\Delta Yc_{i,k}$ were determined as averaged over a sample of N samples with the same concentrations of extracts prepared in the same way from one type of raw material (in our case, $N = 3 \times 4 = 12$), changes in the values of the i-parameter of the test medium (pH, E, or X) that occurred k hours after the start of incubation of this medium in the presence of a given concentration of TE (ΔYt observed in the test MC) or in the absence of TE (ΔYc observed in control-1 MC). For example, $\Delta Yt_{\mathrm{pH},2} = \mathrm{pH}_{\mathrm{T},2} - \mathrm{pH}_{\mathrm{T},0}$ and $\Delta Yc_{X,4} = X_{\mathrm{C},4} - X_{\mathrm{C},0}$ (where $\mathrm{pH}_{\mathrm{T},0}$ is the pH value of the medium in the test MC at the beginning of its incubation, $\mathrm{pH}_{\mathrm{T},2}$ is the pH value of the medium in test MC 2 h after the start of its incubation, $X_{\mathrm{C},0}$ is the X value of the medium in control-1 MC at the beginning of incubation, and $X_{\mathrm{C},4}$ is the X value of the medium in control-1 MC 4 h after the start of incubation).

The error in determining each of the averaged quantities $\varepsilon_{\mathrm{pH},k}$, $\varepsilon_{E,k}$, and $\varepsilon_{X,k}$ was calculated in a standard way [34–36]. On the basis of the standard formula $\Delta z(x_i) = \Sigma_i(\Delta x_i \delta z/\delta x_i)$ [34–36], the total error in determining the value $\varepsilon_{V,k}$ was calculated as $\Delta\varepsilon_{V,k} = (\Delta\varepsilon_{\mathrm{pH},k} + 0.7\Delta\varepsilon_{E,k} + 0.7\Delta\varepsilon_{X,k})/2.4$.

To assess the general degree of activation or inhibition of the vital activity of test microorganisms by the given TE concentrations, we chose the parameters pH, E, and X because they are most reliably measured instrumentally and, at the same time, sensitive enough to be used in controlling the acceleration or deceleration of conversion by viable microorganisms present in the test medium and catabolites present in the same medium into anabolites after k hours of incubation of the mentioned test medium in the presence of TE as compared with the control, in which TE is absent. The sensitivity is due to the transformation of catabolites into anabolites by microorganisms, which significantly changes the acidity, electrochemical redox potential, and electrical conductivity of the test media.

The legitimacy of combining three quantities $\varepsilon_{\mathrm{pH}}$, ε_E, and ε_X into one parameter ε_V can be explained by the fact that each of these quantities was independently normalized to the control values of its defining indicator and, thus, uniformly (percentage relative to the control) reflected the change in metabolism test microorganisms in the presence of TE, at the same time characterizing this change somewhat differently, because changes in pH, E, and X in the test medium caused different metabolic processes carried out by the presence of viable microorganisms. As a result, the total value of ε_V characterized the changes in the metabolic activity of test microorganisms more informatively and adequately than each of the values of $\varepsilon_{\mathrm{pH}}$, ε_E, and ε_X separately.

The latter is confirmed by the fact that for ε_V there was a 90% significant correlation with the change in the number of colonies forming units of test microorganisms, which is determined using the standard method [1–3, 37, 38].

With the proposed method, it is possible to determine the microbial contamination (C_{M}) of the tested samples. For this, the calculation is performed similarly to Equations (1) and (2), where ΔYt is determined for control-1 MC and ΔYc for control-2 MC. The obtained C_{M} value is multiplied

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[3] URL: http://ecosolution.ru. Accessed October 06, 2020.

by the calibration factor, determined previously on the basis of comparing the results obtained using the proposed method with the results obtained for the same concentrations of the same TEs using the aforementioned standard microbiological testing method. In this case, the resulting C_M value will show how many viable microorganisms were initially present in the test sample. Moreover, if the test samples are incubated in selective nutrient media instead of the "general accumulative" nutrient medium used in this study, then the proposed method can be used to determine both the total microbial contamination of these samples and the contamination of individual species and strains of microorganisms.

RESULTS AND DISCUSSION

The table and figure present the most interesting data obtained by the proposed method concerning the objects of this study.

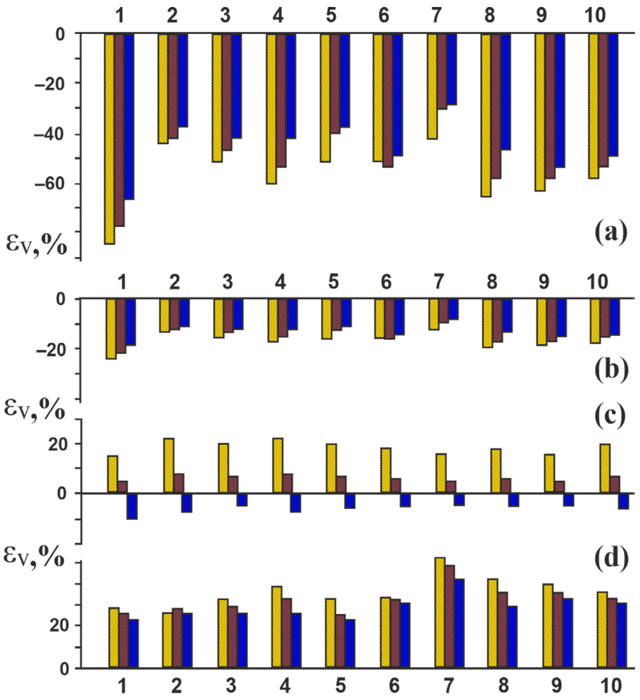
As can be seen in the figure, in the change in the concentration of TEs in the test medium (C_{TE}), the nature of both probiotic and antibiotic activities can change quite significantly.

TEs obtained from different parts of different plants also had different probiotic and antibiotic activities. This is particularly seen in, for example, comparing the antibiotic activity of extracts obtained from the leaves of eucalyptus globular, oregano herb,

The total degree of activation (+) or inhibition (−) of the vital activity of *Lactobacillus acidophilus* ($\varepsilon_{V,k}$, %), determined after 2, 4, and 6 h of their incubation in a liquid nutrient medium in the presence of different amounts of whole subcritical extracts obtained using liquefied CO_2 from various plant materials (CO_2PE)

Biological activity	**No. of raw material**									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
	conc. CO_2PE 3.0 vol %									
$\varepsilon_{V,2}$, %	–84	–44	–51	–60	–51	–51	–42	–65	–63	–58
$\varepsilon_{V,4}$, %	–77	–42	–47	–53	–40	–53	–30	–58	–58	–53
$\varepsilon_{V,6}$, %	–67	–37	–42	–42	–37	–49	–28	–47	–53	–49
	conc. CO_2PE 1.5 vol %									
$\varepsilon_{V,2}$, %	–24	–13	–15	–17	–15	–15	–12	–19	–18	–17
$\varepsilon_{V,4}$, %	–22	–12	–13	–15	–12	–16	–9	–17	–17	–15
$\varepsilon_{V,6}$, %	–19	–11	–12	–12	–11	–14	–8	–13	–15	–14
	conc. CO_2PE 0.5 vol %									
$\varepsilon_{V,2}$, %	15	22	20	22	20	18	16	18	16	20
$\varepsilon_{V,4}$, %	5	8	7	8	7	6	5	6	5	7
$\varepsilon_{V,6}$, %	–10	–7	–5	–7	–6	–5	–4	–5	–5	–6
	conc. CO_2PE 0.2 vol %									
$\varepsilon_{V,2}$, %	28	26	32	38	32	33	52	41	39	36
$\varepsilon_{V,4}$, %	26	28	29	33	25	32	48	36	36	33
$\varepsilon_{V,6}$, %	23	26	26	26	23	31	42	29	33	31

Note. See the Materials and Methods section for the method in determining $\varepsilon_{V,k}$ and the corresponding raw material Nos. 1–10 used to prepare the tested extracts. The relative error in determining ε_V for all values indicated in the table was in the range from 10 to 20%.



Comparative biological activity of the tested extracts (TEs) against *L. acidophilus* at different TE concentrations in the test medium (a: 3.0 vol %; b: 1.5 vol %; c: 0.5 vol %; d: 0.2 vol %). The ordinate shows the ε_V (%) values determined for TE based on the results of measuring the pH, redox potential, and electrical conductivity of liquid nutrient media with *L. acidophilus* after 2, 4, and 6 h of incubation according to Equations (1) and (2). The abscissa shows the number of raw materials from which TEs were obtained.

and meadow mint grass, where at C_{TE} = 3 vol %, the values of $\varepsilon_{V,6}$ were −67 ± 8%, −49 ± 6%, and −28 ± 4% (see table for extracts Nos. 1, 6, and 7). Also, this is seen as well in comparing the probiotic activity of the same extracts, where at C_{TE} = 0.2 vol %, the values of $\varepsilon_{V,6}$ were 23 ± 3%, 31 ± 4%, and 42 ± 5%, respectively).

Among the extracts studied, the most active prolonged (long-term) antibiotic properties (quantitatively characterized in the table by the value of $\varepsilon_{V,6}$, determined after 6 h of incubation of test microorganisms in the presence of TE) were shown by extracts from the leaves of eucalyptus globular and seeds of star anise with $C_{\text{TE}} \geq 3$ vol % (see table for extracts Nos. 1 and 9). The most active prolonged probiotic properties were shown by an extract from the herb of meadow mint at C_{TE} = 0.2 vol % (see table for extract No. 7).

In most cases, the initial (short-term) biological activity of TEs (quantitatively characterized in the table by the value of $\varepsilon_{V,2}$, determined after 2 h of incubation of test microorganisms in the presence of TEs) was significantly greater than their prolonged activity. This was probably because of both the adaptation of the test microorganisms to the presence of TE and a decrease in the activity and the total amount of BAS contained in TE per cell of the test microorganism over time. Moreover, the latter took place because the total number of cells of microorganisms increased during incubation of the test medium containing them, whereas the activity and total amount of BAS contained in TE decreased during incubation because of biochemical and physicochemical denaturation and destruction of the mentioned BAS.

The medium-term (in terms of the interaction time of TE with the test microorganisms) biological activity of TE (quantitatively characterized in the table by the value of $\varepsilon_{V,4}$, determined after 4 h of incubation of test media with TE) was intermediate in value between $\varepsilon_{V,2}$ and $\varepsilon_{V,6}$ and only sometimes (as, for example, in the case of extracts Nos. 2 and 9 with $C_{\text{TE}} \geq 1.5$ vol %) exceeded both $\varepsilon_{V,2}$ and $\varepsilon_{V,6}$ of the same TE (see table and figure).

The decrease in TE concentrations in the test medium decreased their antibiotic activity against test microorganisms significantly and monotonously and increased, on the contrary, their probiotic activity. For example, at C_{TE} = 3.0, 1.5, and 0.2 vol %, the $\varepsilon_{V,6}$ values for the extract from the leaves of the globular eucalyptus were −67 ± 8%, −19 ± 3%, and 23 ± 3%, respectively, and the values of $\varepsilon_{V,6}$ for the extract from the herb of meadow mint were −28 ± 4%, −8 ± 1%, and 42 ± 5%, respectively (see table for extracts Nos. 1 and 7).

The indicated effective concentrations of TEs turned out to be significantly higher than, for example, the widely used synthetic antiseptic with a broad spectrum of action, such as chlorhexidine bigluconate (CHG), which we studied in the form of a 0.05% aqueous solution manufactured by *Rosbio* (Russia) [29], which already at C_{TE} = 0.0001 and 0.001 vol % showed $\varepsilon_{V,6}$ = −35 ± 5% and −1 ± 6% for *L. acidophilus*. However, CHG is not intended for internal use, and the advantages of PEs over antibiotics have already been discussed above. On the basis of these data, the method of rapid instrumental microbiological testing can be successfully used to assess the probiotic and antibiotic properties of not only PEs but also many other drugs and materials (including those obtained synthetically).

CONCLUSIONS

With the proposed method, it is possible to assess the initial microbial contamination much more quickly (within a few hours, not days), objectively, and informatively than using standard methods, as well as to determine the effect on the dynamics of life activity of test microorganisms of samples of various products (for example, PEs).

The greater objectivity of the proposed technique is achieved by reducing the role of the subjective human factor when replacing visual methods with instrumental ones in the measurement process. We achieved greater information content of the proposed technique because of the following. Firstly, instrumental measurement methods are more sensitive than visual ones used in standard methods. Secondly, the proposed method makes it possible to assess the dynamics of changes in the vital activity of microorganisms over a set of arbitrarily selected time intervals, in contrast to standard procedures, where measurements are made only once, at the end of the incubation period of the tested samples. Thirdly, the proposed method involves assessing changes in the vital activity of microorganisms at once by several independent indicators (such as pH, redox potential, and electrical conductivity of the test medium), and not just one (turbidity of the test medium, the number of colonies of microorganisms, or the size of the zone of their growth inhibition), as in the case of using standard techniques. The technique presented here uses fewer materials and is less labor-intensive compared with similar standard methods and also provides many more opportunities for automating the entire analysis process.

All this makes the presented technique much more accessible for mass use than the previously used standard methods of microbiological testing and assessment of microbial contamination of samples of various products, which is very relevant because one of the important conditions for ensuring the proper level of safety and quality of life of people is not only timely and qualitative testing of the probiotic and antibiotic properties of new products and individual ingredients and additives to them but also constant wide monitoring of microbial contamination, as well as probiotic and antibiotic properties of products already admitted for mass consumption to identify the poor quality or that had time to deteriorate before the final sale or undergo chemical or biological contamination of its samples.

Regarding the PEs studied, the most active prolonged (long-term) antibiotic properties were exhibited by extracts of eucalyptus spherical leaves and star anise seeds at their concentrations in the test medium from 3 vol % and higher. The most active long-term probiotic properties were exhibited by an extract from the herb of meadow mint at a concentration of 0.2 vol % in the test medium. In most cases, the initial biological activity of the TEs was significantly higher than their long-term activity. The medium-term (in terms of the time of TE interaction with the test microorganisms) biological activity of TEs was intermediate in value and only sometimes exceeded the prolonged and initial biological activity of TEs. With a decrease in the concentration of TEs in the test medium, their antibiotic activity monotonically decreased and their probiotic activity increased.

It is obvious that the nature of the probiotic and antibiotic activities of pharmaceuticals, cosmetics, foods, feeds, and other products, including those containing various PEs, is largely determined by the choice of not only the raw material and the method for extracting BAS from it but also the concentration of active substances in products. Moreover, the exact nature of these dependencies can be established only empirically, with the help of a significant number of tests, which are convenient to carry out using the proposed method.

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Authors' contribution

V.S. Sibirtsev – concept and design of the study, writing the text of the article;

U.Yu. Nechiporenko – collecting materials, conducting research.

The authors declare no conflicts of interest.

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SYNTHESIS AND PROCESSING OF POLYMERS AND POLYMERIC COMPOSITES

СИНТЕЗ И ПЕРЕРАБОТКА ПОЛИМЕРОВ И КОМПОЗИТОВ НА ИХ ОСНОВЕ

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RESEARCH ARTICLE

Development of technology for producing biodegradable hybrid composites based on polyethylene, starch, and monoglycerides

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Objectives. *This work aimed to develop technology to produce biodegradable hybrid composite (BHC) films based on low-density polyethylene (LDPE) 115030-070 and thermoplastic starches (TPS) of various origins (corn, pea, and rice), with distilled monoglycerides as the plasticizer. The properties of the produced BHC films were studied and the optimal native starch : glycerol : monoglycerides ratio is proposed.*

Methods. *TPS and BHC films based on this material were produced from different types of native starches in laboratory extruders (Brabender and MashPlast, Russia), and the extruded melts were subjected to ultrasonic vibrations. The structure and appearance of the BHC films were studied using scanning electron microscopy and rheology. Their biodegradability was assessed by immersing them in biocompost for three months. To evaluate the mechanical performance of the BHC films produced with and without ultrasound, the changes in tensile stress and elongation at break were determined during the biodegradation process.*

Results. *The BHC films had a homogeneous structure, except small agglomerates (non-melted starch grains), which did not reduce their quality. The films with monoglycerides had high tensile strength, which was comparable with low-density polyethylene. After removing samples of the BHC films from the biocompost, their tensile strength decreased by 20%, which shows their biodegradability.*

Conclusions. *The produced biodegradable composite films and the technology used to produce them will be applicable for the packaging industry to reduce environmental impact.*

Keywords: *polyolefin, thermoplastic starch, biodegradable polymer composite, structural modification, extrusion*

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НАУЧНАЯ СТАТЬЯ

Разработка технологии получения биоразлагаемых композиций на основе полиэтилена, крахмала и моноглицеридов

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Цель. *Совершенствование технологии создания биологически разрушаемых гибридных композиций (БГК) на основе полиэтилена низкой плотности (ПЭНП) 11503-070 и термопластичных крахмалов различного происхождения (кукурузы, гороха, риса) с новыми пластификаторами – моноглицеридами дистиллированными. Разработка технологической схемы производства БГК. Получение и исследование свойств биологически разрушаемых композиционных пленок, пластифицированных смесью дистиллированных моноглицеридов и глицерина. Выбор оптимального соотношения нативный крахмал : глицерин : моноглицериды.*

Методы. *Термопластичный крахмал и композиционные пленки получали на основе нативных крахмалов разных видов в лабораторных экструдерах фирм «Брабендер» и «МашПласт» (Россия), при этом экструдируемый расплав композиции подвергали воздействию ультразвуковых колебаний. Была изучена структура композитных пленок методом сканирующей электронной микроскопии, а также их реологические характеристики. Проведена оценка органолептических свойств композитных пленок. Способность к биоразложению композитных пленок оценивали при помощи погружения их на три месяца в биогумус. Для оценки эксплуатационных свойств БГК, до и после процесса биоразложения, определяли разрушающее напряжение при растяжении и относительное удлинение при разрыве, причем оценка была проведена и для пленок, которые подвергали воздействию ультразвука.*

Результаты. *Был достигнут положительный эффект от использования нового пластификатора – дистиллированных моноглицеридов в композициях термопластичный крахмал : полиэтилен. При производстве композиции получались однородными по структуре, иногда образовывались небольшие агломераты, представляющие собой нерасплавившиеся частицы крахмала, что не ухудшало качество готовых БГК. Композиты с моноглицеридами обладали высокой прочностью на разрыв – практически на одном уровне с ПЭНП. После изъятия образцов композитных пленок из биогумуса их прочность на разрыв снижалась на 20%, что свидетельствует о протекании процесса биоразложения.*

Выводы. *Разработанный состав и технология получения биологически разлагаемых композитных пленок могут быть использованы в дальнейшем для производства композитных пленок с высоким содержанием крахмала для применения в упаковочной отрасли, что позволит снизить негативную нагрузку на окружающую среду.*

Ключевые слова: *полиолефины, термопластичный крахмал, биоразлагаемые полимерные композиции, структурная модификация, экструзия*

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INTRODUCTION

Recently, the rapid growth in the consumption of synthetic plastics in many sectors of the economy, especially in the field of packaging, has been a major concern. Plastic containers are used for packaging food products, medicines, electronic devices, liquids, some of which have an increased hazard class [1]. According to the German research institute, *Nova-Institute*[1], which deals with polymer technologies, global plastic production in 2019 reached almost 400 million tons, whereas the volume of biodegradable plastics obtained from renewable resources was only 3.5 million tons, i.e., approximately 1% of the total production[2] [2]. Since only 25% of plastic wastes are recyclable, there is a need to create biodegradable polymer compositions [3–5]. This issue has economic and environmental facets because it is associated with the need to reduce the cost of raw materials for the production of various products, and ensure environmental protection [6–10].

Some technologies for producing biodegradable polymer hybrid composites (BHCs) and products based on them are presented in [11–15]. One of the most promising approaches to produce BHCs is the use of thermoplastic starch (TPS) as the main component [16, 17]. To obtain TPS, native starch is mixed with various plasticizers by heating [18, 19]. The use of TPS instead of native starch as a filler for polyolefin compositions allows for more effective processing and higher thermal stability of the finished compositions [20–22]. The TPS content in the compositions can be as much as 40–60 wt % [8, 9]. Therefore, the purpose of this work is to improve the technology for producing BHCs, containing distilled monoglycerides (DMG) and intended for use as packaging materials, select the optimal technological parameters, and develop a basic technological scheme for their production.

