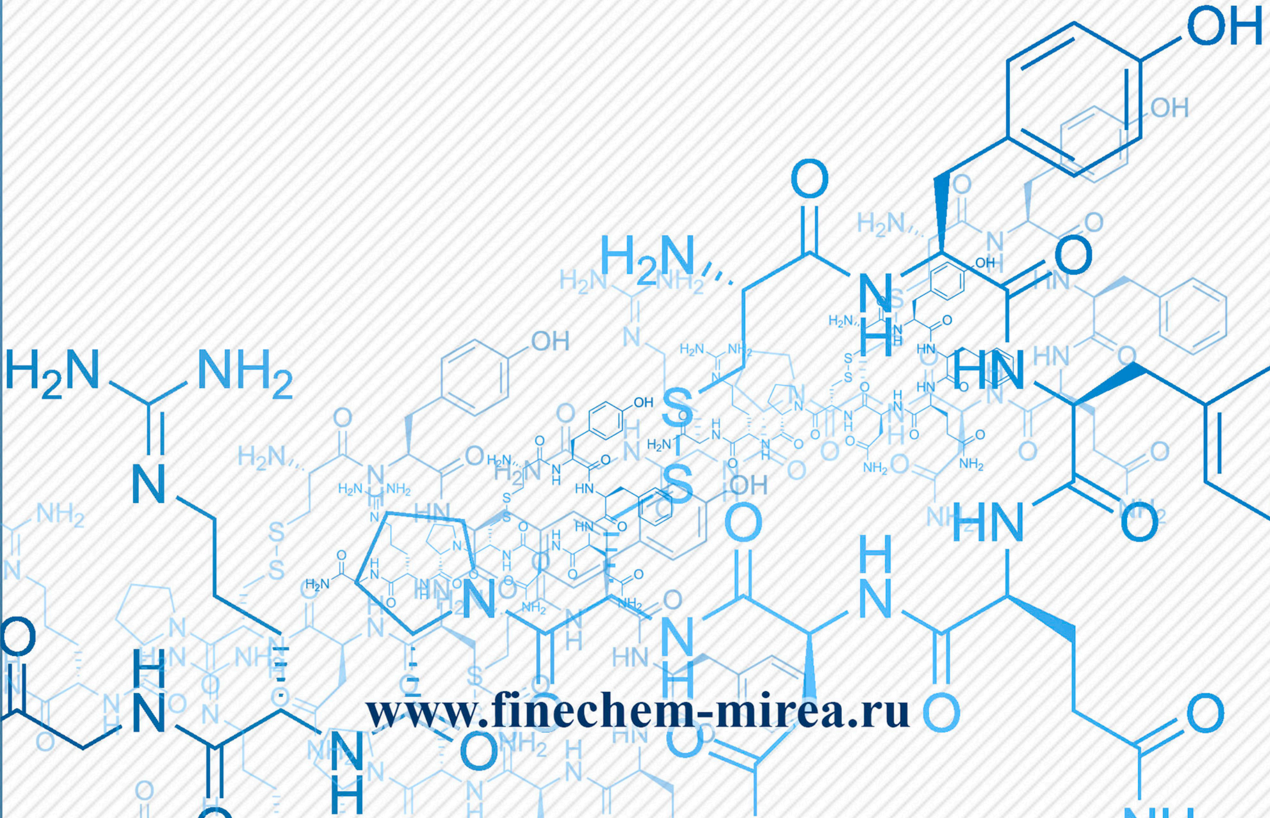
ISSN 2686-7575 (Online)

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
- Biochemistry and Biotechnology
- 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



17(1)

2022

www.finechem-mirea.ru

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Tonkie Khimicheskie Tekhnologii =
Fine Chemical Technologies
Vol. 17, No. 1, 2022