MATERIALS AND METHODS

Low-density polyethylene (LDPE) (Grade 11503-070), produced by *Kazanorgsintez* (Russia), and composite materials based on it, filled with starch-containing products, were used. The average molecular weight of the LDPE was 1.8×10^4. PC-94 glycerin with a density of 1.24 g/cm^3, produced by *TC Vympel* (Russia) and issued in accordance with GOST 6824-96, and DMG produced according to technical specifications TU 10-1197-95 by *Rushimtrade* (Russia) were also used. Corn starch produced by *Krakhmaloprodukt* (Orel, Russia) in accordance with GOST 32159-2013, rice starch—*Vinh Thuan Trading Import-Export Co. Ltd* (Vietnam), and pea starch—*Roquette* (France) were used as filler for LDPE. The grain size and gelatinization temperature of these starches are shown in Table 1.

TPSes of different species were produced based on the native starches in laboratory extruders provided by *Brabender* (Germany) and *MashPlast* (Russia) firms. To do this, starch, glycerol, and DMH were mixed for 20–30 min in the dispersant. The resulting mass was loaded into the extruder and processed into a rod (strand) at extruder outlet temperatures from 115°C to 140°C. The TPS strands were cooled and crushed using a granulator to produce granules from 2 to 4 mm in size. These granules were used for the production of the BHC films through mixing with LDPE in a laboratory flat-die extruder manufactured by *MashPlast* (Russia).

The melt flow rate (MFR) of the films was determined using an IIRT-5 capillary viscometer (*TOCHMASHPRIBOR*, Russia) at a ratio of 60 : 40 of TPS to LDPE mass fractions, a temperature of 190°C, and a load of 2.16 kg.

The mechanical properties of samples of the films under tension were determined using a RM-50 testing machine manufactured by *MashPlast* (Russia) equipped with a computer interface with

Table 1. Properties of native starches

Property	Native starch type		
	Corn	Rice	Pea
Grain size, µm	5–25	8–32	7–30
Gelatinization temperature, °C	62–72	68–78	57–70

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[1] URL: http://nova-institute.eu/.

[2] Bio-based Building Blocks and Polymers – Global Capacities, Production and Trends 2019 – 2024. Hürth, Germany: Michael Carus (V.i.S.d.P.); 2020. URL: http://bio-based.eu/downloads/bio-based-building-blocks-and-polymers-global-capacities-production-and-trends-2019-2024/

the StretchTest software (Russia). The tensile stress and elongation at break of the films were measured at a temperature of 23 ± 2°C and a relative humidity of 50 ± 5% according to the method described in GOST 14236-81. The limit of the permissible load measurement error did not exceed ±1%. The maximum deviation in the width of the samples was ± 0.2 mm. The average value was determined over 3–5 measurements. The tests were performed at a strain rate of 100 mm/min. Samples of the films for testing were obtained using a cutting device, with the shape of the samples corresponding to type 1B (ENISO 527-3).

To assess the biodegradation dynamics of the filled polymer compositions, the composting method was used. The samples were placed in special trays with biocompost at a temperature of 23 ± 2°C and a humidity of 70 ± 10%, and kept there for 3 months. The degree of biodegradation of the films was evaluated by assessing changes in their physical and mechanical properties i.e., breaking stress at tension (σ) and elongation at break (ε), according to GOST 54530-2011.

The surface morphology of the films was studied using a high-resolution, autoemission, scanning electron microscope, JSM-7500F (*JEOL*, Japan).

RESULTS AND DISCUSSION

Dry native starch, in accordance with the scheme shown in Fig. 1, was loaded into the container of a laboratory dispersant, which was fed glycerol and DMH plasticizer through a dispenser to achieve a ratio of 60 : 30 : 10 [10]. Native starch, glycerol, and plasticizer were thoroughly mixed for 20–30 min at a speed of 70 rpm. Here, a homogeneous paste-like mass was obtained. The following steps were performed to produce the TPS:

– dosage of the TPS components: native starch, glycerol and plasticizer;
– pre-mixing of the native starch, glycerol and plasticizer;
– extrusion of the TPS composition;
– cooling of the TPS extrudate;
– pelletizing of TPS and
– packaging of the finished granulate TPS.

The mixture in the extruder was heated, plasticized, and then pressed through the cylindrical holes of the extruder head. The resulting strands were cooled and crushed into granules of 2–4 mm in size at a speed of 120 rpm. The TPS granules were dried in a vacuum cabinet at a temperature of 60°C.

The technological scheme for the manufacture of TPS is shown in Fig. 1.

To select the relevant modes of extrusion production of the BHC films, the rheological properties of the compositions, in particular, MFR, were studied. The results are given in Table 2. It can be seen that the viscosity of the BHC film melts at the maximum TPS : LDPE mass ratio of 60 : 40 increased and the MFR of the films decreased by 20.0–27.1% compared with the original LDPE, which is likely due to the agglomeration of starch particles in the melt during the formation of the BHC structure. The minimum value of MFR was observed in the BHC film made from rice starch. This reduction in MFR can lead to a slight decrease in the productivity of extrusion equipment in the manufacture of such compositions.

The obtained TPS granules based on different types of starches were mixed with LDPE in a laboratory twin-screw extruder equipped with an ultrasonic melt processing unit at TPS : LDPE ratios ranging from 40 : 60 to 60 : 40, and BHC was obtained in the form of strands under the temperature conditions, shown in Table 3.

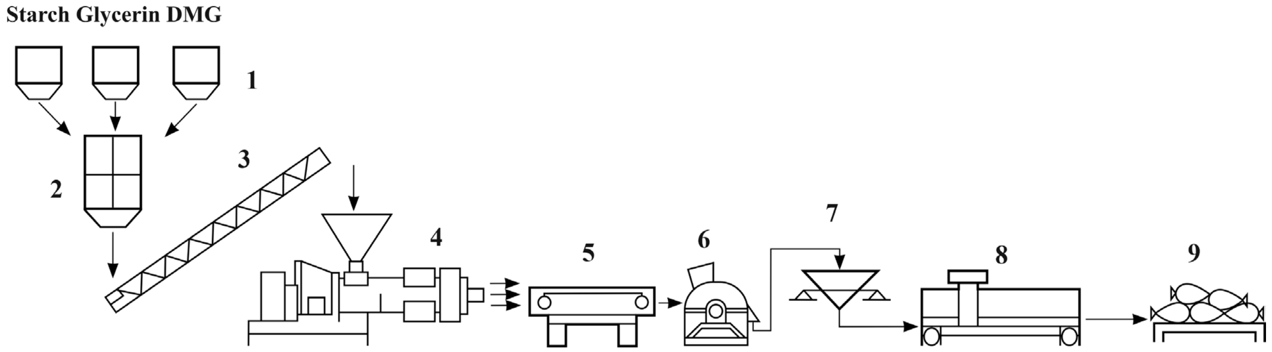


Fig. 1. Technological scheme for the manufacture of TPS:
(1) loading hopper, (2) disperser, (3) screw conveyor, (4) extruder, (5) cooling bath, (6) granulating device, (7) scales, (8) bag sewing machine, and (9) finished products.

Table 2. Melt flow rate (MFR) of the initial LDPE and LDPE-based BHC films

No.	Compositions	MFR, g/10 min
1	Original LDPE	7.0 ± 0.2
2	BHC (TPS with pea starch)	5.6 ± 0.1
3	BHC (TPS with corn starch)	5.4 ± 0.3
4	BHC (TPS with rice starch)	5.1 ± 0.2

Table 3. Temperature ranges of BHC production

BHC type	Cylinder zone temperature, ℃				
	Zone of the extruder				
	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5
BHC based on corn TPS	110	125	135	140	140
BHC based on pea TPS	110	120	125	130	130
BHC based on rice TPS	110	115	120	125	125

The diameter of the extruder screws was 16 mm. The speed of the screws was 60–80 rpm. The strands were cut into granules of approximately 2 mm in size at a knife speed of 140–160 rpm.

A schematic diagram of the used twin-screw extruder apparatus is shown in Fig. 2.

Then, the granules obtained using the twin-screw extruder were loaded into a laboratory single-screw extruder with a screw diameter of 12 mm, which was also equipped with an ultrasonic melt processing unit, and extruded through a flat-slot head with a width of 130 mm. A barrier screw was used, which during the extrusion process ensured homogenization of the LDPE/TPS mixture and high quality of the polymer film. The speed of rotation of the screw varied from 70 to 90 rpm.

The mass coming out of the head was transferred to cooled receiving shafts, stretched using a broaching device, and rolled, resulting in the BHC film.

A schematic diagram of the flat-slot single-screw extruder is shown in Fig. 3.

In the manufacture of the BHC films, the polymer melt was exposed to ultrasonic vibrations, and processed by ultrasound directly in the extruder using an ultrasonic attachment, which was a magnetostrictive converter with a titanium waveguide. To remove heat from the ultrasonic attachment, a water jacket was used. A schematic diagram of the ultrasonic attachment is shown in Fig. 4.

The ultrasonic attachment was installed between the screw zone and the extrusion head. The waveguide of the ultrasonic attachment was immersed directly in the melt. The attachment was equipped with an oscillator with a frequency of 22 kHz, and the oscillation amplitude of the waveguide end was up to 10 µm. In the manufacture of the BHC film, a frequency of 22 kHz and power up to 1.0 kW was used for melt processing. With a higher power of the ultrasonic unit, the melt began to foam when leaving the flat-slot head due to the destruction of the polymer composition, resulting in through holes in the film.

After BHCs were obtained in the form of polymer films, their organoleptic characteristics were determined.

The appearance of the BHC film samples prepared from the maximum achievable TPS : LDPE ratio is shown in Fig. 5.

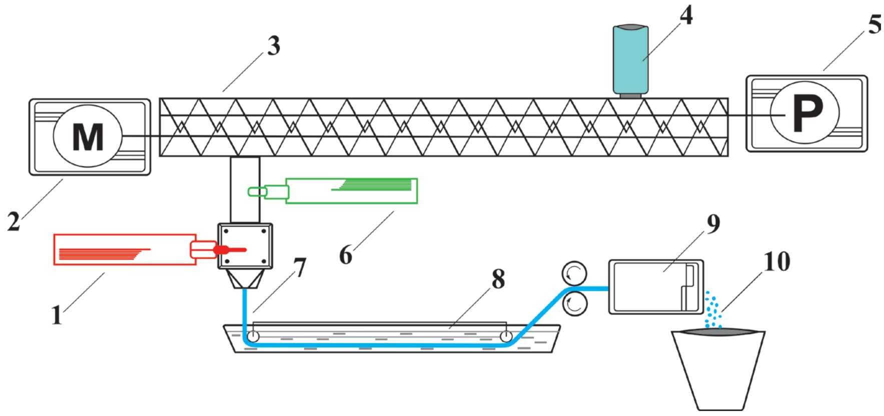


Fig. 2. Schematic of the twin-screw extruder for obtaining composite granules: (1) ultrasonic attachment, (2) engine, (3) twin-screw extruder, (4) loading hopper, (5) gearbox synchronized with the engine, (6) pressure sensor, (7) strand, (8) cooling bath, (9) granulator, and (10) composite granules.

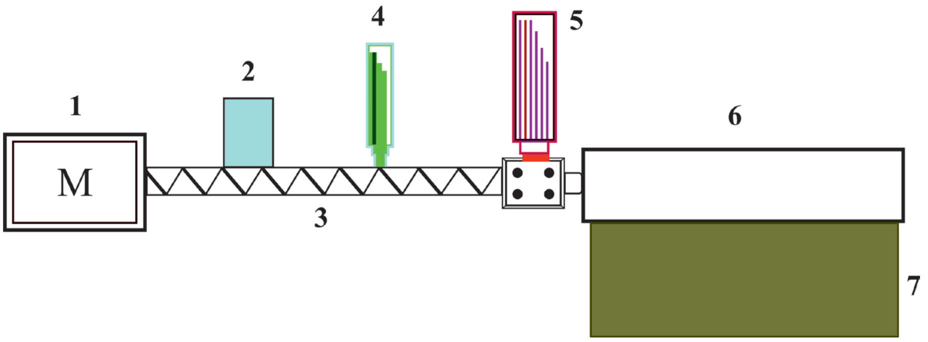


Fig. 3. Schematic of the flat-slot single-screw extruder: (1) engine, (2) loading hopper, (3) screw, (4) pressure sensor, (5) ultrasonic attachment, (6) flat-slot head, and (7) melt of the finished composite.

The films produced at the maximum achievable TPS : LDPE ratio with the three types of TPS had a uniform matte-white surface without agglomerates in the form of non-melted starch particles, and no cracks or other damage. This indicates that homogenization of the compositions was achieved.

Although the initial assessment of the organoleptic properties of the finished BHC films showed positive results, it was important to consider the structural changes in the BHC films. As an example, Fig. 6 shows micrographs of the BHC films obtained at the maximum TPS : LDPE ratio of 60 : 40, based on rice starch.

Figure 6a shows agglomerates of thermoplastic starch, some with a “grain” phase interface, while Fig. 6b showed oriented structures formed in the film composition.

For BHC to be used as a raw material for polymer packaging, it is important to achieve high mechanical performance. For this purpose, the following mechanical characteristics of the BHC films were studied: breaking stress at tension (σ) and elongation at break (ε). The test results are shown in Table 4.

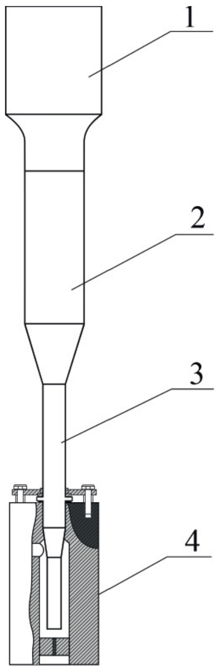


Fig. 4. Schematic of the ultrasonic attachment: (1) transducer of ultrasonic vibrations, (2) concentrator (waveguide), (3) emitter, and (4) extrusion head.

As can be seen from the test results, the BHC films demonstrated high strength, almost at the level of LDPE, and strong deformation characteristics, which makes BHC applicable for use in packaging.

Furthermore, the effect of ultrasonic vibrations on the melt for all compositions improved both strength and deformation indicators, which shows that the compositions were homogenous and that there was an increase in the interaction between the polymer matrix of polyethylene and TPS of various origins.

a b c

Fig. 5. Appearance of representative BHC film samples with a TPS : LDPE ratio of 60 : 40, using (a) corn TPS, (b) pea TPS, and (c) rice TPS.

The resulting compositions were tested for the possibility of biodegradation by placing the film samples in biocompost. In the production of polymer film materials, it is of great importance to ensure that a certain value of breaking stress at tension and elongation at break is achieved, as well as to maintain these indicators within acceptable limits during operation. Moreover, the appearance of the films is preserved when in contact with the environment. To simulate the long-term operation of the films, they were immersed in biocompost with active microorganisms for 3 months. After removing the samples from the biocompost, their destructive tensile strength and relative elongation at break were measured. The test results are shown in Table 5.

On analyzing the data in Table 5, it can be noted that the mechanical properties of the film samples changed after 3 months of storage in a biocompost, and these changes happened faster for samples subjected to ultrasonic treatment. The decrease in strength of the BHC films based on corn, pea and rice starch without ultrasound was 1.2, 1.3, and 1.6 times, respectively, and the decrease in strength of the BHC films based on corn, pea and rice starch with ultrasound was 1.5, 1.5, and 1.7 times, respectively. We can conclude that the biodegradation period would be shorter in the recycling of such films.

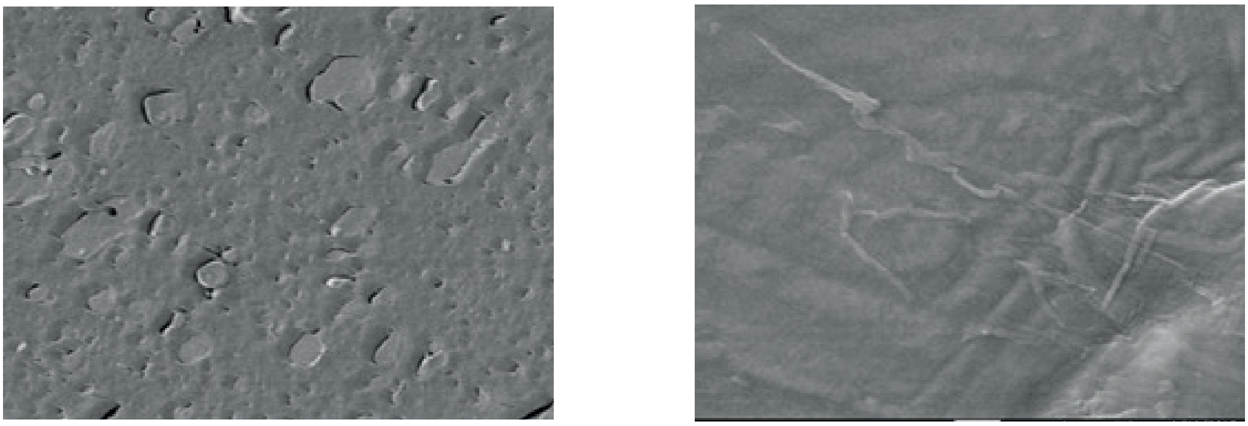
CONCLUSIONS

Films have been produced from biologically degradable hybrid composite material based on LDPE and TPS, with the addition of DMG as the plasticizer component.

Laboratory samples of the BHC films based on different ratios of LDPE and TPS of various types: corn, pea and rice from 40 : 60 to 60 : 40 wt %, with the addition of DMG plasticizer with and without the use of ultrasound were produced using flat-panel extrusion.

The optimal native starch/glycerol/DMG ratio was established to be 60 : 30 : 10 wt %.

MFR of the BHC films were measured. The BHC film with a maximum mass fraction of 60%



a b

Fig. 6. SEM micrographs of the BHC films based on a TPS : LDPE ratio of 60 : 40 under a magnification of (a) 500×, and (b) 10000×.

Table 4. Physical and mechanical properties of BHC films

No.	TPS : LDPE ratio	σ, MPa (Δ ± 0.2)	ε, % (Δ ± 5)	σ, MPa (Δ ± 0.2)	ε, % (Δ ± 5)
1	LDPE only	13	115	–	
–		With DMG without US exposure*		With DMG and US exposure*	
2	Corn-based TPS				
	60 : 40	9.8	62	10.9	78
	50 : 50	10.4	68	11.6	84
	40 : 60	11.4	72	12.8	93
3	Pea-based TPS				
	60 : 40	6.7	68	7.8	82
	50 : 50	7.8	73	9.3	91
	40 : 60	8.9	78	10.1	102
4	Rice-based TPS				
	60 : 40	10.4	74	11.2	96
	50 : 50	10.9	79	11.9	104
	40 : 60	11.6	93	12.8	115

* *Note:* US is ultrasound.

Table 5. Physical and mechanical properties of BHC films in biocompost

No.	TPS : LDPE ratio	σ, MPa (Δ ± 0.2)	ε, % (Δ ± 5)	σ, MPa (Δ ± 0.2)	ε, % (Δ ± 5)
		With DMG without US exposure*		With DMG and US exposure*	
1	Corn-based TPS				
	60 : 40	8.1	49	7.1	47
	50 : 50	8.4	56	7.6	53
	40 : 60	9.4	68	8.8	64
2	Pea-based TPS				
	60 : 40	5.3	52	5.1	50
	50 : 50	7.6	64	5.9	62
	40 : 60	8.3	70	6.6	68

Table 5. Continued

No.	TPS : LDPE ratio	σ, MPa (Δ ± 0.2)	ε, % (Δ ± 5)	σ, MPa (Δ ± 0.2)	ε, % (Δ ± 5)
		With DMG without US exposure*		With DMG and US exposure*	
3	Rice-based TPS				
	60 : 40	6.3	43	6.0	41
	50 : 50	7.3	55	6.7	53
	40 : 60	9.3	70	7.8	67

* *Note:* US is ultrasound.

TPS, showed an increase in melt viscosity by up to 60%. This may reduce the productivity of process equipment in the production of BHC films.

A technological scheme for manufacturing TPS for the production of BHC with DMG plasticizer under the influence of ultrasonic vibrations is proposed.

The structural properties of the obtained BHC films were studied. It is shown that the addition of the DMG plasticizer to the BHC films has a favorable effect on the properties of the films.