Тонкие химические технологии =
Fine Chemical Technologies
Том 17, № 1, 2022

https://doi.org/10.32362/2410-6593-2022-17-1
www.finechem-mirea.ru

https://doi.org/10.32362/2410-6593 ***www.finechem-mirea.ru***

Tonkie Khimicheskie Tekhnologii = Fine Chemical Technologies
2022, vol. 17, no. 1

The peer-reviewed scientific and technical journal Fine Chemical Technologies highlights the modern achievements of fundamental and applied research in the field of fine chemical technologies, including theoretical bases of chemical technology, chemistry and technology of medicinal compounds and biologically active substances, organic substances and inorganic materials, biochemistry and biotechnology, synthesis and processing of polymers and polymeric composites, analytical and mathematical methods and information systems in chemistry and chemical technology.

Founder and Publisher

Federal State Budget
Educational Institution of Higher Education
"MIREA – Russian Technological University"
78, Vernadskogo pr., Moscow, 119454, Russian Federation.
Publication frequency: bimonthly.
The journal was founded in 2006. The name was Vestnik MITHT until 2015 (ISSN 1819-1487).

The journal is included into the List of peer-reviewed science press of the State Commission for Academic Degrees and Titles of the Russian Federation.
The journal is indexed:
SCOPUS, DOAJ, Chemical Abstracts, Science Index, RSCI, Ulrich's International Periodicals Directory

86, Vernadskogo pr., Moscow, 119571, Russian Federation.
Phone: +7(495) 246-05-55 (#2-88)
E-mail: *seredina@mirea.ru*

Registration Certificate ПИ № ФС 77–74580, issued on December 14, 2018 by the Federal Service for Supervision of Communications, Information Technology, and Mass Media of Russia

The subscription index of *Pressa Rossii*: **36924**

Тонкие химические технологии = Fine Chemical Technologies
2022, том 17, № 1

Научно-технический рецензируемый журнал «Тонкие химические технологии» освещает современные достижения фундаментальных и прикладных исследований в области тонких химических технологий, включая теоретические основы химической технологии, химию и технологию лекарственных препаратов и биологически активных соединений, органических веществ и неорганических материалов, биохимию и биотехнологию, синтез и переработку полимеров и композитов на их основе, аналитические и математические методы и информационные системы в химии и химической технологии.

Учредитель и издатель

федеральное государственное бюджетное
образовательное учреждение высшего образования
«МИРЭА – Российский технологический университет»
119454, РФ, Москва, пр-кт Вернадского, д. 78.
Периодичность: один раз в два месяца.
Журнал основан в 2006 году. До 2015 года издавался под названием «Вестник МИТХТ» (ISSN 1819-1487).

Журнал входит в Перечень ведущих рецензируемых научных журналов ВАК РФ.
Индексируется:
SCOPUS, DOAJ, Chemical Abstracts, РИНЦ (Science Index), RSCI, Ulrich's International Periodicals Directory

119571, Москва, пр. Вернадского, 86, оф. Л-119.
Тел.: +7(495) 246-05-55 (#2-88)
E-mail: *seredina@mirea.ru*

Свидетельство о регистрации СМИ: ПИ № ФС 77-74580 от 14.12.2018 г. выдано Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор)

Индекс по Объединенному каталогу «Пресса России»: **36924**

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blokhin@bsu.by

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ivanov_i@mirea.ru.

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aiv@ibch.ru.

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Dr. Sci. (Chem.), Professor, A.N. Nesmeyanov Institute
of Organoelement Compounds of the RAS, Moscow,
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Scopus Author ID 7101971167, ResearcherID AAF-8122-2019
https://orcid.org/0000-0003-4778-5872
blokhin@bsu.by

Верёвкин Сергей Петрович – д.т.н., профессор
Университета г. Росток, Росток, Германия.
Scopus Author ID 7006607848, ResearcherID G-3243-2011,
https://orcid.org/0000-0002-0957-5594,
sergey.verevkin@uni-rostock.de.

Жижин Константин Юрьевич – член-корр.
Российской академии наук (РАН), д.х.н., профессор,
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Scopus Author ID 6701495620, ResearcherID C-5681-2013,
http://orcid.org/0000-0002-4475-124X,
kyuzhizhin@igic.ras.ru.

Иванов Игорь Владимирович – д.х.н., профессор,
МИРЭА – Российский технологический университет,
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Scopus Author ID 34770109800, ResearcherID I-5606-2016,
http://orcid.org/0000-0003-0543-2067,
ivanov_i@mirea.ru.

Кардона Карлос Ариэль – PhD, профессор
Национального университета Колумбии, Манизалес, Колумбия.
Scopus Author ID 7004278560,
http://orcid.org/0000-0002-0237-2313,
ccardonaal@unal.edu.co.

Койфман Оскар Иосифович – член-корр. РАН,
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Российская Федерация.
Scopus Author ID 6602070468, ResearcherID R-1020-2016,
http://orcid.org/0000-0002-1764-0819,
president@isuct.ru.

Крутько Эльвира Тихоновна – д.т.н., профессор
Белорусского государственного технологического университета,
Минск, Беларусь.
Scopus Author ID 6602297257,
ela_krutko@mail.ru.

Мирошников Анатолий Иванович – академик РАН,
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aiv@ibch.ru.

Музафаров Азиз Мансурович – академик РАН,
д.х.н., профессор, Институт элементоорганических
соединений им. А.Н. Несмеянова РАН, Москва,
Российская Федерация.
Scopus Author ID 7004472780, ResearcherID G-1644-2011,
https://orcid.org/0000-0002-3050-3253,
aziz@ineos.ac.ru.

Ivan A. Novakov – Academician at the RAS,
Dr. Sci. (Chem.), Professor, President of the Volgograd
State Technical University, Volgograd,
Russian Federation.
Scopus Author ID 7003436556, ResearcherID I-4668-2015,
http://orcid.org/0000-0002-0980-6591,
president@vstu.ru.

Alexander N. Ozerin – Corresponding Member of the RAS,
Dr. Sci. (Chem.), Professor, Enikolopov Institute
of Synthetic Polymeric Materials of the RAS,
Moscow, Russian Federation.
Scopus Author ID 7006188944, ResearcherID J-1866-2018,
https://orcid.org/0000-0001-7505-6090,
ozerin@ispm.ru.

Tapani A. Pakkanen – PhD, Professor, Department
of Chemistry, University of Eastern Finland, Joensuu,
Finland.
Scopus Author ID 7102310323,
tapani.pakkanen@uef.fi.

Armando J.L. Pombeiro – Academician at the Academy
of Sciences of Lisbon, PhD, Professor, President of the Center
for Structural Chemistry of the Higher Technical Institute
of the University of Lisbon, Lisbon, Portugal.
Scopus Author ID 7006067269, ResearcherID I-5945-2012,
https://orcid.org/0000-0001-8323-888X,
pombeiro@ist.utl.pt.

Dmitrii V. Pyshnyi – Corresponding Member of the RAS,
Dr. Sci. (Chem.), Professor, Institute of Chemical Biologyand
Fundamental Medicine, Siberian Branch of the RAS,
Novosibirsk, Russian Federation.
Scopus Author ID 7006677629, ResearcherID F-4729-2013,
https://orcid.org/0000-0002-2587-3719,
pyshnyi@niboch.nsc.ru.

Alexander S. Sigov – Academician at the RAS,
Dr. Sci. (Phys. and Math.), Professor, President
of MIREA – Russian Technological University, Moscow,
Russian Federation.
Scopus Author ID 35557510600, ResearcherID L-4103-2017,
sigov@mirea.ru.

Alexander M. Toikka – Dr. Sci. (Chem.), Professor,
Institute of Chemistry, Saint Petersburg State University,
St. Petersburg, Russian Federation.
Scopus Author ID 6603464176, ResearcherI D A-5698-2010,
http://orcid.org/0000-0002-1863-5528,
a.toikka@spbu.ru.