The mechanical properties of the BHC films were also evaluated. It is shown that the effect of ultrasonic vibrations on the melt in the manufacture of the films improves the mechanical properties, as well as accelerates their biodegradation.

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Authors' contribution

I.Yu. Vasilyev – conducting the study, collection and provision of the material, writing the article;

V.V. Ananyev – planning the experiment, scientific editing.

The rest of the authors equally contributed to the experiment, writing, and design of the article.

The authors declare no conflicts of interest.

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SYNTHESIS AND PROCESSING OF POLYMERS AND POLYMERIC COMPOSITES

СИНТЕЗ И ПЕРЕРАБОТКА ПОЛИМЕРОВ И КОМПОЗИТОВ НА ИХ ОСНОВЕ

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RESEARCH ARTICLE

Change of electrical characteristics of rubber in the process of "swelling–deswelling"

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Objectives. *The main indicator that determines electrical conductivity of rubbers is specific volumetric electrical resistance (ρ_v). The purpose of this work is to investigate changes in this indicator during swelling and deswelling of electrically conductive rubbers. When considering the swelling process of rubbers in liquid media at a molecular level, an analogy of this process with mechanical deformation of the material is drawn and common features and differences of these processes are revealed.*
Methods. *For rubber compositions based on paraffinate and alkyl sulfonate nitrile butadiene rubbers, the degree of their swelling and the change in linear dimensions in heptane and in gasoline grades 80, 92, and 95 were determined. The ρ_v value was determined by a potentiometric method: the initial value was measured after temperature control of rubbers for 1 h at 120°C, and the second measurement was carried out after these rubbers were swollen in the solvents for 48 h, followed by drying at 20°C to a constant weight and repeated temperature control under the same conditions. Using an IR Fourier spectrometer, spectra of the solvents used were obtained before and after identification of the investigated rubber samples in them.*
Results. *It was shown that the type of rubber and solvent used influence the degree of rubber swelling. Rubber compositions based on natural rubbers with a large amount of attached acrylonitrile, obtained in the presence of an alkyl sulfonate emulsifier, have the highest resistance to swelling. The effect of the used solvent on the change in the degree of swelling is determined by its affinity for rubber and the presence of polar additives that increase the octane number of gasoline. It was established that the linear change of the samples upon swelling in the indicated solvents varies according to the length and thickness of the samples. Results show that depending on the type of rubber used and the degree of its filling, the described rubber processing technology leads to a decrease in the ρ_v value by 2 to 20 times. The greatest effect of ρ_v reduction is observed in low-filled rubber compositions based on paraffinate nitrile rubbers. The spectra of the frustrated total internal reflection of the solvents after their interaction with the studied rubbers show that particulate extraction of dibutyl phthalate, which was used as a plasticizer in rubber compounding, takes place as a result of rubber swelling.*

Conclusions. *The proposed method of rubber processing reduces the* ρ_v *value by removing dibutyl phthalate from the studied rubbers and forming a more developed carbon–elastomer structure. Furthermore, it solves the problem of the negative effect of the plasticizer on the* ρ_v *value of rubber without excluding it from the rubber composition.*

Keywords: *rubber, specific volume electrical resistance, deformation, degree of swelling, linear change, reduction factor, dibutyl phthalate, extraction, developed carbon–elastomer structure*

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НАУЧНАЯ СТАТЬЯ

Изменение электрических характеристик резин в процессе «набухание-отбухание»

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Цели. *Основным показателем, определяющим электропроводность резин, является удельное объемное электросопротивление. Цель работы – исследовать изменения данного показателя при набухании и отбухании электропроводящих резин. При рассмотрении процесса набухания резин в жидких средах на молекулярном уровне проведена аналогия этого процесса с механической деформацией материала, выявлены общие черты и различия этих процессов.*

Методы. *Для резин на основе парафинатных и алкилсульфонатных бутадиен-нитрильных каучуков были определены степень их набухания и изменение линейных размеров в гептане, бензинах марок АИ-80, АИ-92, АИ-95. Удельное объемное электросопротивление определено потенциометрическим методом: исходное значение измерено после термостатирования резин в течение 1 ч при 120 °С, а повторное измерение проведено после набухания этих резин в растворителях в течение 48 ч с последующей сушкой при 20 °С до постоянной массы и повторного термостатирования при тех же условиях. С помощью ИК-спектрометра Фурье были получены спектры растворителей до и после нахождения в них исследованных резин.*

Результаты. *Показано, что на степень набухания резин оказывает влияние тип используемого каучука и растворителя. Наибольшей стойкостью к набуханию обладают резины на основе каучуков с большим количеством присоединенного НАК, полученные в присутствии алкилсульфонатного эмульгатора. Влияние используемого растворителя на изменение степени набухания определяется его сродством к каучуку и наличием полярных добавок, повышающих октановое число бензина. Установлено, что изменение линейных размеров образцов при набухании в указанных растворителях различно по длине и толщине образца. Результаты измерения удельного объемного электросопротивления показали, что в зависимости от типа используемого каучука и степени его наполнения описанная технология обработки резины приводит к снижению данного показателя от 2 до 20 раз. Наибольший эффект снижения удельного объемного электросопротивления наблюдается у малонаполненных резин на основе парафинатных бутадиен-нитрильных каучуков. Представленные в работе спектры нарушенного полного внутреннего отражения растворителей после их взаимодействия с исследованными резинами показали, что в результате набухания резин происходит частичная экстракция из них дибутилфталата, использованного в рецептуре в качестве пластификатора.*

Выводы. *Предложенный способ обработки резины позволяет снизить ее удельное объемное электросопротивление за счет удаления из нее дибутилфталата и формирования более развитой углерод-эластомерной структуры и решить проблему отрицательного влияния пластификатора на удельное объемное электросопротивление резин без исключения его из состава резиновой смеси.*

Ключевые слова: *резина, удельное объемное электросопротивление, деформация, степень набухания, изменение линейных размеров, кратность снижения, дибутилфталат, экстракция, развитая углерод-эластомерная структура*

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INTRODUCTION

Rubbers, like the vast majority of currently known polymers, are dielectrics. However, it is possible to make electrically conductive rubber compositions, which are widely used in various industries and in everyday life, and their range of applications is constantly expanding. To create such materials, special grades of carbon black are added into elastomers, which have high specific adsorption surface, dispersion, structure, and roughness [1–3]. These indicators play a decisive role in the formation of a developed spatial carbon–elastomer structure, which ensures charge transfer during direct contact of filler particles or through thin rubber layers by a tunneling mechanism [4–7].

The level of electrical characteristics of electrically conductive rubbers determines their specific volumetric electrical resistance, ρ_v. A decrease in the ρ_v value results from increasing the content of electrically conductive filler or using filler with a higher level of specific adsorption surface, dispersity, and structure [8, 9]. However, after reaching the optimum filling, a further increase in the content of carbon black causes a sharp increase in the viscosity of the rubber compound and, as a consequence, a deterioration in the processability of the composition, a decrease in the elastic-strength properties of rubbers, and an increase in their cost [10]. The gain in electrical characteristics of the material when filled above the optimum is relatively small.

The current level of development of science, technology, and medicine requires finding new approaches to improving the electrical characteristics of rubbers, for example, using the influence of external factors on the carbon–elastomer structure already formed in the process of rubber production.

It is known from the literature [11] that the specific volumetric electrical resistance of rubber is influenced not only by various technological factors, such as the order of addition of ingredients and vulcanization, or prescription factors (introduction of plasticizers and fillers into the rubber mixture) but also by the conditions of its operation. These include the effect of elevated temperature, the presence of deformation, the deformation rate and magnitude, and the degree of swelling of rubber in solvents.

The effect of elevated temperature on rubber leads to a noticeable decrease in the ρ_v value of the vulcanizate [12], which, according to many researchers, is associated with the desorption of the elastomer from the surface of carbon black particles and the formation of larger extended structures—clusters, which facilitates charge transfer. In this case, the intensity of the decrease in the ρ_v value is determined by the temperature acting on rubber.

When a sample of an electrically conductive rubber is deformed by stretching, compression, or shear, a number of complex processes occur in it, leading to a nonmonotonic change in the initial specific volumetric electrical resistance: an increase in the ρ_v value upon deformation of up to 50% due to destruction of the carbon–elastomer structure, a subsequent decrease in the ρ_v value due to orientation of the elements of the carbon–elastomer structure along the direction of deformation at its significant value, and a sharp increase in the ρ_v value upon removal of the deforming force and reduction of sample due to disorientation of the carbon–elastomer structure [11]. Thus, any deformation of tension, compression, and shear of a sample of an electrically conductive rubber will ultimately lead to a significant increase in the ρ_v value, making it more electrically conductive.

According to the general definition of the concept of “deformation,” swelling of rubbers in liquid media can also be considered as their deformation. When considering the process of swelling at a molecular level, direct contact of rubber and liquid leads to diffusion of the latter into the sample volume due to the presence of free space between elastomer macromolecules. Due to this, liquid molecules easily and quickly penetrate between macromolecules, pushing and deforming molecular chains. The amount of solvent absorbed by rubbers is different and is determined by the affinity of the elastomer and the solvent, the time of their interaction, as well as the density of the spatial vulcanization network. However, when rubber swells, in contrast to tensile, compression, and shear deformation, the sample volume increases and all of its linear dimensions simultaneously increase. This, naturally, is accompanied by an increase in the distance between filler particles, which complicates the charge transfer and leads to a noticeable increase in the ρ_v value.

However, in the process of solvent evaporation—"deswelling" of rubber—the initial electrical conductivity is restored. Thus, the nature of the effect on the electrical conductivity of rubbers is one of the main differences in the deformation process during swelling and deswelling from, for example, stretching the sample under mechanical action and returning it to its original state, and it requires more careful attention and study.

In this regard, the purpose of this work is to study the change in the ρ_v value of electrically conductive rubbers during the swelling and deswelling process.

MATERIALS AND METHODS

Elastomeric compositions based on nitrile butadiene rubbers (NBRs) were manufactured and investigated: NBR18 and NBR26 (alkyl sulfonate), and NBR1845 and NBR2645 (paraffinic) (*Krasnoyarsk Synthetic Rubber Plant*, Russia). These brands of rubbers differ not only in the content of bound acrylic acid nitrile but also in the type of emulsifier used during the polymerization process, which has a decisive effect on both the vulcanization properties and the physicomechanical and operational properties of rubbers [13–16]. In order to impart electrically conductive properties into rubbers, mixed compositions [17] were used, consisting of conductive carbon black grade UM76 (*KHIMPLAST*, Russia), the content of which varied from 25 to 50 mass fractions in combination with 50 mass fractions of low-activity carbon black P803 (*Tuymazytehuglerod*, Russia) and 10 mass fractions of graphite GK-1 (*Zavalivskiy Graphite*, Ukraine). Mixture composition of fillers provides the rubber compound with satisfactory processing properties even with a total filler content of 110 mass fractions per 100 mass fractions of natural rubber, and rubbers have high and stable electrical characteristics. For vulcanization, a standard vulcanizing group was used, consisting of zinc oxide, stearic acid, sulfenamide C, and sulfur (*VitaKhim Group*, Russia). In addition, to facilitate processing operations, dibutyl phthalate (DBP) (*RosKhim Group*, Russia) was used.

Elastomeric compositions were made on LB 320 160/160 rollers (*Metallist*, Russia), and the electrically conductive filler was introduced into the rubber mixture already containing carbon black P803 [9]. After curing, the rubber compounds were vulcanized at the optimum vulcanization time determined on an RPA-2000 rheometer (*Alpha Technologies*, USA). Degree of swelling of rubbers after 48 h of exposure to organic solvents (heptane (*ORGKHIM*, Russia) and gasoline grades AI-80, AI-92, and AI-95 (*Gazpromneft-MNPZ*, Russia)) was determined in accordance with GOST 9.030-74[1].

The main characteristic of electrically conductive rubbers— the indicator of the specific volumetric electrical resistance—was determined by a potentiometric method (ISO 1853:1998[2]). Before measurements, the rubber samples were thermostated for 1 h at 120°C. After measuring the initial ρ_v value, they were placed in the organic solvents for 48 h. After that, the solvent was completely removed by drying the swollen samples to a constant weight at a temperature of 20°C and thermostated them again in an air thermostat for 1 h at 120°C, and then the ρ_v value was measured.

To determine the nature of substances extracted from the rubber samples as a result of exposure to the solvents, spectra of the solvents used were obtained by an IR Fourier spectrometer (*Bruker*, Germany) before and after identification of the investigated rubbers in them.

RESULTS AND DISCUSSION

The values of the degree of swelling of the manufactured rubbers are given in Table 1.

The data in Table 1 show that the degree of swelling is determined by the type of rubber and solvent used. More resistant to swelling are rubber compositions based on rubbers with a high content of acrylonitrile (ACN), regardless of the type of emulsifier used. Rubber compositions based on paraffinic rubbers are inferior in resistance to swelling compared to those that are based on alkyl sulfonate rubbers. This is especially pronounced for rubbers based on rubbers containing 18% ACN.

The type of solvent used has a significant influence on the degree of swelling of rubbers. The smallest

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[1] GOST 9.030-74. Unified system of corrosion and ageing protection. Vulcanized rubbers. Method of testing resistance to attack by corrosive media in limp state. Moscow: Standartinform; 2008.

[2] ISO 1853:1998. Conducting and dissipative rubbers, vulcanized or thermoplastic – Measurement of resistivity.

Table 1. Degree of swelling of rubbers in the organic solvents
(for example, rubber containing 35.0 mass fractions of carbon black UM76)

Elastomeric rubber base	Degree of swelling after 48 h, %			
	Heptane	AI-80	AI-92	AI-95
NBR18	1.6	30.7	18.7	36.1
NBR26	−0.8	15.1	11.4	17.7
NBR1845	5.0	42.6	39.2	60.0
NBR2645	−0.8	14.9	14.0	20.3

degree of swelling was observed in heptane due to a significant difference in the solubility parameters of the rubber samples and the solvent. For rubbers based on NBR26 and NBR2645, there was even a decrease in the mass of samples after swelling compared to the initial values. This is probably due to leaching of some of the ingredients from the sample during its swelling. The studied rubbers swelled more intensively in gasoline grades AI-80, AI-92, and AI-95 than in heptane, which is due to the presence of polar additives in their composition that increase the octane number. By increasing the degree of swelling, the gasolines used in this work can be arranged in the following sequence: AI-95 > AI-80 > AI-92. An increase in the content of ACN in rubber leads to a noticeable decrease in the influence of the gasoline brand on the degree of swelling of rubbers.

Table 2 shows the change in the linear dimensions of the rubber samples based on NBR18, containing 30.0 mass fractions of conductive carbon black UM76, 50.0 mass fractions of low-activity carbon black P803, and 10.0 mass fractions of graphite GK-1, before and after their swelling in the selected solvents.

The data presented in Table 2 clearly demonstrate a significant change in the linear dimensions of the samples after prolonged (48 h) exposure to the solvents, which is evident of the occurrence of deformation processes that affect the carbon–elastomer structure formed in the rubber compounds. It can be noted that the degree of deformation of the samples along the length and thickness was different under the action of any of the considered solvents, i.e., the sample was unevenly deformed upon swelling. The amount of deformation along the thickness of the samples was noticeably greater than the deformation along the length for all the samples and media.

Thus, the solvents used in this work interacted to varying degrees with the studied rubbers from the point of view of the intensity of their absorption by the test material and, consequently, the change in the size of the swollen samples. This allows a more complete assessment of the effect of deformation process during swelling on specific volumetric electrical resistance.

Figures 1–4 show the dependence of the ρ_v value on the content of technical carbon in rubber, as well as the reduction factor of the ρ_v value, which was determined as the ratio between the values of this indicator before and after the above-described exposure.

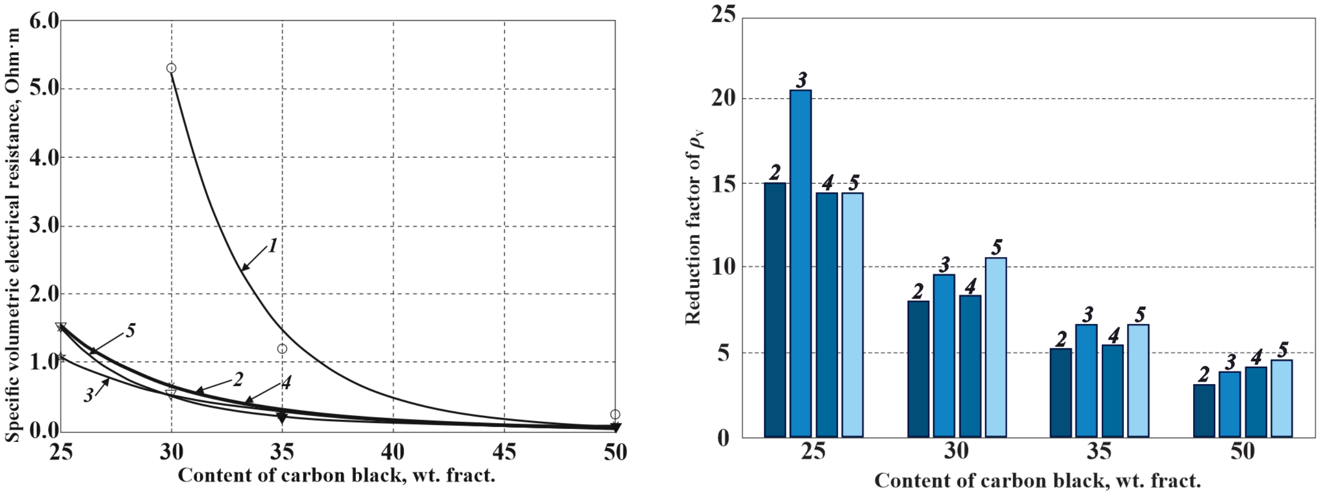
As seen from Figs. 1 to 4, swelling of the rubber samples in any of the considered solvents followed by the complete removal of the solvent according to the scheme described above made it possible to obtain a material with a lower specific volumetric electrical resistivity as compared to the initial value. The reduction factor of the ρ_v value varied over a wide range of values. From the presented data, it can be seen that the greatest effect of reducing the ρ_v value was observed for rubbers containing the minimum of the considered dosages of electrical conductive carbon black UM76 (25 mass fractions). The reduction factor of the specific volumetric electrical resistance for these rubbers was 15.0–20.5. For rubbers with carbon black UM76 content of 30 mass fractions and more, the effect of reducing the ρ_v value was less pronounced; the reduction factor was in the range of 1.1–5.0.

It should be noted that the type of elastomeric binder used to obtain electrically conductive rubbers [14] affects the ρ_v value of the material obtained by the method described above. The increase in the reduction factor of the ρ_v value was most pronounced for rubbers based on paraffinic NBR.

When comparing the electrical properties of equally filled rubbers based on the studied rubbers, it can be noted that the reduction factor of the ρ_v value for most rubbers increased with an increase in the degree of swelling and, accordingly, an increase in their deformation during the swelling process.

Table 2. Change in the linear dimensions of the rubber samples based on NBR18 before and after swelling in various solvents

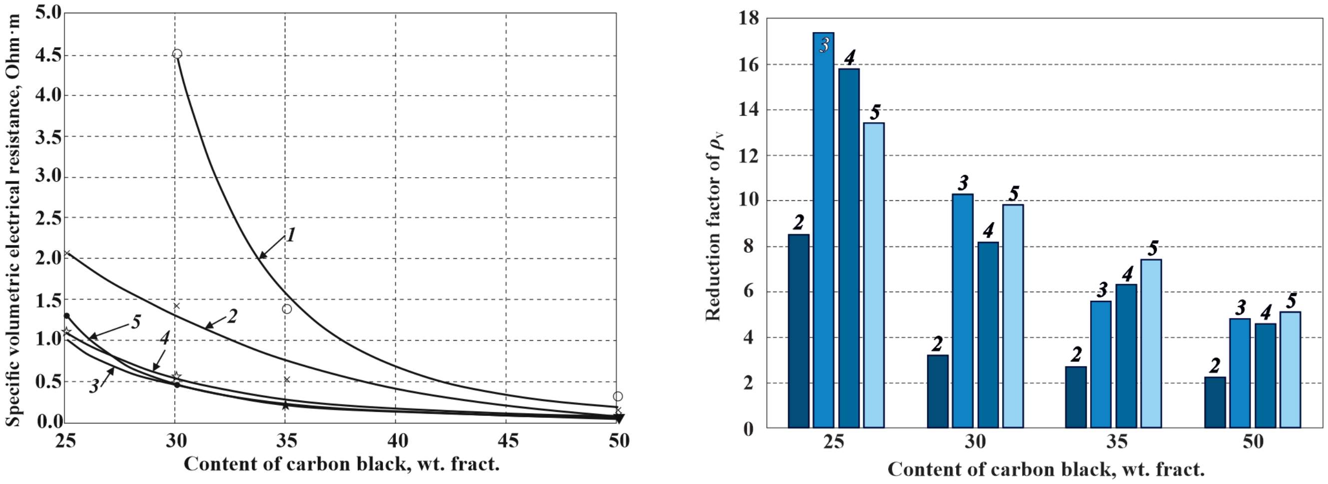
Linear dimension and mass of sample	Sample linear dimension value		Change, %
	Before swelling	After swelling	
Heptane			
Width, mm	1.87	1.94	3.74
Length, mm	60.0	61.0	1.67
Mass, g	1.926	1.963	1.92
Gasoline grade AI-80			
Width, mm	1.87	2.29	22.5
Length, mm	60.0	68.0	13.3
Mass, g	1.930	2.580	33.7
Gasoline grade AI-92			
Width, mm	1.87	2.21	18,2
Length, mm	60.0	67.0	11.7
Mass, g	1.912	2.408	25.9
Gasoline grade AI-95			
Width, mm	2.08	2.56	23.1
Length, mm	60.0	69.0	15.0
Mass, g	2.139	2.934	37.2



a

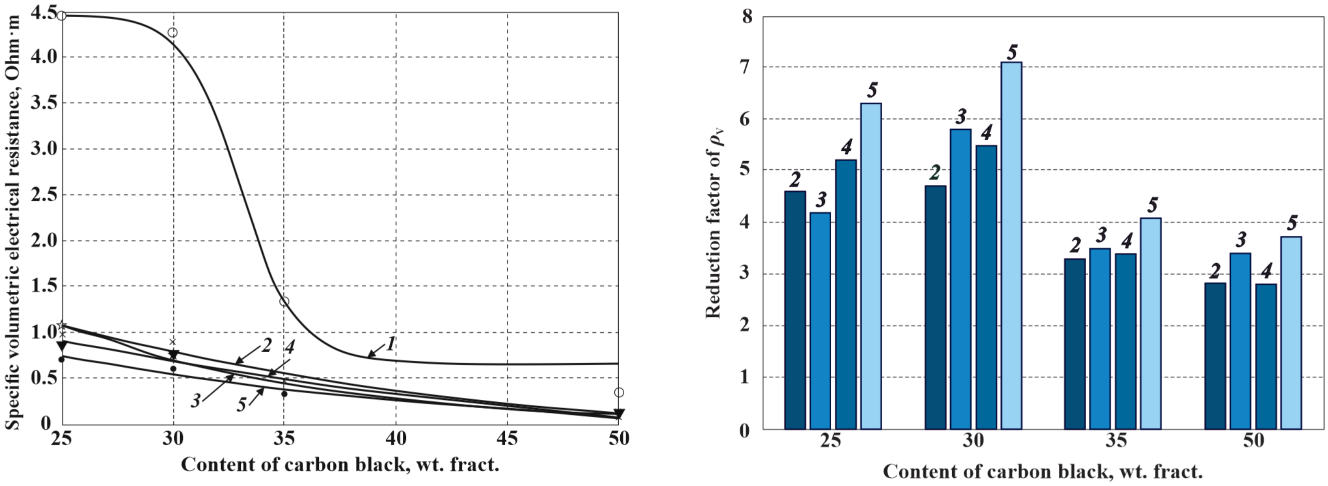
b

Fig. 1. Dependence of the ρ_v value on the content of carbon black UM76 (a) and reduction factor of the ρ_v value (b) for electrically conductive rubbers based on NBR18:
(*1*) before interaction, (*2*) heptane, (*3*) AI-80 gasoline, (*4*) AI-92 gasoline, and (*5*) AI-95 gasoline.



a b

Fig. 2. Dependence of the ρ_v value on the content of carbon black UM76 (a) and reduction factor of the ρ_v value (b) for electrically conductive rubbers based on NBR26:
(*1*) before interaction, (*2*) heptane, (*3*) AI-80 gasoline, (*4*) AI-92 gasoline, and (*5*) AI-95 gasoline.



a b

Fig. 3. Dependence of the ρ_v value on the content of carbon black UM76 (a) and reduction factor of the ρ_v value (b) for electrically conductive rubbers based on NBR1845:
(*1*) before interaction, (*2*) heptane, (*3*) AI-80 gasoline, (*4*) AI-92 gasoline, and (*5*) AI-95 gasoline.

The results shown in Figs. 1–4 show that an increase in the content of carbon black UM76 in the mixed filler in the dosage range of 25–50 mass fractions, in the case of rubber processing according to the proposed technology, changed the value of the ρ_v value within the same order. Thus, the considered method of rubber processing allows reducing the content of the expensive filler in the composition, which will lead to a decrease in the cost of the material and an increase in the complex of technological and physical and mechanical properties of rubbers.

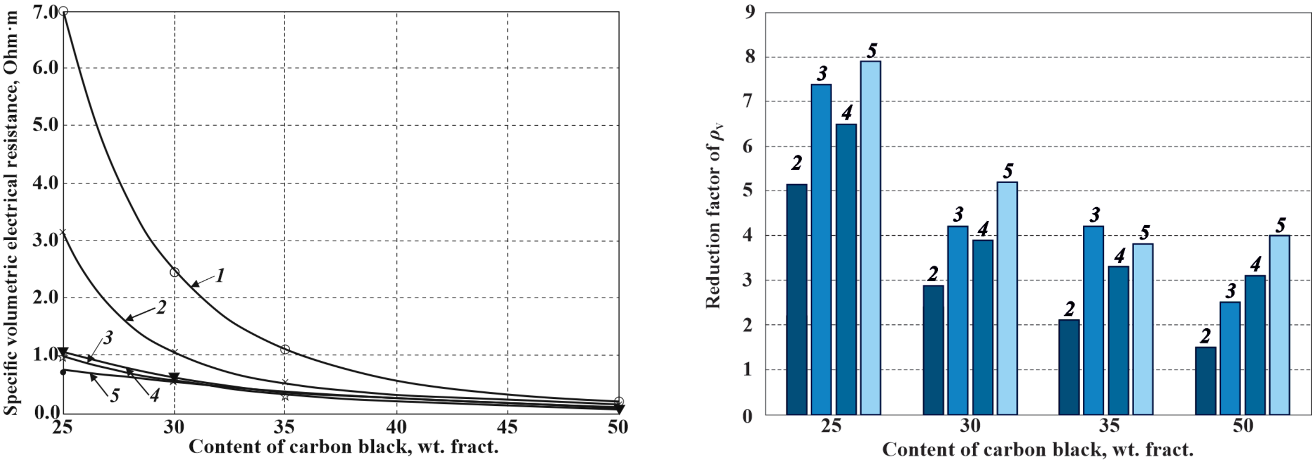
When rubber swells, solvent molecules increase the distance between macromolecules, which can facilitate the transition of the rubber ingredients into the solvent. Therefore, it is natural to assume that the effect of reducing the ρ_v value of rubbers upon contact with the organic solvents is due to the processes of extracting ingredients from rubber that affect the formation of the carbon–elastomer structure and the formation of a more developed carbon–elastomer structure during the removal of the solvent.

Figures 5 and 6 both show the spectra of the used solvents before and after identification of the studied rubbers in them, which were obtained using an IR Fourier spectrometer.

When comparing the IR spectra of the solvent (AI-95 gasoline) before and after its interaction with the rubber compositions based on NBR18 and NBR1845 (Figs. 5 and 6), one can note the appearance of bands, indicating that low-molecular substances are extracted as a result of the swelling process of the samples with the solvent. For all the considered solvents, the presence of characteristic absorption bands at 1284 and 1121 cm^{-1} can be noted. According to [18], such bands are characteristic of compounds containing an ether group. In the rubber samples investigated in the framework of this work, of all the ingredients in their composition, the ether group is contained only in the plasticizer dibutyl phthalate.

The negative effect of a plasticizer on the electrical conductivity of rubbers while maintaining a constant content of carbon black is understandable and has been known for a long time. However, its exclusion from the rubber composition in order to reduce the ρ_v value is not always possible. In the case of rubber compounds based on NBR, due to their high polarity and, as a result, high viscosity, the absence of a plasticizer complicates the production and processing on mixing and forming equipment.

In this regard, in the case of electrically conductive rubbers based on NBR, a choice arises between making a more technologically advanced rubber compound and obtaining a finished product with a higher level of electrical characteristics. The processing method considered above makes it possible to eliminate the negative effect of the plasticizer on the ρ_v value of the material. After selecting the



a

b

Fig. 4. Dependence of the ρ_v value on the content of carbon black UM76 (a) and reduction factor of the ρ_v value (b) for electrically conductive rubbers based on NBR2645:
(*1*) before interaction, (*2*) heptane, (*3*) AI-80 gasoline, (*4*) AI-92 gasoline, and (*5*) AI-95 gasoline.

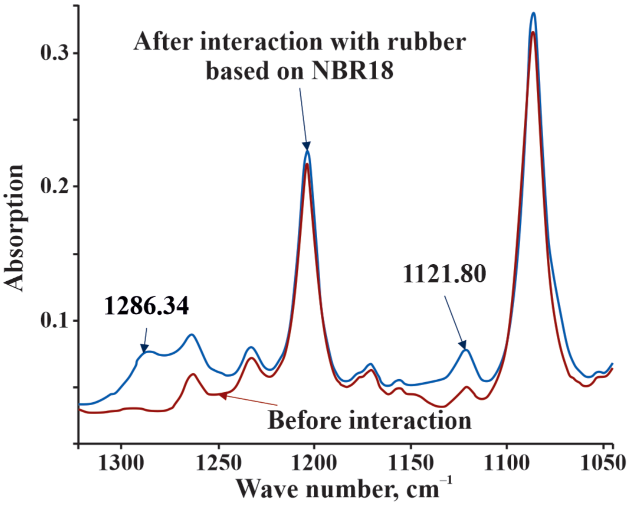


Fig. 5. Attenuated total reflection spectrum of AI-95 gasoline before and after interaction with the rubber compositions based on NBR18.

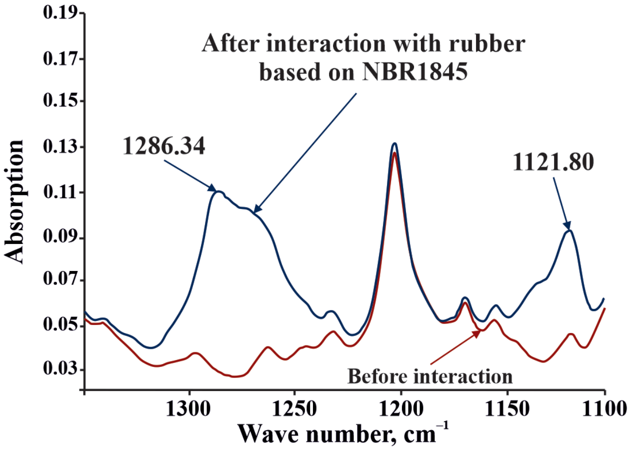


Fig. 6. Attenuated total reflection spectrum of AI-95 gasoline before and after interaction with the rubber compositions based on NBR1845.

appropriate solvent, the described method can also be applied to rubbers for general applications [19].

CONCLUSIONS

Thus, the paper considers a method of directed physical action on the carbon–elastomer structure formed in rubber during its manufacture, which provides a 2- to 20-fold decrease in the ρ_v value of electrically conductive rubbers. A decrease in the ρ_v value upon contact of an elastomeric material with a certain solvent occurs due to the formation of a more developed carbon–elastomer structure during the swelling–deswelling process of rubber and partial removal of a plasticizer from it. The proposed method of directed physical action on the carbon–elastomer structure allows one to solve the problem of the negative effect of a plasticizer on the ρ_v without excluding it from the rubber composition.

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Authors’ contribution

All authors equally contributed to the research work.

The authors declare no conflicts of interest.

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CHEMISTRY AND TECHNOLOGY OF INORGANIC MATERIALS

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RESEARCH ARTICLE

Alcoxotechnology for obtaining heat-resistant materials based on rhenium and ruthenium

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Objectives. *To develop physical and chemical bases and methods to obtain rhenium–ruthenium isoproxide* $Re_{4-y}Ru_yO_6(OPr^i)_{10}$*—a precursor for obtaining a high-temperature alloy—from ruthenium acetylacetonate and rhenium isoproxide acquired by electrochemical methods.*
Methods. *IR spectroscopy (EQUINOX 55 Bruker, Germany), X-ray phase and elemental analyses, energy-dispersive microanalysis (EDMA, SEM JSM5910-LV, analytical system AZTEC), powder X-ray diffraction (diffractometer D8 Advance Bruker, Germany), experimental station XSA beamline at the Kurchatov Synchrotron Radiation Source.*
Results. *The isoproxide complex of rhenium–ruthenium* $Re_{4-y}Ru_yO_6(OPr^i)_{10}$ *was obtained, and its composition and structure were established. Previously conducted quantum chemical calculations on the possibility of replacing rhenium atoms with ruthenium atoms in the isopropylate complex were experimentally proven, and the influence of the electroconductive additive on the composition of the obtained alloy was revealed.*
Conclusions. *Physical and chemical bases and methods for obtaining rhenium–ruthenium isoproxide* $Re_{4-y}Ru_yO_6(OPr^i)_{10}$ *were developed. The possibility of using rhenium–ruthenium* $Re_{4-y}Ru_yO_6(OPr^i)_{10}$ *as a precursor in the production of ultra- and nanodisperse rhenium–ruthenium alloy powders at a record low temperature of 650°C were shown.*

Keywords: *alkoxotechnology, electrochemical synthesis, rhenium isopropoxide, ruthenium acetylacetonate, rhenium–ruthenium isopropoxide, rhenium–ruthenium alloy, low-temperature reduction*

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НАУЧНАЯ СТАТЬЯ

Алкоксотехнология получения жаропрочных материалов на основе рения и рутения

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Цели. *Разработка физико-химических основ и способов получения изопроксида рения-рутения $Re_{4-y}Ru_yO_6(OPr^i)_{10}$ из ацетилацетоната рутения и изопроксида рения, полученного электрохимическим методом – прекурсора получения высокотемпературного сплава.*
Методы. *ИК-спектроскопия (EQUINOX 55 Bruker, Германия), рентгенофазовый и элементный анализ, энергодисперсионный микроанализ (ЭДМА, СЭМ JSM5910–LV, аналитическая система AZTEC), порошковая рентгеновская дифракция (дифрактометр D8 Advance Bruker, Германия), экспериментальная станция «РСА» Курчатовского источника синхротронного излучения.*
Результаты. *Получен изопроксидный комплекс рения-рутения $Re_{4-y}Ru_yO_6(OPr^i)_{10}$, подтверждены его состав и строение. Экспериментально подтверждены ранее проведенные квантово-химические расчеты, свидетельствующие о возможности замещения атомов рения атомами рутения в изопропилатном комплексе. Выявлено влияние электропроводящей добавки на состав получаемого сплава.*
Выводы. *Разработаны физико-химические основы и предложены способы получения изопроксида рения-рутения $Re_{4-y}Ru_yO_6(OPr^i)_{10}$, который может найти применение в качестве предшественника при получении ультра- и нанодисперсных порошков сплавов рений-рутений при рекордно низкой температуре 650°С.*

Ключевые слова: *алкоксотехнология, электрохимический синтез, изопроксид рения, ацетилацетонат рутения, изопроксид рения-рутения, сплав рения-рутения, низкотемпературное восстановление*

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INTRODUCTION

Functional materials based on rhenium have a variety of applications, such as in aerospace and power engineering as well as in the production of catalysts for processing renewable and nontraditional raw materials [1, 2]. Alloys containing rhenium are resistant to high temperatures and aggressive environments and have high strength performance and wear resistance.

The classic methods for producing rhenium-containing alloys, such as induction and electric arc melting and powder metallurgy, have significant disadvantages: high process temperatures (over 2500°C), the inability to uniformly introduce alloying components or control the microstructure of samples, and enormous energy costs [1, 2]. Thus, in the last two decades, vacuum smelting in induction and arc furnaces with consumable electrodes, directional crystallization, and heat treatments have been widely used [3–5].

Alcoxotechnology is a promising method for obtaining alloy powder precursors with a given set of properties and allows for obtaining ultrafine and nanoscale materials of high phase and chemical purity at low temperatures (below 950°C).

Oxoalcoxy derivatives of rhenium can act as such precursors. Rhenium isoproxide is of particular interest as rhenium atoms form an almost regular rhombus in its structure [6, 7].

Using quantum chemical calculations in the Priroda 06 program, the possibility of replacing rhenium atoms with ruthenium atoms in an isoproxide complex while preserving the tetranuclear cluster has been shown [8]. Ruthenium is chosen because in the periodic table, it is in close proximity to rhenium, and both elements are transients and have close atomic radii values. Moreover, it has been known that the addition of ruthenium increases the temperature limit for heat-resistant nickel alloys [9, 10].

The aim of this study is to develop physical and chemical bases and methods for obtaining rhenium–ruthenium isoproxide $Re_{4-y}Ru_yO_6(OPr^i)_{10}$ to establish its composition, structure, and use as a precursor in the preparation of ultra- and nanodisperse powders of rhenium–ruthenium alloys.

EXPERIMENTAL

The synthesis of the rhenium–ruthenium isoproxide complex $Re_{4-y}Ru_yO_6(OPr^i)_{10}$ was performed in three stages: synthesis of rhenium isoproxide, synthesis of ruthenium acetylacetonate, and direct synthesis of the rhenium–ruthenium isoproxide complex.

Rhenium isoproxide was synthesized by an electrochemical method according to the methods in [11, 12]. For the synthesis, a cell without a separated anode and cathode space with a thermostatic jacket was used. Platinum was used as the cathode, and rhenium was used as the anode. The voltage was 130–210 V, the current was 30–80 mA, and the alcohol volume was 200 mL. The synthesis time was 92 h in the presence of a background electrolyte of lithium chloride (C_{LiCl} = 0.1 mol/L) and 28 h in the presence of tetrabutylammonium bromide ($C_{C16H36BrN}$ = 2.5% by weight of alcohol). At the stage of obtaining the rhenium isoproxide, the following reagents were used: metal plates of rhenium and platinum (purity 99.9%), metal sodium (purity 99.9%), isopropyl alcohol (TU 2632-011-29483781-2009, extra-pure grade), lithium aluminum hydride (*Merck KgaA*, pure), lithium chloride (*Merck KgaA*, pure), and tetrabutylammonium bromide (TU 6-09-1859-77, pure). Isoproxides are sensitive to moisture, so the isopropyl alcohol was dried by sequentially introducing sodium into the system at the first stage and lithium aluminum hydride at the second stage when heated. The final water content was less than 0.01%. The lithium chloride was dehydrated according to the method described in [13]. Similarly, the tetrabutylammonium bromide was dehydrated.

Ruthenium (III) acetylacetonate was obtained by the method described in [14]. The following reagents were used in the synthesis: acetylacetone (*Merck KgaA*, purity ≥ 99%, chemically pure), acetone (TU 6-09-3513-86, extra-pure grade), ruthenium hydrochloid (purity 41.67%), sodium bicarbonate (GOST 4201-79, chemically pure), ethanol (*Merck KgaA*, purity ≥ 99%, pure). The product yield was 60%, and the obtained ruthenium acetylacetonate crystals were studied by X-ray phase analysis.

The following method for the rhenium–ruthenium isoproxide synthesis was proposed. The synthesis was carried out by mixing rhenium isoproxide and ruthenium acetylacetonate in a conical flask in a “dry” box. The ratio of rhenium to ruthenium 1 : 1 was chosen from quantum chemical calculations [8]. When the ruthenium acetylacetonate was added, the rhenium isoproxide solution changed in color from brownish-green to blood red. Next, the solution was heated to boiling in a reflux flask for 3 h with constant stirring. The resulting complex was identified by IR spectroscopy and elemental analysis.