Andrzej W. Trochimczuk – Dr. Sci. (Chem.),
Professor, Faculty of Chemistry, Wrocław University
of Science and Technology, Wrocław, Poland.
Scopus Author ID 7003604847,
andrzej.trochimczuk@pwr.edu.pl.

Aslan Yu. Tsivadze – Academician at the RAS,
Dr. Sci. (Chem.), Professor, A.N. Frumkin Institute
of Physical Chemistry and Electrochemistry of the RAS,
Moscow, Russian Federation.
Scopus Author ID 7004245066, ResearcherID G-7422-2014,
tsiv@phyche.ac.ru.

Новаков Иван Александрович – академик РАН,
д.х.н., профессор, президент Волгоградского
государственного технического университета, Волгоград,
Российская Федерация.
Scopus Author ID 7003436556, ResearcherID I-4668-2015,
http://orcid.org/0000-0002-0980-6591,
president@vstu.ru.

Озерин Александр Никифорович – член-корр. РАН,
д.х.н., профессор, Институт синтетических
полимерных материалов им. Н.С. Ениколопова РАН,
Москва, Российская Федерация.
Scopus Author ID 7006188944, ResearcherID J-1866-2018,
https://orcid.org/0000-0001-7505-6090,
ozerin@ispm.ru.

Пакканен Тапани – PhD, профессор, Департамент
химии, Университет Восточной Финляндии, Йоенсуу,
Финляндия.
Scopus Author ID 7102310323,
tapani.pakkanen@uef.fi.

Помбейро Армандо – академик Академии наук
Лиссабона, PhD, профессор, президент Центра
структурной химии Высшего технического института
Университета Лиссабона, Португалия.
Scopus Author ID 7006067269, ResearcherID I-5945-2012,
https://orcid.org/0000-0001-8323-888X,
pombeiro@ist.utl.pt.

Пышный Дмитрий Владимирович – член-корр.РАН,
д.х.н., профессор, Институт химической биологии
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Новосибирск, Российская Федерация.
Scopus Author ID 7006677629, ResearcherID F-4729-2013,
https://orcid.org/0000-0002-2587-3719,
pyshnyi@niboch.nsc.ru.

Сигов Александр Сергеевич – академик РАН,
д.ф.-м.н., профессор, президент МИРЭА – Российского
технологического университета, Москва,
Российская Федерация.
Scopus Author ID 35557510600, ResearcherID L-4103-2017,
sigov@mirea.ru.

Тойкка Александр Матвеевич – д.х.н., профессор,
Институт химии, Санкт-Петербургский государственный
университет, Санкт-Петербург, Российская Федерация.
Scopus Author ID 6603464176, Researcher ID A-5698-2010,
http://orcid.org/0000-0002-1863-5528,
a.toikka@spbu.ru.

Трохимчук Анджей – д.х.н., профессор,
Химический факультет Вроцлавского политехнического
университета, Вроцлав, Польша.
Scopus Author ID 7003604847,
andrzej.trochimczuk@pwr.edu.pl.

Цивадзе Аслан Юсупович – академик РАН,
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Scopus Author ID 7004245066, ResearcherID G-7422-2014,
tsiv@phyche.ac.ru.