The resulting alkoxy rhenium complex was used as a precursor in the production of the rhenium–ruthenium alloy powders. Two methods were used to obtain it. In the first method, pre-evaporated rhenium–ruthenium isoproxide in a porcelain boat was placed in a recovery unit (flow reactor), after which all connections of the unit were sealed. Before starting the synthesis, the system was purged with an inert gas (argon) for 30 min. After the purging, hydrogen was supplied, and recovery was performed for 60 min under the following conditions: hydrogen flow, 4 L/h; pressure, 1 atm. The temperature conditions in the first experiments were set in the range of 400–450°C but, in subsequent experiments, were adjusted to 600–650°C. After the recovery process was completed, an inert atmosphere was created in the system for 30 min. Then, the furnace was turned off, and after it was cooled, the sample boats were removed and weighed.

The flow reactor for the reduction of the rhenium–ruthenium isoproxide could not provide a hydrogen pressure of more than 1 atm, so the second method for producing alloy powders in a hydrogen atmosphere using an autoclave installation was used. Evaporated and weighed samples in porcelain boats were immersed in the autoclave. Before the recovery process was started, the system was purged with hydrogen, creating an excess of it in the installation. After 10 min of purging, the hydrogen supply was turned off, and the final pressure was set to 5 atm. Next, the furnace heating was connected, and the rhenium–ruthenium isoproxide reduction was performed at 650°C for 90 min, after which the cooled samples were removed and reweighed. The autoclave method was used to obtain samples from precursors that did not contain lithium chloride. Samples obtained by the two methods described were examined using X-ray phase analysis.

The infrared spectra of liquids in the region of 3600–50 cm^{-1} were recorded on the EQUINOX 55 Bruker (Germany) device [15, 16]. The resolution of the device was 2 cm^{-1}, and the accuracy of the wavenumber determination was 0.1 cm^{-1}. Energy-dispersive microanalysis was used to analyze the distribution of elements in the samples (SEM JSM5910LV, AZTEC analytical system).

The powder X-ray diffraction examinations were performed with two installations:

1. The D8 Advance Bruker diffractometer, Germany (Cu Kα radiation, sample rotation, continuous [1 deg/min], step-by-step [0.02° step, 10 s exposure] modes in the angle range $2\Theta = 5°–100°$) [17]. The ICDD PDF-2 and Crystallography Open Database[1] were used for phase identification.

2. The XSA experimental station [18] of the Kurchatov Synchrotron Radiation Source. To measure the diffraction patterns, we used monochromatic radiation with wavelength $\lambda = 0.802575$ Å (photon energy $E = 15448.3$ eV) focused on a 400 × 400-µm sample. The survey was carried out in the Debye–Scherrer geometry (for transmission) using a two-dimensional Rayonix SX165 detector located perpendicular to the synchronous radiation beam at a distance of 80 mm. The sample was placed in a cryoloop with a diameter of 300 µm and rotated around the horizontal axis during the measurement to average the diffractograms over the sample orientations. The exposure time was 3–5 min. The two-dimensional patterns obtained at the detector were integrated, i.e., reduced to the standard one-dimensional form of the intensity dependence on the scattering angle I (2Θ) in the Dionis program [19]. The angular scale of the detector was calibrated, and the hardware broadening of the diffraction reflexes was determined by measuring polycrystalline standard LaB_6 (NIST SRM 660a). The qualitative phase composition was determined in the Match! program[2] using the PDF-4+ powder database based on the corundum number method [20].

RESULTS AND DISCUSSION

The rhenium isoproxides obtained by the anodic dissolution of rhenium in isopropyl alcohol were studied by a set of physical and chemical methods.

All studied solutions had identical absorption bands in the IR spectra regardless of the selected conductive additive: 3350–3310 cm^{-1}, ν(O–H); 2970–2928 cm^{-1}, $\nu_{str}(C–H)_{(as)}$; 2885–2830 cm^{-1}, $\nu_{str}(C–H)_{(s)}$; 1466–1456 cm^{-1}, $\nu_{as}(C–C)$; 1376–1306 cm^{-1}, ν(C–C); 1161–1128 cm^{-1}, ν(C–O); 950–906 cm^{-1}, ν(Re=O); 817–815 cm^{-1}, ν(Re–O–(R)–Re) (bridge); 678–602 cm^{-1}, ν(Re–O–(R)); 486–463 cm^{-1}, ν(Re–O–(R)); 427–414 cm^{-1}, ν_a(Re–O); 356–318 cm^{-1}, ν_s(Re–O); 287–201 cm^{-1}, ν(Re–Re); 213–166 cm^{-1}, δ(O–Re–O) + δ(O–Re); 137–104 cm^{-1}, δ(O–Re–O); and 92 cm^{-1}, t(Re–Re) [21–25].

The elemental composition of the pre-evaporated samples was examined. Figure 1 shows electron microscopy images of rhenium isoproxide, displaying the areas for which the elemental analysis was performed (Table 1).

The small amount of copper impurities was due to the fact that during the electrochemical synthesis, copper wire was used as a current supply

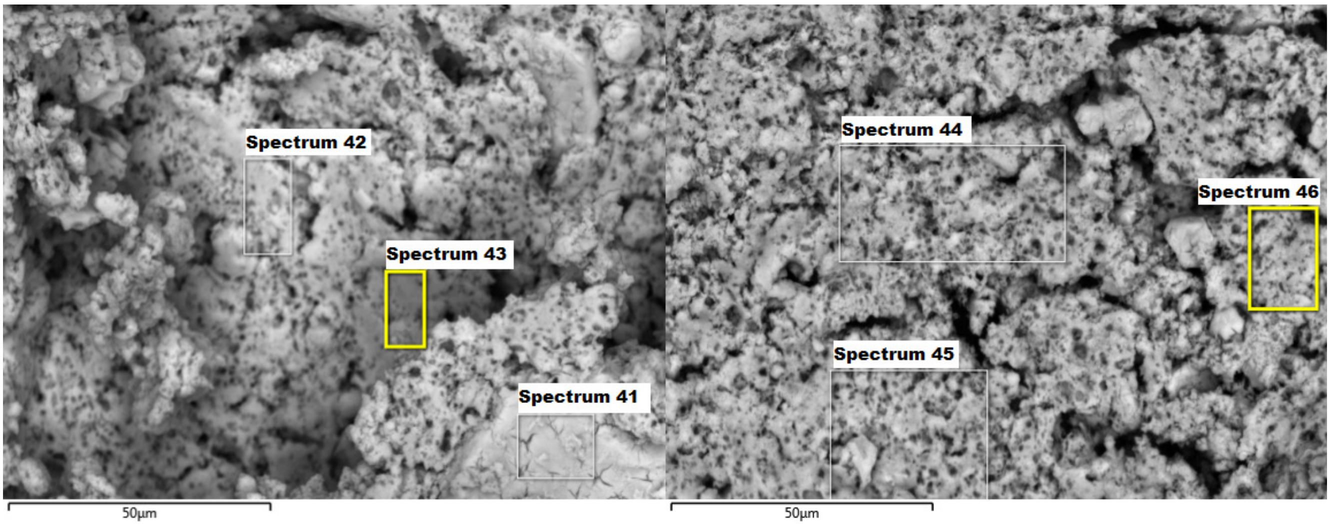

Fig. 1. Electron microscopy of rhenium isoproxide.

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[1] http://www.crystallography.net/cod/. Accessed May 15, 2020.

[2] Match! – Phase Analysis using Powder Diffraction, Crystal Impact – Dr. H. Putz & Dr. K. Brandenburg GbR, Kreuzherrenstr. 102, 53227 Bonn, Germany, https://www.crystalimpact.de/match. Accessed September 03, 2020.

to the rhenium anode. The presence of aluminum was because Li[AlH_4] was used for dewatering the isopropyl alcohol, and the unreacted aluminum remained in the solution.

The synthesized ruthenium acetylacetonate was studied using X-ray phase analysis on two installations (D8 Advance Bruker, Germany, and XSA diffractometer, Belok station, Russia), which showed that the product was single-phase with the cell parameters indicated in Table 2.

The obtained $Ru(AcAc)_3$ was characterized by elemental analysis (for the C, H, N, and S content). In the $Ru(AcAc)_3$ (m = 2.995 mg), the carbon content was 51.41%, and the hydrogen content was 6.44%, corresponding to the theoretical calculations. Nitrogen and sulfur were not detected.

The IR spectra in the range of 4000–50 cm^{-1} were studied for the obtained rhenium–ruthenium isoproxides. In the investigated range, the following absorption bands are observed: 3350–3310 cm^{-1}, ν(O–H); 2970–2928 cm^{-1}, $\nu_{str}(C–H)_{(as)}$; 2885–2830 cm^{-1}, $\nu_{str}(C–H)_{(s)}$; 1466–1456 cm^{-1}, ν_{as}(C–C); 1376–1306 cm^{-1}, ν(C–C); 1120–1114 cm^{-1}, ν(C–O); 949–910 cm^{-1}, ν(Re=O); 817–816 cm^{-1}, ν(Re–O–(R)–Re) (bridge); 678–612 cm^{-1}, ν(Re–O–(R)); 583–520 $см^{-1}$, ν(Ru–C); 493–453 cm^{-1}, ν(Re–O–(R)); 440–410 cm^{-1}, ν(C–Ru–C); 385–344 cm^{-1}, ν(Ru–C–O); 325–301 cm^{-1}, ν(Re–O); 286–229 cm^{-1}, ν(Re–Re); 212–162 cm^{-1}, δ(O–Re–O) + + δ(O–Re); 159–144 cm^{-1}, ν(Ru–Ru); 140–111 cm^{-1}, ν(Ru–Re); 107–88 cm^{-1}, ν((CO)–Ru–(CO)); 92 cm^{-1}, t(Re–Re) и 89–80 cm^{-1}, ν(C–Ru–C); and 76–59 cm^{-1}, $\nu_{dis}(RuCO_3)$.

The absorption bands Re–Ru, Re–Re, and Ru–Ru were present in the 950–59-cm^{-1} spectral region, which confirmed the presence of bonds as established by quantum chemical calculations and experimentally proved the possibility of replacing rhenium atoms with ruthenium atoms in the rhenium–ruthenium isoproxide complex.

The elemental composition of the surface was studied for the pre-evaporated rhenium–ruthenium isoproxide samples. Figure 2 shows electron microscopy images of the rhenium–ruthenium isoproxide; the selected regions are the points for which elemental analysis was performed (Table 3).

The presence of copper and aluminum impurities in the samples was explained in the same way as for the rhenium isoproxide samples.

The products obtained during the hydrogen reduction process were characterized by X-ray

Table 1. Elemental analysis of rhenium isoproxide

Spectrum	C	O	Al	Cu	Re	Sum of atoms, %
41	62.24	27.86	–	–	9.90	100
42	59.06	19.74	0.40	–	20.80	100
43	61.08	25.66	–	–	13.26	100
44	69.70	21.64	–	0.14	8.52	100
45	67.53	24.09	–	0.14	8.24	100
46	67.48	25.45	–	0.11	6.96	100

Table 2. Comparative table of the X-ray diffraction data of ruthenium acetylacetonate

Cell parameters, Å		Data PDF-4+ Organic, No. 02-066-6916 monoclinic structure, gr. P21/c, cell parameters: a = 14.025, b = 7.533, c = 16.309, β = 99°
D8 Advance Bruker	Diffractometer of the Belok station	
a = 14.040, b = 7.552, c = 16.364, β = 98.93°	a = 14.024, b = 7.530, c = 16.376, β = 98.90°	

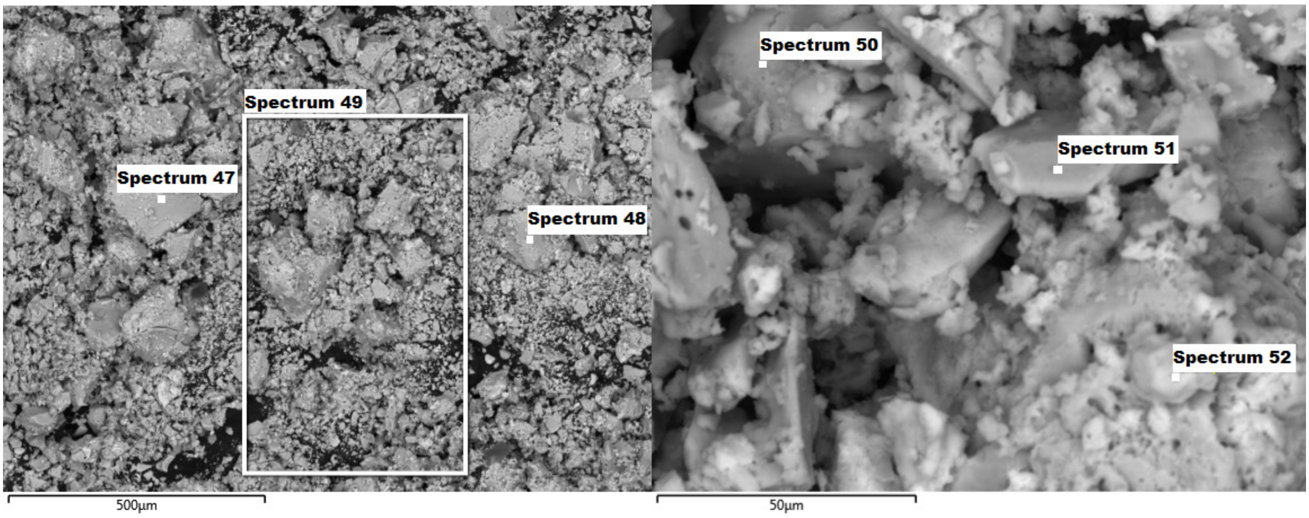

Fig. 2. Electron microscopy of rhenium–ruthenium isoproxide.

Table 3. Elemental analysis of rhenium–ruthenium isoproxide

Spectrum	C	O	Al	Cu	Ru	Re	Sum of atoms, %
47	62.67	27.44	2.40	–	2.00	5.49	100
48	58.96	19.89	2.37	–	2.80	15.98	100
49	61.39	24.43	–	0.42	2.05	11.71	100
50	69.23	22.03	–	0.17	2.94	5.63	100
51	67.83	23.89	2.39	–	3.07	2.82	100
52	67.02	25.95	–	–	–	7.03	100

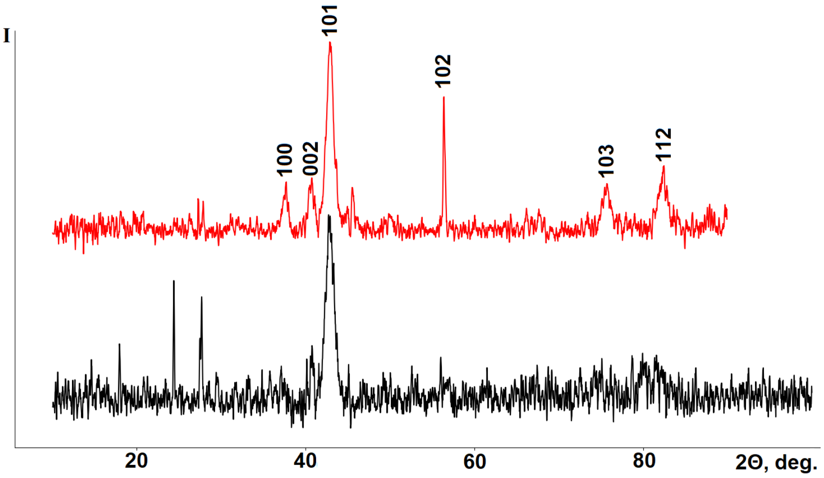

Fig. 3. Results of X-ray phase analysis of the rhenium–ruthenium alloy
(black is the sample obtained from the flow reactor, and red is the sample obtained from the autoclave).

Table 4. Comparative table of the radiometric data of the rhenium–ruthenium alloy

Synthesis	Cell parameters, Å		
	D8 Advance Bruker	**Diffractometer of the Belok station**	**PDF-2, PDF-4+, COD databases Hexagonal ($P6_3/mmc$)–$Re_{0.9}Ru_{0.1}$**
In a flow reactor	$Re_{0.9}Ru_{0.1}$ $a = 2.771$, $c = 4.424$	$Re_{0.9}Ru_{0.1}$ $a = 2.779$, $c = 4.439$	$Re_{0.9}Ru_{0.1}$ $a = 2.753$, $c = 4.432$
In an autoclave	$Re_{0.9}Ru_{0.1}$ $a = 2.757$, $c = 4.430$	$Re_{0.9}Ru_{0.1}$ $a = 2.754$, $c = 4.424$	

phase analysis. The powder samples obtained from the rhenium–ruthenium isoproxide at 400–450°C were X-ray amorphous. When the temperature was increased to 650°C, the obtained rhenium–ruthenium samples were double-phase. The main phase was $Re_{0.9}Ru_{0.1}$. The cell parameters are shown in Table 4. The impurity phase was $LiReO_4 \cdot H_2O$ with the following parameters: $a = 5.712$ Å, $b = 10.782$ Å, $c = 7.453$ Å, $\beta = 102.49°$ (card number 52-1579, P21/a, cell parameters: $a = 5.671$ Å, $b = 10.770$ Å, $c = 7.475$ Å, $\beta = 102.45°$). The samples obtained by the autoclave method at the same temperature were single-phase and of the composition $Re_{0.9}Ru_{0.1}$ (Fig. 3, Table 4).

The phase composition was refined using powder X-ray diffraction on a synchrotron radiation source. Comparative parameters are given in Table 4.

Based on the results of the X-ray phase analysis and the rhenium–ruthenium phase diagram [26], it was concluded that the samples obtained were rhenium–ruthenium alloys.

The sizes of the alloy particles calculated from the width of the diffraction peaks were 7.2 nm according to the Scherrer formula and 16.5 nm according to the Williamson–Hall method, which confirms the receipt of nanoscale samples.

CONCLUSIONS

In this study, a method for obtaining a rhenium–ruthenium isoproxide complex from rhenium isopropylate $Re_4O_6(OPr^i)_{10}$, and ruthenium acetylacetonate $Ru(AcAc)_3$ was developed. The resulting complex was characterized by a set of methods that confirmed previously performed quantum chemical calculations. It was shown that the $Re_{4-y}Ru_yO_6(OPr^i)_{10}$ complex formed nanodisperse powders of rhenium–ruthenium alloys at low-temperature reduction (650°C) in a hydrogen atmosphere. Moreover, the effect of an electrically conductive additive on the resulting alloy's composition was demonstrated. The use of lithium chloride led to the formation of the $LiReO_4$ phase in the final product in contrast with tetrabutylammonium bromide, which was not involved in the formation of the intermediate phases in the rhenium–ruthenium alloy.

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Authors' contribution

E.S. Kulikova – conducting syntheses of research, review of publications on the topic of the article, collection and processing the material, writing the text of the article;

O.V. Chernyshova – consultation for carrying out of separate stages of research, scientific editing;

L.A. Novikova – conducting research and consultation on processing the obtained results;

R.D. Svetogorov – conducting research using powder X-ray diffraction on the synchrotron radiation source, processing the obtained results;

D.V. Drobot – development of the concept of scientific work, critical revision with the introduction of valuable intellectual content, consultation on all stages of research;

I.A. Mikheev – collection and processing the material, statistical processing.

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MATHEMATICS METHODS AND INFORMATION SYSTEMS IN CHEMICAL TECHNOLOGY

МАТЕМАТИЧЕСКИЕ МЕТОДЫ И ИНФОРМАЦИОННЫЕ СИСТЕМЫ В ХИМИЧЕСКОЙ ТЕХНОЛОГИИ

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RESEARCH ARTICLE

Information method for control of green glass production

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Objectives. *The technological process for the production of sheet glass by the float method is continuous and large-scale. Most European cars (up to 90%) are factory-tinted green; the bulk of the glass is painted in the desired color during the production process. The introduction of modern information technologies and digitalization has opened up opportunities for a significant increase in the efficiency of glass production. Accounting for the amount of drawn and cut glass allows you to evaluate an important indicator of the production work—the glass utilization rate, which determines the percentage of quality glass in the total output. The yield of the quality glass depends on the technological waste in the production process. To assess the effect of waste arising at the production stages on the glass utilization rate, an analysis of the statistical data of the float line operation was carried out. These statistical data differ from the normal law of probability distribution, which limits the use of traditional statistical control methods. Regression models do not always give an accurate mathematical description of the process since the variance of the conditional mathematical expectation of the output variable relative to the input is not a consistent characteristic of the relationship between the input and output variables. The purpose of this work is to study the application of information modeling theory for the analysis and control of the technological process of green glass production in terms of its utilization rate.*

Methods. *The technique of modeling technological chains has some peculiarities with that for operations modeling. It analyzes operations to identify possible information links between parameters. Thus, the process of obtaining the utilization rate of green glass in the production process can be followed. This study analyzes the influence of the paired and triple interactions of waste on the process of affording the utilization rate of glass at the stages of green glass production.*

Results. *Information modeling of the technological process of affording the utilization rate of green glass in the production process has been carried out. Informational analysis results in a conclusion about the sufficiency of the control of the utilization rate of green glass in the production process according to informatively related parameters—waste at the stages of glass melting, annealing, and flanging.*

Conclusions. *The selected method of information control of the glass utilization rate can be used in quality management systems in the production of green glass by the float method.*

Keywords: *technological process, green sheet glass, glass utilization rate, information, modeling*

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НАУЧНАЯ СТАТЬЯ

Информационный метод контроля производства зеленого стекла

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Цели. *Технологический процесс производства листового стекла флоат-способом является непрерывным и крупнотоннажным. Европейские автомобили в большинстве (до 90%) имеют зеленую заводскую тонировку стекол, поэтому в процессе производства стекло в своей массе окрашивается в желаемый цвет. Внедрение современных информационных технологий и цифровизация открывают возможности существенного повышения эффективности стекольных производств. Учет количества вытянутого и нарезанного стекла позволяет оценить важный показатель работы производства – коэффициент использования стекла, определяющий долю качественного стекла в процентах в общем объеме выработки. Выход годного стекла зависит от технологических отходов в процессе производства. Для оценки влияния отходов, возникающих на стадиях производства, на коэффициент использования стекла проводился анализ статистических данных работы флоат-линии. Эти выборки отличаются от нормального закона распределения вероятностей, что ограничивает использование традиционных статистических методов контроля. Регрессионные модели не всегда дают точное математическое описание процесса, поскольку дисперсия условного математического ожидания выходной переменной относительно входных не является состоятельной характеристикой связи между входными и выходными переменными. Целью данной работы является исследование применения информационной теории моделирования для анализа и контроля технологического процесса производства зеленого стекла по коэффициенту его использования.*

Методы. *Методика моделирования технологических цепей имеет некоторые особенности по сравнению с моделированием операций. В ней проводится анализ операций для выявления возможных информационных связей между параметрами, что позволяет проследить за формированием коэффициента использования зеленого стекла в процессе производства. Анализируется влияние на величину коэффициента использования стекла парных и тройных взаимодействий отходов на стадиях производства зеленого стекла.*

Результаты. *Проведено информационное моделирование технологического процесса формирования коэффициента использования зеленого стекла. Информационный анализ позволяет сделать заключение о достаточности контроля коэффициента использования зеленого стекла в процессе производства по информативно связанными с ним параметрами – отходами на стадиях стекловарения, отжига и отбортовки.*

Выводы. *Выбранная методика информационного контроля коэффициента использования стекла может применяться в системах менеджмента качества в производстве зеленого стекла флоат-способом.*

Ключевые слова: *технологический процесс, зеленое листовое стекло, коэффициент использования стекла, информация, моделирование*

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The float method, a chemical technology, is used for the production of sheet glass. The production process is continuous and large-scale. Sheet glass is the most important product in the glass industry. Sheet glass is mostly used in industrial, civil, residential, and agricultural constructions. The major consumers are the automotive industry, railway coach manufacturing, and railway transport[1].

Most European cars (up to 90%) are factory-tinted green; the bulk of the glass is painted in the desired color during the production process[2]. The production of green glass has been mastered at Russian glass factories, including AGC Bor Glassworks (Russia)[3] [1].

Over the past 10–15 years, the production and consumption of glass in Russia have significantly increased. This has led to increased requirements for sheet glass quality. The planning and management of large-scale production, which includes the production of polished sheet glass, has special aspects [2]. The technological processes of such industries are continuous, multistage, interdependent, and inertial. The introduction of modern information technologies and digitalization has opened up opportunities for a significant increase in the efficiency of glass production [3–6].

Accounting for the amount of drawn and cut glass makes it possible to estimate an important indicator of the production: the glass utilization rate, which determines the percentage of high-quality glass in the total out-turn. The yield of suitable glass depends on the technological waste in the production process[4,5]. The type of waste that depends on the quality of melting and producing sheet glass includes smelting defects (bubbles, striae, glass stones, etc.), glass ribbon forming defects (crystallization, tin flakes, poly thickness, optical distortions visible in translucent light (“zebra”), stepwise rubbings and cuts from the shafts, lack of border width, etc.,), annealing quality (residual stresses, flection, poor glass cutting), and waste from cutting and shaping glass strip (crizzles, cracks, cutter breaks, scratches from transverse cutting, etc.).

To assess the effect of the waste arising in the production on glass utilization rate, an analysis of the statistical data of the float line operation was carried out. These statistical data differ from the normal law of probability distribution, which limits the use of traditional statistical control methods. Regression models do not always give an accurate mathematical description of the process since the variance of the conditional mathematical expectation of the output variable relative to the input is not a justifiable characteristic of the relationship between input and output variables [7–9].

The informational approach based on the principles of discretization and diversity makes it possible to single out the main part, which is essential in complex technical systems [10, 11].

This study aims to applicate the information modeling theory for analyzing and controlling the technological process of green glass production in terms of its utilization rate.

MATERIALS AND METHODS

To identify the influence of waste arising at different stages of production on glass utilization rate, an analysis

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was carried out using retrospective data related to the operation of a float line for 60 days. The production of green glass was characterized by an average productivity of 168 tons per shift with a standard deviation of 15 tons. The average thickness of the produced glass was 3.1 mm with a standard deviation of 1.0 mm.

To carry out the analysis, a transition from continuous random variables to discrete ones was made. Four partition ranges were chosen for optimal filtration [10, 12]. Entropy was estimated for the obtained discrete random variables.

The values of the entropy of the analyzed variables calculated based on the experimental data were outside the confidence interval of the normal distribution curve. This confirmed that they differ from the normal distribution law.

Information analysis of the technological process of glass production at individual stages consists of the sequential determination of the amount of information with the use of the following equation:

$$I(X_i \to Y) = H(X_i) + H(Y) - H(X_i Y), \quad i = 1,2,3,4. \quad (1)$$

where $H(X_i)$ and $H(Y)$ are estimates of the entropy (the quantitative measure of uncertainty) of X_i and Y, respectively, i.e., estimates of information content; $H(X_i,Y)$ is the entropy of interdependent systems (the entropy of the co-appearance of statistically dependent magnitudes X_i and Y).

The system of equation (1) makes it possible to estimate the influence of each technological operation on the glass utilization rate.

The degree of the influence of information about waste at the production stages on the glass utilization rate is estimated using data connection coefficients:

$$R_i(X_i \to Y) = I(X_i \to Y) / H(Y), \quad i = 1,2,3,4\ . \quad (2)$$

The method for technological chain modeling has some peculiarities with operations modeling. According to this method, operations are analyzed to identify possible information links between parameters. Thus, the process of affording green glass utilization rate in the production can be traced [10].

The influence of the paired and triple interactions of parameters associated with waste at different production stages on the formation of glass utilization rate was analyzed. Information analysis resulted in a conclusion on the sufficiency of the control of green glass utilization rate in the production process, according to informatively related parameters.

RESULTS AND DISCUSSION

Let us carry out information modeling of the technological process of forming green glass utilization rate.

The technological chain of green glass production (production stages) is presented as an information channel receiving information about waste at production stages X_i (i = 1, 2, 3, 4). The information is sequentially transformed into information about glass utilization rate Y at the technological chain output.

Let us estimate the amount of information contained in the parameter of green glass produced at production stages: melting waste $H(X_1)$, molding waste $H(X_2)$, annealing waste $H(X_3)$, and flanging waste $H(X_4)$. The amount of information contained in the parameters of the produced glass is $H(X)$ = 1.38 {nat}. (Here, {nat} is the logarithmic unit for measuring the amount of information).

Let us determine the impact of waste from individual production stages (X_1, X_2, X_3, X_4) on the glass utilization rate (Y). Calculating the information model parameters is reduced to determining the amount of information transmitted to the glass utilization rate Y from the waste at the production stages (X_1, X_2, X_3, X_4). The analysis comprises the sequential determination of the amount of mutual information I between the parameters using the system of equation (1). The calculation results are shown in the table below.

The information transmitted from parameters X_2 and X_3 to Y turned out to be statistically insignificant. This indicates that there is no influence of waste from the glass strip molding and annealing stages on the green glass utilization rate. The information transmitted from the parameter X_1 (glass melting waste) and X_4 (flanging waste) to the glass utilization rate Y turned out to be statistically significant. This indicates the influence of glass melting and flanging waste on the green glass utilization rate in the production process.

The degree of influence of the information on wastes at the stages of production on the glass utilization rate was determined using the data connection coefficients (2). These results are also shown in the table.

The data connection between the parameters is interpreted as follows: parameter X_1 (melting waste) transfers 16% of information to parameter Y (glass utilization rate); parameter X_4 (flanging waste) transfers 20% of information to Y. Calculation showed a weak data connection between waste at certain production stages and green glass utilization rate.

Analysis of the impact of waste from individual stages of production on the glass utilization rate

Stages of sheet glass production	Amount of information transmitted to the glass utilization rate $I\ (X \to Y)$	Impact of waste information on the glass utilization rate $R\ (X \to Y)$	Statistical significance of transmitted information
Melting waste, X_1	0.23	0.16	significant
Molding waste, X_2	0.05	0.04	insignificant
Annealing waste, X_3	0.13	0.10	insignificant
Flanging waste, X_4	0.27	0.20	significant

Using the basic provisions of information theory let us determine the sequential increment of information transmitted to the output parameter Y after each operation [10]:

$$I(X_1 \to Y) = 0.23;$$
$$I(X_4 \to Y / X_1, X_3) = 0.52.$$

The degree of influence of the information increment on the glass utilization rate Y is determined using the data connection coefficient:

$$R_1(X_1 \to Y) = 0.16;$$
$$R_4(X_4 \to Y / X_1, X_3) = 0.38.$$

Let us analyze the effect of the paired and triple interactions of the parameters associated with wastes at different production stages on the formation of the glass utilization rate [10]:

$$I(X_1, X_4 \to Y) = 0.52;$$
$$R_{14}(X_1, X_4 \to Y) = 0.38;$$
$$I(X_1, X_3, X_4 \to Y) = 1.04;$$
$$R_{134}(X_1, X_3, X_4 \to Y) = 0.75.$$

Thus, information from the paired interaction of parameters X_1 and X_4 makes up 38% of the information of parameter Y; information from the triple interaction of parameters X_1, X_3, and X_4 makes up 75% of the information of Y.

The works presented in the monograph [10] are devoted to the application of information methods in quality management. The obtained research results are consistent with previously published works [13, 14].

CONCLUSIONS

The carried-out information analysis leads to the conclusion that it is sufficient to control green glass production according to three parameters: waste at the stages of glass melting X_1, annealing X_3, and flanging X_4, as they are the most informative concerning the glass utilization rate.

The proposed method of information control of the green glass utilization rate can be used in quality management systems in the production of glass by the float method.

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Authors' contribution

All authors equally contributed to the research work.

The authors declare no conflicts of interest.

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MATHEMATICS METHODS AND INFORMATION SYSTEMS IN CHEMICAL TECHNOLOGY

МАТЕМАТИЧЕСКИЕ МЕТОДЫ И ИНФОРМАЦИОННЫЕ СИСТЕМЫ В ХИМИЧЕСКОЙ ТЕХНОЛОГИИ

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RESEARCH ARTICLE

Structure–property models of organic compounds based on molecular graphs with elements of the spatial structures of the molecules

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Objectives. *This article aims to describe, elaborate, and test a general algorithmic method for constructing the structure–property models for organic compounds.*

Results. *The construction of the models is based on the statistical analysis of some sets of chemical structures of definite classes with known property values. These models have some forms of correlation equations. For the representation of chemical structures in this method, the special weighted molecular graphs (MGs) that reflect some peculiarities of the spatial structures of the corresponding molecules are used. The proposed method is realized in two steps. First, it is assumed that the required structure–property equation has a definite form and depends on several adjusted numerical parameters and two changeable functions of one variable. In this step, from some set of functions, the pair of functions that provide the best model is selected. In the second step, the best model (from the previous step) is modified. For this purpose, the classification of the vertices of MG by the chemical symbols of the corresponding atoms and their first-order environments is fulfilled. Further, the graph edges are classified according to the classes of the vertices which they connect. Furthermore, the numerical correction terms for the initial weights of the vertices and edges are introduced, and they improve the obtained model. The final result of the model-construction process is the equation of the definite form containing concrete numerical values of its parameters. Some examples of the application of the elaborated method for constructing the structure–property models for the concrete properties and classes of compounds are presented. The following classes of organic compounds and their physicochemical properties are considered: 1) the boiling point of alcohols, 2) the water solubility of alcohols, 3) the boiling point of sulfides, and 4) the retention indices of alkylphenols. The obtained results indicate the efficiency of the proposed approach and the significance of introducing the second step to the method.*

Conclusions. *In this work, a general algorithmic and computerized method for constructing the structure–property models of organic compounds is suggested. Examples of the application of this method demonstrated its high efficiency. The method is suitable for any class of organic compounds and properties, which are quantitatively measured. Owing to its high efficiency, the structure–property models obtained by this approach can be employed to calculate the properties of chemical compounds for which experimental data are unavailable.*

Keywords: *structure–property correlations, weighted molecular graphs, graph invariants, computer chemistry, mathematical chemistry, length of the chemical bond, covalent atomic radius*

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НАУЧНАЯ СТАТЬЯ

Модели связи «структура-свойство» органических соединений на основе молекулярных графов с элементами пространственного строения молекул

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Цели. *Цель работы – разработать, описать и протестировать общий алгоритмический метод построения моделей связи «структура-свойство» для органических соединений.*

Результаты. *Вышеуказанные модели строятся на основе статистического анализа данных по выборкам структур и свойств химических соединений и имеют вид корреляционных уравнений. Химические структуры в предложенном подходе представляются в виде специальных молекулярных графов с весами вершин и ребер, отражающих определенные особенности пространственного строения соответствующих молекул. Реализация метода происходит в два этапа. На первом этапе предполагается, что искомое уравнение связи «структура-свойство» имеет определенный аналитический вид и зависит от ряда подгоночных параметров и двух функций одной переменной, которые могут варьироваться. На этом этапе происходит отбор пары функций из заданного множества функций, дающих наилучшую модель. На втором этапе происходит модификация полученной наилучшей модели. Для этой цели первоначально проводится классификация вершин молекулярного графа по химическим символам соответствующих атомов и картинам их первого окружения; проводится также классификация ребер графа в соответствии с классами вершин, которые они соединяют. На основе полученной классификации вводятся числовые «поправки» к исходным весам вершин и ребер молекулярных графов, что позволяет улучшить модель, полученную на первом этапе. Конечным результатом процесса построения модели служит уравнение определенного вида с конкретными числовыми значениями всех его параметров. Приведены примеры применения предложенного метода для построения моделей связи «структура-свойство» для конкретных свойств и классов соединений, показывающие его эффективность. Рассматривались следующие физико-химические свойства и классы органических соединений: 1) температура кипения спиртов; 2) растворимость спиртов в воде; 3) температура кипения сульфидов; 4) индексы удерживания алкилфенолов.*

Выводы. *Предложен общий алгоритмический метод построения корреляционных уравнений, связывающих структуру и свойства органических соединений. Приведены примеры его реализации. Метод может быть использован для любых классов органических соединений и любых их свойств, которые измеряются количественно. Модели, построенные на основе предложенного подхода, обладающие достаточно высоким качеством, могут быть использованы для расчета свойств соединений, для которых отсутствуют экспериментальные данные.*

Ключевые слова: *корреляции «структура-свойство», молекулярные графы, инварианты графа, компьютерная химия, математическая химия, длина химической связи, ковалентный радиус атома*

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INTRODUCTION

One of the important problems of mathematical and computational chemistry is to determine the quantitative correlations between the structures and properties of chemical compounds [1–11]. The obtained relationships enable the prediction of the properties of given compounds (both real and hypothetical) from their structures through appropriate calculations, which can be employed for a targeted search for compounds with a predetermined set of properties. Notably, a large number of different chemical substances have been synthesized thus far. However, the experimental determination of their various properties for a targeted search for compounds is technically largely difficult; moreover, it requires significant finance and time. Hence, the development of various mathematical methods for modeling the correlations between the structure and properties of chemical compounds is an essential task.

Generally, a statistical approach that is based on the analysis of a given set of chemical structures with known values of the studied property is employed to construct models for the structure–property correlations. For the quantitative description of the structures of chemical compounds, a certain set of molecular parameters $x_1,..., x_n$ is first selected; as these parameters can be used, for example, any topological, electronic, or geometric characteristic of molecules. It is further assumed that the property, y, is related to these parameters through the function, f: $y = f(x_1,..., x_n)$. The analytic form of f is generally set by the researcher, e.g., f is a linear or quadratic function, but it depends on several selected parameters. These parameters are obtained from the known data of the initial (training) sample of chemical compounds so that the equation, $y = f(x_1,..., x_n)$, would be calculated with extensive accuracy (in a sense) for the initial data set.

To assess the accuracy of the approximation in the constructed model, a correlation is usually established between the calculated and experimental values of the studied properties of the training sample of the compounds. Therefore, the correlation coefficient, R, is determined, as well as the average relative error, δ (in %), which are subsequently employed to draw conclusions on the quality of the model. For example, in [12], the following characteristics of the quality of the model, which were determined by the value of R were proposed thus: $R \geq 0.990$ (outstanding), $R \geq 0.975$ (excellent), $R \geq 0.950$ (very good), $R \geq 0.925$ (good), and $R \geq 0.900$ (fair). Notably, these criteria, which express the acceptability of the model, can be selected differently in some cases.

In the studies of structure–property correlations, the methods for quantitatively describing the molecular structures are very crucial. One of the most common and conventional methods of representing the structure of a molecule is by a graph with numerical weights (or symbolic labels). The vertices and edges of such graph correspond to the atoms and bonds in the molecule, and their weights quantitatively characterize the peculiarities of atoms and bonds of different types. As topological molecular descriptors, $x_1,..., x_n$ in the structure–property correlation models, some numerical invariants of theses graphs are used [13–21].

Evidently, the mathematical models for the structure–property correlations that were obtained within the framework of this approach depend significantly on the selected weights of the graphs representing the chemical structures since the aforementioned graph invariants significantly depend on these weights. Generally, the selected weights of vertices and edges of a graph in a particular context do not depend on the considered class of compounds or properties. For example, for the molecular graphs (MGs) of alkanes (these graphs are constructed without considering the hydrogen atoms), it is generally assumed that the weights of all the vertices are equal to zero. Examples of weights of vertices and edges of the weighted graphs of heteroatomic molecules are presented in the paper [15]. These weights depend on atomic characteristics, such as the total number of electrons, the number of valence electrons, the number of neighboring hydrogen atoms, and the parameters that characterize the multiplicity of the chemical bonds. There are also examples of weights of vertices and edges of MGs in the literature based on the covalent atomic radii, degrees of vertices in the graph, and distances between the vertices [22–24].

Notably, during the construction of models connecting the structure and properties of chemical compounds, the questions about the best selection of the graph invariants, $x_1,\ldots, x_n$ (molecular descriptors), approximating function f and weights of vertices and edges of MGs representing chemical structures arise. These problems are generally due to the lack of *a priori* information on what structural features and how the considered property depends for a given class of compounds, and an infinite number of variants to select the graph invariants, approximating function f, and the weights of a graph.

We shall now in more details describe the method for constructing the models of the structure–property correlations based on the optimal (in a sense) selection of the weights of the vertices in weighted MGs that represent the chemical structures described in [25]. Initially, some classification of the atoms present in the molecular structures of the studied compounds was performed. For example, the atoms can be divided into classes according to their chemical symbols taking into account the distribution of the bond types. A further detailed classification of the atoms can be obtained if, for this purpose, the pictures of their first-order environments are used. All the atoms of one, kth, class (k = 1,2,...) are assigned some weights z_k (k = 1,2,...) (the number of classes is unknown at this stage). For further constructions, all the atoms in each molecule are numbered. Thereafter, it is assumed that the dependence of the studied property, y, on the structure of the molecule has the following special form (Equation (1)):

$$y = \sum w_i w_j + c\,, \tag{1}$$

where w_i and w_j are the numerical weights of the atoms in the molecule with numbers i and j, which are determined by their class in the adopted classification, i.e., $w_i = z_k$, if the atom, i, is in the kth class. In Equation (1), the sum is for all the bonds (i,j) in the molecule, and c is a constant.

Further, the unknown weights of the classes, (k = 1,2,…), are selected so that the relation (1) would be as accurate as possible for a given sample of the compounds. Consequently, a nonlinear function of the k variables of the following form is introduced, as shown in Equation (2):

$$F(z_1,\ldots,z_k) = \sum\nolimits_p (y_p^{\mathrm{exp}} - y_p^{\mathrm{calc}})^2\,, \tag{2}$$

for which we obtained the minimum and corresponding values of the variables, $z_1,\ldots, z_k$. In Equation (2), y_p^{exp} is the experimental value of y of the pth compound, and y_p^{calc} is the analytical expression for calculating the property of the pth compound that was obtained from Equation (1) and depending on the parameters, $z_1,\ldots, z_k$.

Thus, the resulting equation of the structure–property correlations has the form of Equation (1) in which $z_1,\ldots, z_k$ are known and selected in the optimal method (in the above sense). Equation (1) can be employed afterward to calculate the property values of other compounds of the same class that are not present in the initial sample.

The following facts are the basis for selecting Equation (1) in the above studies. One of the most widely employed MG invariant for modeling structure–property correlations is the molecular connectivity index (the Randić index) χ, as shown in Equation (3):

$$\chi = \sum \left(v_i v_j\right)^{-\frac{1}{2}}\,, \tag{3}$$

where v_i, v_j are the degrees of vertices i and j in the graph, and the sum is the sum of all the edges (i,j) of the graph [26]. This index possesses the following property: for a tree graph with a fixed number of vertices, it takes its extreme values (the highest and lowest) on the most- and least-branched trees, i.e., chain and star graphs. Owing to this property, χ can serve as the quantitative measure of the degree of branching in an acyclic molecule. There are generalizations of χ for cases involving more general subgraphs (chains of different lengths; notably, χ corresponds to a chain length of 1, i.e., an edge of the graph), as well as cases, when in formula for χ instead of vertex degrees state some weights of vertices, depending on the characteristics of the corresponding atoms. The above modifications of χ also have wide applications in structure–property correlations [27, 28].

The replacement of the values of v_i with those of the form, $v_i + x$, in the formula for χ have been proposed when constructing the structure–property correlations [29]. Further, x are the selected parameters based on the chemical symbols of the corresponding atoms. As a specific example, it was demonstrated that a more accurate correlation of the structure–property type could be obtained with such a "variable" χ than with the original χ. Additionally, it was noted that for each property and class of compounds the set of optimal selected parameters is own set [29].

The idea of generalizing χ by introducing the selected atomic parameters was also implemented in [30–35] particularly for classes of compounds, such as alkanes, alcohols, and ethers, for their enthalpies of vaporization. The compounds were represented by graphs without considering the hydrogen atoms. In these works, a molecular descriptor of the following type was considered, as expressed in Equation (4):

$$ {}^{0-3}\chi = {}^{0}\chi + \frac{{}^{1}\chi}{2} + \frac{{}^{2}\chi}{3} + \frac{{}^{3}\chi}{4}, \qquad (4)$$

where

$$ {}^{0}\chi = \sum \left(\ln \delta_i\right)^{-1}, \; {}^{1}\chi = \sum \left(\ln\left(\delta_i \delta_j\right)\right)^{-1}, $$
$$ {}^{2}\chi = \sum \left(\ln\left(\delta_i \delta_j \delta_k\right)\right)^{-1}, \; {}^{3}\chi = \sum \left(\ln\left(\delta_i \delta_j \delta_k \delta_l\right)\right)^{-1}. \qquad (5)$$

In Equation (5) for ${}^{0}\chi$, the summation is for all the non-hydrogen atoms of the molecule, numbered $i = 1,2,\ldots,n$. In Equation (5) for ${}^{1}\chi$, ${}^{2}\chi$, ${}^{3}\chi$, the summation is for all the chains of the atoms containing 1, 2, and 3 consecutive bonds, with the numbers of atoms in these chains corresponding to i,j, i,j,k, or i,j,k,l, respectively. The numbers of the kind, δ_i, were the selected parameters of the atoms depending on the method of their classification. Further, it was assumed that the dependence of the considered property on the parameter, ${}^{0-3}\chi$, has the following form (Equation (6)):

$$ y = a \times {}^{0-3}\chi + b, \qquad (6)$$

where the constants, a and b, were selected according to the least-squares method.

In [36], a modification of the classical Randić index according to the selection of the atomic parameters was considered. In that case, some of the parameters that were attributed to the carbon atoms were fixed (they were assumed to be equal to the degrees of the vertices in the corresponding graph), and the other part was selected.

In this study, we proposed and verified a new general method, which was developed within the framework of a statistical approach for solving such problems, to establish quantitative correlations between the structures and properties of organic compounds. The method is based on representing the structures of the studied compounds as weighted MGs with weights of vertices and edges reflecting the elements of spatial structure of corresponding molecules, with the subsequent corrections of these weights. The proposed approach is a generalized development of a previously described approach [25].

DESCRIPTION OF THE METHOD FOR CONSTRUCTING THE STRUCTURE–PROPERTY CORRELATION MODELS

Construction of weighted MGs of organic compounds

Let there be a certain sample with structural formulas of organic compounds of a certain class and known numerical values of some physicochemical property obtained experimentally and reported in the literature.

The construction of any structure–property correlation model within the framework of the above-described statistical approach presupposes the preliminary construction of special MGs for the compounds under consideration. In the given paper weighted MGs with vertices corresponding to the non-hydrogen atoms of the molecule, and edges corresponding to the chemical bonds between these atoms, are considered. The MG vertices were assumed to be numbered $1,2,\ldots,n$, and edge, which was formed by a pair of vertices that were numbered i and j ($i < j$), was denoted by the symbol (i,j). The weights of the vertices and edges of MG reflect the elements of the spatial structure of the molecule, namely, the vertex weights w_{ii} are taken as the covalent radii of the corresponding atoms, and edge weights w_{ij} are taken as the lengths of the corresponding bonds. The values of the atomic radii and bond lengths used in this work are presented in Tables 1 and 2, respectively [23], [37].

Table 1. Covalent radii of the atoms (Å) [23]

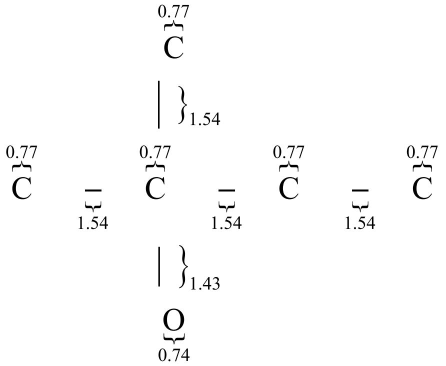
No.	Atom	Atom radius, Å
1	Csp^3	0.77
2	Csp^2	0.67
3	Csp	0.60
4	Nsp^3	0.74
5	Nsp^2	0.62
6	Nsp	0.55
7	Osp^3	0.74
8	Osp^2	0.62
9	F	0.72
10	Psp^3	0.10
11	Psp^2	1.00
12	Ssp^3	1.04
13	Ssp^2	0.94
14	Cl	0.99
15	Br	1.14
16	I	1.33

Table 2. Average bond lengths in the organic molecules (Å) [37]

No.	Bond	Bond length, Å	No.	Bond	Bond length, Å
1	C4–C4	1.54	23	C2–C1	1.63
2	C4–C3	1.52	24	C3=C3	1.34
3	C4–C2	1.46	25	C3=C2	1.31
4	C4–N3	1.47	26	C3=N2	1.32
5	C4–N2	1.47	27	C3=O1	1.22
6	C4–O2	1.43	28	C2=C2	1.28
7	C4–S2	1.81	29	C2=N2	1.32
8	C4–F	1.40	30	C2=O1	1.16
9	C4–Cl	1.76	31	N3=O1	1.24
10	C4–Br	1.94	32	N2=O1	1.22
11	C4–I	2.14	33	N2=N2	1.25
12	C3–C3	1.46	34	C2≡C2	1.20
13	C3–C2	1.45	35	C2≡N1	1.16
14	C3–N3^1	1.40	36	C3=C3^2	1.40
15	C3–N2	1.40	37	C3=N2^2	1.34
16	C3–O2	1.36	38	C3–F^2	1.32
17	C3–F	1.33	39	C3–Cl^2	1.71
18	C3–Cl	1.73	40	C3–Br^2	1.89
19	C2–C2	1.38	41	C3–I^2	2.10
20	C2–N3	1.33	42	C3–O2^2	1.36
21	C2–O2	1.33	43	C3–N3^2	1.48
22	C2–F	1.30	44	C3–S2^2	1.81

In Table 2, the numbers that are placed after the symbols of atoms are those of the neighboring atoms of a given atom in a molecule; the superscript, 1, in No. 14 implies that the bond length of the N–C=O group is 1.32; superscript, 2, in Nos. 36–44 implies that C3 is a carbon atom in the benzene ring.

An example of the described weighted MG, which corresponded to the structural formula of 2-methyl-2-butanol, is shown in the figure (the MG vertices are not numbered).



Weighted molecular graph of 2-methyl-2-butanol.

Description of the initial structure–property correlation model and the method of selecting its parameters

In the proposed approach to modeling the structure–property correlations, it was initially assumed that the corresponding equation that connects the property, y, to some structural characteristics of the molecule (or its MG) has the following form (Equation (7)):

$$y = a\sum f_1\left(w_{ij}\right) + b\sum f_2\left(w_{ii} \times w_{jj}\right) + c, \tag{7}$$

where w_{ij} is the weight of the edge (i,j) in MG; w_{ii} is the weight of the vertex, i, of MG, the summation in each sum is for all edges (i,j) in MG. The functions, $f_1(x)$ and $f_2(x)$, are some fixed functions of one variable. Both functions were selected independently from any given set of functions. The following set of functions was considered in this paper: $f(x) = \ln x$, $f(x) = x^k$, where k takes the values, ±1 and ±0.5, i.e., five functions were considered. Notably, this set of functions could be extended or changed. Thus, the model was determined by specifying a pair of functions, $f_1(x)$ and $f_2(x)$. The parameters, a, b, and c, were selected by the least-squares method according to a given (training) sample of compounds for each pair of $f_1(x)$ and $f_2(x)$. Therefore, 25 different models could be built in this case.

To assess the accuracy of each of these 25 models (its quality) for a training set of compounds, R and the standard deviation, s, were calculated for the correlation between the experimental and calculated values of y. From the obtained set of models based on the parameters, R and s, one (the most accurate model) was selected. Moreover, this model can be further improved.

Notably, to assess the accuracy of the model on the initial sample of compounds, the average and maximum absolute (or relative) errors in calculating y (Δ_{avg}, $\Delta_{\max}$, δ_{avg}, $\delta_{\max}$, respectively) could be used.

Correction of the model based on the modifications of weights of vertices and edges of MGs

To improve the constructed model (with a selected pair of functions, $f_1(x)$ and $f_2(x)$), we performed the corrections of w_{ii} and w_{ij} of MG. This adjustment was performed as follows: initially, the vertices and the edges (i,j) of MG were divided into some classes according to certain criteria.

The classification of the MG vertices was performed according to the chemical symbols of the corresponding atoms and the pictures of their first-order environment. The classes of the vertices were numbered arbitrarily as $1,2,\ldots,n_1$. The class with the number, p, was initially assigned some indefinite numerical "weight," x_p ($p = 1,2,\ldots,n_1$). The bonds were classified according to the classes of atoms that they connect; the bond classes were also numbered arbitrarily with numbers $1,2,\ldots,n_2$. The class with the number, q, was initially assigned some undefined numerical "weight," z_q ($q = 1,2,\ldots,n_2$).

Instead of the initial w_{ii}, the weights with the form, $w_{ii} + x_p$, were considered, where p is the number of the class, to which the ith atom belongs. Further, instead of w_{ij}, the weights were similarly corrected to the form, $w_{ij} + z_q$, where q is the class number to which the edge (i,j) belongs.

Further, these corrections, as well as the coefficients, a, b, and c, which are assumed to be unknown, were selected simultaneously by minimizing a function of many variables of the following form, as shown in Equation (8):

$$F\left(a,b,c,x_1,x_2,x_3,\ldots,z_1,z_2,z_3,\ldots\right) = \\ = \sum_k \left(y_{\exp,k} - y_{\text{calc},k}\right)^2, \tag{8}$$

where $y_{\exp,k}$ is the experimental value of y of the kth compound, $y_{\text{calc},k}$ is the calculated value of y of this compound that is obtained by Equation (7), where instead of the initial weights, w_{ij} and w_{ii} are their corrected expressions; the summation is for all the compounds of the training set.

For the optimal selection of the parameters, a, b, c, x_1, x_2, x_3,..., in this task, the add-in, "Load the Solver," of the Microsoft Excel program could be used.

Notably, to refine the model, only w_{ii} can be adjusted, while w_{ij} remains unchanged.

To evaluate the quality of the model on the training set of compounds, R and s were determined for the correlation between the experimental and calculated values of the studied property, as well as the average and maximum absolute (or relative) errors (Δ_{avg}, $\Delta_{\max}$, δ_{avg}, $\delta_{\max}$, respectively) in calculating the property value.

To assess the predictive power of the model, a new set of chemical compounds of the same class and known values of y was used (test sample). For these compounds, the obtained formula was employed to calculate y and determine R_1 and s_1 for the correlation between the experimental and calculated values of y, as well as the parameters, $\Delta_{\text{avg},1}$, $\Delta_{\max,1}$, $\delta_{\text{avg},1}$, $\delta_{\max,1}$, similar to the above parameters for the training sample.

EXAMPLES OF CONSTRUCTING THE STRUCTURE–PROPERTY CORRELATIONS ON THE BASE OF THE PROPOSED METHOD

This section offers examples for the application of the developed method in the construction of models of the structure–property correlations for a range of physicochemical properties of organic compounds of some classes, as well as the analysis of the results.

In each example, a certain sample of compounds is considered and divided into training and test samples. N is the number of compounds in the initial sample (N_1 and N_2 are the numbers of compounds in the training and test samples, respectively). The initial data are presented as a table containing the names of the compounds and values of their considered physicochemical property, which were culled from the literature. The compounds included in the test set are marked as *.

Following the method described herein, the weighted MGs of the compounds under consideration were constructed at the first stage of research in each example. Thereafter, for the training set, the unknown constants, a, b, c, were calculated for each pair of the selected functions, $f_1(x)$ and $f_2(x)$, by the least-squares method, as well as the parameters, R and s. The best model was selected from the obtained models by the parameters, R and s, i.e., the best pair of $f_1(x)$ and $f_2(x)$ was selected. For this model, R, s, δ_{avg}, and $\delta_{\max}$, as well as similar parameters, R_1, s_1, $\delta_{\text{avg},1}$, $\delta_{\max,1}$, were determined, thereby characterizing the qualities of the model on the training and test samples, respectively.

The obtained best model was refined in the second stage of the research. Therefore, the MG vertices were initially classified according to the chemical symbols of the corresponding atoms and the patterns of their first-order environments. The classification results are summarized in a table containing the structural fragments that define the classes and their descriptions.

Further, based on the obtained classification of the vertices, corrections x_1, x_2,… were introduced to the initial w_{ii}. The obtained values of corrections x_1, x_2,… and the coefficients a, b, c for the improved model are summarized in another table. The final result of the model-building process is an equation of a certain form with the specific numerical values of all its parameters, which enables the calculation of y for any compound of a given class. For this equation, R, s, δ_{avg}, $\delta_{\max}$ and R_1, s_1, $\delta_{\text{avg},1}$, and $\delta_{\max,1}$ were also determined, thus characterizing the qualities of the model on the training and test sets, respectively.

Finally, the results were analyzed at the third stage of the research. Thus, all the statistical characteristics of the four cases (initial/refined models and training/test samples) are summarized in one table, after which these characteristics were compared in the initial and refined models, and a conclusion was made about the advisability of introducing corrections to w_{ii} of MG to improve the model. Moreover, the quality of the final, refined model was assessed.

a) Boiling points of alcohols

A sample of alcohols with their boiling points, $N = 31$, $N_1 = 21$, $N_2 = 10$ [29] was considered as the initial data for constructing the model. The initial data are presented in Table 3.

The best model selected at the first stage was an equation of the following form (9):

$$y = a\sum\left(w_{ij}\right)^{-1} + b\sum\left(w_{ii} \times w_{jj}\right)^{-\frac{1}{2}} + c. \tag{9}$$

Further, the MG vertices were classified, and the results are presented in Table 4.

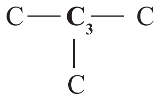
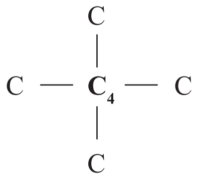
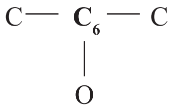
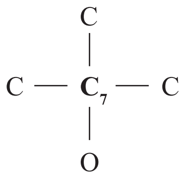
Table 3. Alcohols and their boiling points [29]

No.	Compound	Boiling point, °C
1	Ethanol	78.0
2	Propanol	97.1
3	2-Propanol	82.4
4	Butanol*	117.6
5	2-Methyl-1-propanol	108.1
6	2-Butanol*	99.5
7	2-Methyl-2-propanol	82.4
8	Pentanol*	138.0
9	3-Methyl-1-butanol	131.0
10	2-Methyl-1-butanol	128.0
11	2-Pentanol*	119.3
12	3-Pentanol	116.2
13	3-Methyl-2-butanol*	112.9
14	2-Methyl-2-butanol	102.3
15	Hexanol	157.6
16	3-Methyl-1-pentanol	153.0
17	4-Methyl-1-pentanol	151.9
18	2-Methyl-1-pentanol*	149.0
19	2-Ethyl-1-butanol	147.0
20	2,3-Dimethyl-1-butanol*	144.5
21	3,3-Dimethyl-1-butanol	143.0

Table 3. Continued

No.	Compound	Boiling point, °C
22	2-Hexanol*	140.0
23	2,2-Dimethyl-1-butanol	136.5
24	3-Hexanol	135.0
25	3-Methyl-2-pentanol*	134.3
26	4-Methyl-2-pentanol	131.6
27	2-Methyl-3-pentanol*	126.5
28	3-Methyl-3-pentanol	122.4
29	2-Methyl-2-pentanol	121.1
30	3,3-Dimethyl-2-butanol	120.4
31	2,3-Dimethyl-2-butanol	118.4

Table 4. Classification of vertices of MG, corresponding to alcohol molecules

No.	Structural fragment that defines the class of atoms	Description of the atom class
1	$\mathbf{C_1}$—C	The central C_1 atom is bonded to one C atom
2	C—$\mathbf{C_2}$—C	The central C_2 atom is bonded to two C atoms
3	 $\mathrm{C-\mathbf{C_3}(-C)-C}$	The central C_3 atom is bonded to three C atoms
4	 $\mathrm{C-\mathbf{C_4}(-C)(-C)-C}$	The central C_4 atom is bonded to four C atoms
5	C—$\mathbf{C_5}$—O	The central C_5 atom is bonded to one C and one O atoms
6	 $\mathrm{C-\mathbf{C_6}(-O)-C}$	The central C_6 atom is bonded to two C and one O atoms
7	 $\mathrm{C-\mathbf{C_7}(-C)(-O)-C}$	The central C_7 atom is bonded to three C and one O atoms
8	C—**O**	The central O atom is bonded to one C atom

Based on this classification, corrections x_1–x_8 (correction parameters) were introduced to the weights of the MG vertices. The determined corrections x_1, x_2, …, x_8 and the coefficients *a*, *b*, and *c* are presented in Table 5.

Thus, the improved model is expressed as Equation (10):

$$y = a\sum\left(w_{ij}\right)^{-1} + b\sum\left(\left(w_{ii}+x_n\right)\times\left(w_{jj}+x_m\right)\right)^{-\frac{1}{2}} + c, \qquad (10)$$

where *n* and *m* are the numbers of the classes of vertices to which the corresponding vertices *i* and *j* belong. The values of the corrections, x_n and x_m, as well as the coefficients a, b, and c were obtained from Table 5. The summation in each sum is for all edges (i,j) in MG.

Table 6 presents some statistical parameters of the constructed models for the four cases (initial/refined models; training/test samples).

As presented in Table 6, the introduction of corrections to w_{ii} of MG significantly improved the initial model (on all characteristics). Thus, an equation of the form of Equation (10) was more accurate than Equation (9) in expressing the relationship between the structures and boiling points of alcohols.

b) Solubilities of alcohols in water

A sample of alcohols, $N = 30$, $N_1 = 20$, $N_2 = 10$ [38], with their water-solubility values, $-\log X$ (X is the molar fraction of a substance in solution), was considered as the initial data (Table 7) for constructing the model.

Table 5. Values of the correction parameters, x_1–x_8, and the coefficients a, b, and c for the improved model

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	a	b	c
0.0348	0.0003	0.0112	0.0170	0.0001	0.0117	0.0174	0.00303	15898	7936.4	−549.4

Table 6. Some statistical parameters of the initial/modified models for the training/test samples for the boiling point of alcohols

Statistical parameters of the model	Initial model (without the corrections of w_{ii} of MG)		Modified model (with the corrections of w_{ii} of MG)	
	Training sample	Test sample	Training sample	Test sample
s	13.19	10.09	1.82	2.04
R	0.838	0.796	0.997	0.992
δ_{avg}	9.23%	6.18%	1.21%	1.39%
δ_{max}	25.43%	13.25%	3.96%	3.05%

The best model that was selected at the first stage is an equation of the following form (11):

$$y = a\sum\left(w_{ij}\right)^{\frac{1}{2}} + b\sum\left(w_{ii}\times w_{jj}\right)^{-\frac{1}{2}} + c. \qquad (11)$$

Further, the MG vertices were classified, and the results are presented in Table 4. Corrections x_1–x_8 (correction parameters) were introduced to the weights of the MG vertices based on this classification. The obtained corrections, $x_1, x_2, \ldots, x_8$, and the coefficients a, b, and c are presented in Table 8.

Thus, the improved model is expressed as Equation (12):

$$y = a\sum\left(w_{ij}\right)^{\frac{1}{2}} + \\ + b\sum\left(\left(w_{ii}+x_n\right)\times\left(w_{jj}+x_m\right)\right)^{-\frac{1}{2}} + c, \qquad (12)$$

where n and m are the numbers of vertex classes to which the corresponding vertices, i and j, belong. The values of corrections x_n and x_m, as well as the coefficients a, b, and c were obtained from Table 8. The summation in each sum is for all edges (i,j) of MG.

Table 9 presents some statistical parameters of the constructed models for the four cases (initial/refined models; training/test samples).

According to Table 9, the introduction of corrections to w_{ii} of MG significantly improved the initial model (on all characteristics). Thus, an equation of the form of Equation (12) was more accurate than Equation (11) in reflecting the relationship between the structures of alcohols and their water solubility.

To further improve the model, a classification of edges in MG (or bonds in structural formula) based on mentioned above classification of the MG vertices, was fulfilled. Therefore, the following edge classes were determined:

1) C_1–C_2, 2) C_1–C_3, 3) C_1–C_4, 4) C_1–C_5, 5) C_1–C_6, 6) C_1–C_7, 7) C_2–C_2, 8) C_2–C_3, 9) C_2–C_4, 10) C_2–C_5, 11) C_2–C_6, 12) C_2–C_7, 13) C_3–C_5, 14) C_3–C_6, 15) C_3–C_7, 16) C_4–C_5, 17) C_4–C_6, 18) O–C_5, 19) O–C_6, 20) O–C_7.

Table 7. Alcohols and their water-solubility values [38]

No.	Compound	Solubility in water, $-\log X$
1	1-Butanol	1.750
2	2-Methyl-1-propanol	1.743
3	2-Butanol*	1.724
4	1-Pentanol	2.332
5	3-Methyl-1-butanol	2.254
6	2-Methyl-1-butanol*	2.207
7	2-Pentanol	2.025
8	3-Pentanol*	1.961
9	3-Methyl-2-butanol	1.926
10	2-Methyl-2-butanol	1.608
11	2,2-Dimethyl-1-propanol	2.030
12	1-Hexanol*	2.957
13	2-Hexanol	2.612
14	3-Hexanol	2.542
15	3-Methyl-3-pentanol*	2.109
16	2-Methyl-2-pentanol	2.233
17	2-Methyl-3-pentanol*	2.445
18	3-Methyl-2-pentanol*	2.458
19	2,3-Dimethyl-2-butanol	2.118
20	3,3-Dimethyl-1-butanol	2.870
21	3,3-Dimethyl-2-butanol	2.359
22	4-Methyl-1-pentanol	2.737
23	4-Methyl-2-pentanol*	2.534
24	2-Ethyl-1-butanol	2.956
25	1-Heptanol	3.554
26	2-Methyl-2-hexanol	2.820
27	3-Methyl-3-hexanol*	2.729
28	3-Ethyl-3-pentanol	2.579
29	2,3-Dimethyl-2-pentanol	2.615
30	2,3-Dimethyl-3-pentanol*	2.588

Table 8. Values of the correction parameters, x_1–x_8, and the coefficients *a*, *b*, and *c* for the improved model

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	a	b	c
0.0005	0.0011	0.0011	0.0011	0.0001	0.0002	−0.0003	−0.0002	213.25	−203.61	15.14

By this classification, corrections z_1–z_{20} to w_{ij} were introduced and obtained, and new values of the parameters, *a*, *b*, *c*, and x_1–x_8 were simultaneously obtained. Table 10 shows some statistical parameters of the constructed modified models for the four cases (model with corrections to the weights of vertices/the weights of vertices and edges; training/test samples).

Table 9. Some statistical parameters of the initial/modified models for the training/test samples for the water solubility of alcohols

Statistical parameters of the model	Initial model (without the corrections of w_{ii} of MG)		Modified model (with the corrections of w_{ii} of MG)	
	Training sample	Test sample	Training sample	Test sample
s	0.301	0.239	0.078	0.091
R	0.794	0.798	0.988	0.973
δ_{avg}	9.25%	6.31%	2.40%	3.43%
δ_{max}	28.53%	17.49%	6.29%	17.40%

Table 10. Some statistical parameters of the modified models with the correction parameters to vertex weights and to weights of vertices and edges for the training and test samples for the water solubility of alcohols

Statistical parameters of the model	Modified model (with corrections to the vertex weights of MG)		Modified model (with corrections to the weights of vertices and edges of MG)	
	Training sample	Test sample	Training sample	Test sample
s	0.078	0.091	0.026	0.099
R	0.988	0.973	0.999	0.968
δ_{avg}	2.40%	3.43%	0.69%	3.43%
δ_{max}	6.29%	17.40%	2.48%	18.86%

Table 11. Sulfides and their boiling points [39]

No.	Compound	Boiling point, °C
1	Methyl ethyl sulfide	66.6
2	Methyl propyl sulfide	95.5
3	Diethyl sulfide	92.0
4	Methylisopropyl sulfide	84.4
5	Ethylisopropyl sulfide	107.4
6	Methyl butyl sulfide*	123.2
7	Methyl isobutyl sulfide	112.5
8	Ethylpropyl sulfide*	118.5
9	Methyl *tert*-butyl sulfide	101.5
10	Methylamyl sulfide	145.0
11	Ethyl butyl sulfide	144.2
12	Dipropyl sulfide*	142.8
13	Propylisopropyl sulfide	132.0
14	Ethyl isobutyl sulfide	134.2
15	Methylisoamyl sulfide	137.0

Table 11. Continued

No.	Compound	Boiling point, °C
16	Methyl 2-methylbutyl sulfide*	139.0
17	Ethyl *sec*-butyl sulfide	133.6
18	Ethyl *tert*-butyl sulfide*	120.4
19	Diisopropyl sulfide	120.0
20	Methyl 1-ethylpropyl sulfide	137.0
21	Methyl *sec*-butyl sulfide*	114.5
22	Methyl *tert*-amyl sulfide	128.3
23	Methyl-1,2-dimethylpropyl sulfide	133.0
24	Methylhexyl sulfide*	171.0
25	Propyl butyl sulfide	166.0
26	Propyl isobutyl sulfide	155.0
27	Isopropyl isobutyl sulfide*	145.0
28	Ethyl 2-methylbutyl sulfide*	159.0
29	Propyl *tert*-butyl sulfide	138.0
30	Isopropyl *sec*-butyl sulfide*	142.0

Notably, the introduction of additional parameters to the correlation equation improved all the model characteristics on the training set. However, in the test sample, the model became slightly worse. In this regard, it was not sensible to further classify edges of MG.

c) Boiling point of sulfides

A sample of sulfides, $N = 30$, $N_1 = 20$, $N_2 = 10$ [39], with their boiling points was considered as the initial data (Table 11) for constructing the model.

The best model that was selected at the first stage is an equation of the following form (13):

$$y = a\sum\left(w_{ij}\right)^{-1} + b\sum\ln\left(w_{ii}\times w_{jj}\right) + c\,. \qquad (13)$$

Further, the MG vertices were classified, as presented in Table 12.

Corrections x_1–x_8 to w_{ii} of MG were introduced based on this classification. The obtained corrections,

Table 12. Classification of vertices of MG, corresponding to sulfide molecules

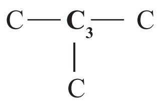
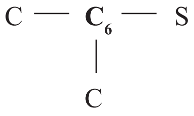
No.	Structural fragment that defines the class of atoms	Description of the atom class
1	$\mathbf{C_1}-\mathrm{C}$	The central C_1 atom is bonded to one C atom
2	$\mathrm{C}-\mathbf{C_2}-\mathrm{C}$	The central C_2 atom is bonded to two C atoms
3	 $\mathrm{C}-\mathbf{C_3}(-\mathrm{C})-\mathrm{C}$	The central C_3 atom is bonded to three C atoms
4	$\mathbf{C_4}-\mathrm{S}$	The central C_4 atom is bonded to one S atom
5	$\mathrm{C}-\mathbf{C_5}-\mathrm{S}$	The central C_5 atom is bonded to one C and one S atoms
6	 $\mathrm{C}-\mathbf{C_6}(-\mathrm{C})-\mathrm{S}$	The central C_6 atom is bonded to two C and one S atoms

Table 12. Continued

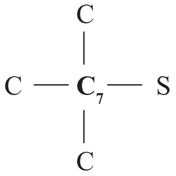
No.	Structural fragment that defines the class of atoms	Description of the atom class
7	 $\mathrm{C}-\mathbf{C}_7(\mathrm{C})(\mathrm{C})-\mathrm{S}$	The central C_7 atom is bonded to three C and one S atoms
8	C — **S** — C	The central S atom is bonded to two C atoms

Table 13. Values of the correction parameters, x_1–x_8, and the coefficients *a*, *b*, and *c* for the improved model

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	*a*	*b*	*c*
0.00016	0.00014	0.00002	0.00017	0.00006	0.00006	0.00021	0.00006	7284.7	9091.2	4055.93

$x_1, x_2, \ldots, x_8$, and the coefficients *a*, *b*, and *c* are shown in Table 13.

Thus, the best model is expressed as Equation (14):

$$y = a\sum\left(w_{ij}\right)^{-1} + \\ + b\sum \ln\left(\left(w_{ii}+x_n\right)\times\left(w_{jj}+x_m\right)\right) + c, \qquad (14)$$

where *n* and *m* are the numbers of the vertex classes to which the corresponding vertices, *i* and *j*, belong. The values of the corrections, x_n and x_m, as well as the coefficients *a*, *b*, and *c* were obtained from Table 13. The summation in each sum is for all edges (*i*,*j*) in MG.

Table 14 presents some statistical parameters of the models for the four cases (initial/refined models; training/test samples).

According to Table 14, the introduction of corrections to w_{ii} of MG significantly improved the initial model (on all characteristics). Thus, an equation of the form of Equation (14) was more accurate than Equation (13) in reflecting the correlation between the structures and boiling points of sulfides.

d) Alkylphenol retention indices

A sample of alkylphenols, $N = 30$, $N_1 = 20$, $N_2 = 10$ [40], with their values of retention indices was considered as the initial data (Table 15) for constructing the model.

The best model that was selected at the first stage is an equation of the following form (15):

$$y = a\sum\left(w_{ij}\right)^{-1} + b\sum\left(w_{ii}\times w_{jj}\right)^{\frac{1}{2}} + c\,. \qquad (15)$$

Further, the MG vertices were classified, as presented in Table 16. The C atoms included in the benzene ring are denoted as C^b.

Corrections x_1–x_9 to w_{ii} were introduced based on this classification. The obtained corrections, $x_1, x_2, \ldots, x_9$, and the coefficients *a*, *b*, and *c* are presented in Table 17.

Table 14. Some statistical parameters of the initial/modified models of the training/test samples for the boiling point of sulfides

Statistical parameters of the model	Initial model (without the corrections of w_{ii} of MG)		Modified model (with the corrections of w_{ii} of MG)	
	Training sample	Test sample	Training sample	Test sample
s	7.76	10.47	2.73	2.64
R	0.954	0.846	0.994	0.991
δ_{avg}	4.41%	6.77%	1.83%	1.81%
δ_{max}	12.48%	10.72%	5.60%	4.07%

Table 15. Alkylphenols and their retention indices [40]

No.	Compound	Retention indices
1	Phenol	1281
2	2-Methylphenol	1354
3	3-Methylphenol*	1386
4	4-Methylphenol	1385
5	2-Ethylphenol	1430
6	3-Ethylphenol	1483
7	4-Ethylphenol*	1473
8	2,3-Dimethylphenol	1495
9	2,4-Dimethylphenol	1456
10	2,5-Dimethylphenol	1453
11	2,6-Dimethylphenol*	1416
12	3,5-Dimethylphenol*	1489
13	3,4-Dimethylphenol	1530
14	4-Isopropylphenol	1527
15	2-*n*-Propylphenol*	1502
16	3-*n*-Propylphenol	1565
17	4-*n*-Propylphenol	1563
18	2-Ethyl-4-methylphenol*	1523
19	2-Ethyl-5-methylphenol	1529
20	2-Ethyl-6-methylphenol	1485
21	3-Ethyl-5-methylphenol*	1581
22	4-Ethyl-2-methylphenol*	1539
23	4-Ethyl-3-methylphenol	1608
24	2,3,4-Trimethylphenol	1638
25	2,3,5-Trimethylphenol	1593
26	2,3,6-Trimethylphenol*	1551
27	2,4,5-Trimethylphenol*	1593
28	3,4,5-Trimethylphenol	1667
29	4-*sec*-Butylphenol	1612
30	2-*n*-Butylphenol	1600

Table 16. Classification of vertices of MG, corresponding to alkylphenol molecules

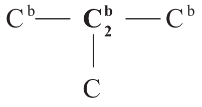
No.	Structural fragment that defines the class of atoms	Description of the atom class
1	$C^b - \mathbf{C^b_1} - C^b$	The central C^b_1 atom is bonded to two C^b atoms
2	 $C^b - \mathbf{C^b_2}(-C) - C^b$	The central C^b_2 atom is bonded to two C^b and one C atoms
3	$C^b - \mathbf{C_3}$	The central C_3 atom is bonded to the C^b atom

Table 16. Continued

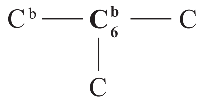
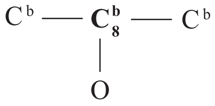
No.	Structural fragment that defines the class of atoms	Description of the atom class
4	$C-\mathbf{C_4}$	The central C_4 atom is bonded to the C atom
5	$C^b-\mathbf{C_5}-C$	The central C_5 atom is bonded to one C^b and one C atoms
6	 $C^b-\underset{\overset{\vert}{C}}{\mathbf{C_6^b}}-C$	The central C_6^b atom is bonded to one C^b and two C atoms
7	$C-\mathbf{C_7}-C$	The central C_7 atom is bonded to two C atoms
8	 $C^b-\underset{\overset{\vert}{O}}{\mathbf{C_8^b}}-C^b$	The central C_8^b atom is bonded to two C^b and one O atoms
9	$C^b-\mathbf{O}$	The central O atom is bonded to one C^b atom

Table 17. Values of the corrections parameters, x_1–x_9, and the coefficients *a*, *b*, and *c* for the improved model

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9	*a*	*b*	*c*
0.6198	0.5934	0.7245	0.2346	0.4256	0.5157	0.3836	0.9956	0.9777	780.9	1055.5	28.2

Thus, the best model is expressed as Equation (16):

$$y = a\sum\left(w_{ij}\right)^{-1} + \\ +b\sum\left(\left(w_{ii}+x_n\right)\times\left(w_{jj}+x_m\right)\right)^{\frac{1}{2}}+c, \quad (16)$$

where *n* and *m* are the numbers of the vertex classes containing the corresponding vertices, *i* and *j*. The values of the corrections, x_n and x_m, as well as the coefficients *a*, *b*, and *c* were obtained from Table 17. The summation in each sum is for all edges (*i*,*j*) in MG.

Table 18 presents some statistical parameters of the models for the four cases (initial/refined models; training/test samples).

According to Table 18, the introduction of the corrections to w_{ii} of MG significantly improved the initial model (on all characteristics). Thus, an equation of the form of Equation (16) was more accurate than Equation (15) in reflecting the correlation between the structures and retention indices of alkylphenols.

Table 18. Some statistical parameters of the initial/modified models of the training/test samples for the retention indices of alkylphenols

Statistical parameters of the model	Initial model (without the corrections of w_{ii} of MG)		Modified model (with the corrections of w_{ii} of MG)	
	Training sample	Test sample	Training sample	Test sample
s	36.92	30.37	15.03	16.18
R	0.934	0.904	0.989	0.974
δ_{avg}	1.94%	2.01%	0.72%	1.00%
δ_{max}	5.86%	5.42%	2.16%	3.17%

CONCLUSIONS

In this study, a general algorithmic method for constructing the mathematical models for the structure–property correlations of organic molecules was developed. The abovementioned models were built based on the statistical analysis of the data of the samples of structures and properties of chemical compounds of some classes, and they have the forms of correlation equations. The method is suitable to any classes of organic compounds and any properties, which can be measured quantitatively.

To represent chemical structures within the framework of the proposed method, special weighted MGs reflecting some elements of the spatial structure of the corresponding molecules were used.

The method is realized in several stages. At the first stage, it was assumed that the desired equation for the structure–property correlation has a well-defined form and depends on several adjustable numerical parameters and selected pair of function on one variable. Additionally, the best pair of functions (according to certain criteria) from a given set, i.e., the best model, is selected at this stage. In addition, the preassigned set of functions can be extended, that promote the increasing of the accuracy of the best selected model.

The second stage is only required if the construction of a more accurate model was desired.

At the second stage, the obtained best model undergoes some modifications, which are aimed at improving its accuracy. Therefore, the MG vertices are initially classified according to the chemical symbols of the corresponding atoms and the patterns of the first-order environment, as well as the edges according to the vertex classes that they connect. Based on the obtained classification of vertices and edges, several numerical "corrections" were introduced to the initial weights of vertices and edges. The final result of the model-building process is an equation of a certain form containing the specific numerical values of all its parameters, thereby allowing the calculation of the value of y for any compound of a given class.

Notably, at the second stage, the modeling can be restricted only to the classification of the MG vertices, because the further classification of the edges is only required if the resulting model (based on the classification of the vertices) is not sufficiently accurate. In this case, the new model might be better than the previous one on the training set and worse on the test set. Let us indicate one more method of improving the model obtained at the second stage through the classification of the MG vertices described above—the more detailed classification of the vertices, e.g., according to the pictures of the second-order environment.

Additionally, the paper presents examples of the application of the developed method for constructing models of the structure–property correlations of specific properties and classes of compounds, thereby demonstrating its effectiveness. Moreover, the feasibility of introducing the second stage in this method was also analyzed.

Models of structure–property correlations (built according to the above method), which have sufficiently high quality, can be employed to calculate the properties of compounds for which there are no experimental data.

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Authors' contribution

All authors equally contributed to the research work.

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