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ХИМИЯ И ТЕХНОЛОГИЯ ОРГАНИЧЕСКИХ ВЕЩЕСТВ

ISSN 2686-7575 (Online)

https://doi.org/10.32362/2410-6593-2022-17-1-7-17

UDC 661.11+547.427.1

RESEARCH ARTICLE

Features of the synthesis of pentaerythritol esters and carboxylic acids of aliphatic isomeric structure

Vladimir V. Emelyanov, Eugen L. Krasnykh✉, Dmitriy A. Fetisov, Svetlana V. Levanova, Vladimir A. Shakun

Samara State Technical University, Samara, 443100 Russia
✉Corrresponding author, e-mail: ekras73@mail.ru

Abstract

Objectives. *Due to their structures, pentaerythritol esters have a number of appealing properties such as high viscosity index when used as oils and excellent compatibility with polyvinyl chloride when used as plasticizers. For the production of pentaerythritol and carboxylic acids, natural gas can be used as a feedstock, which implies a strategic development of the petrochemical industry, a decrease in the amount of gas used for combustion, and its applications for the production of chemical products.*
Methods. *The synthesis process was conducted in a self-catalysis mode with excess acids in a molar ratio of 8:1 and in the presence of a solvent (toluene) of ~30% per reaction mass. This ensures a uniform distillation of the reaction water at a constant temperature of 100–110°C, a decrease in the side reaction products, and an increase in process selectivity. The products from the reaction mass were isolated by vacuum distillation, and identification of all the synthesized tetraesters was performed by chromatography–mass spectrometry analysis.*
Results. *This work proposes options for optimizing the conditions of the thermal esterification of pentaerythritol with isomeric monocarboxylic acids (isobutyric, isovaleric, pivalic, and 2-ethylhexanoic acids) that have different reactivities due to their structures. Methods for isolating tetraesters of pentaerythritol and corresponding acids have been developed. The characteristics of the main series of ions of tetraesters of pentaerythritol and aliphatic isomeric acids C_4–C_8 in the mass spectra were obtained.*

Conclusions. *The yields of tetraesters were at 95%–96% of the theoretical value, and product purity was >99.6%. The resulting target products (tetraesters) were characterized by relative color stability, where the maximum degree of color after cleaning was less than 20 units according to Hazen (180 units for tetra-2-ethylhexnoate), which corresponds to the standards in GOST 29131-91 (ISO 2211-73). The esterification rates were compared, and it was shown that the quantitative yields of isomeric tetraesters at 100–110 °C were achieved in 12–15 h for isobutyric and isovaleric acids, 25–27 h for 2-ethyl-hexanoic acid, and ~40 h for pivalic acid.*

Keywords: *pentaerythritol, carboxylic acids, esters, esterification, gas chromatography–mass spectrometry*

For citation: Emelyanov V.V., Krasnykh E.L., Fetisov D.A., Levanova S.V., Shakun V.A. Features of the synthesis of pentaerythritol esters and carboxylic acids of aliphatic isomeric structure. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(1):7–17 (Russ., Eng.). https://doi.org/10.32362/2410-6593-2022-17-1-7-17

НАУЧНАЯ СТАТЬЯ

Особенности синтеза сложных эфиров пентаэритрита и алифатических карбоновых кислот изомерного строения

В.В. Емельянов, Е.Л. Красных✉, Д.А. Фетисов, С.В. Леванова, В.А. Шакун

Самарский государственный технический университет, Самара, 443100 Россия
✉Автор для переписки, e-mail: ekras73@mail.ru

Аннотация

Цели. *Сложные эфиры пентаэритрита за счет своей структуры обладают рядом привлекательных свойств: высоким индексом вязкости при их использовании в качестве масел и отличной совместимостью с поливинилхлоридными (ПВХ) полимерами при их использовании в качестве пластификаторов. При этом исходным сырьем для производства как пентаэритрита, так и карбоновых кислот может служить природный газ, что актуально с точки зрения снижения объемов газа, направляемого на сжигание, и его использование в производстве химической продукции. Цель работы – разработка новых методов синтеза тетраэфиров пентаэритрита и алифатических изомерных кислот* C_4*–*C_8*.*
Методы. *Процесс проводили в режиме самокатализа при избытке кислоты в мольном соотношении 8:1, а также в присутствии растворителя (толуола) ~30% на реакционную массу, обеспечивающего равномерный отгон реакционной воды при постоянной температуре 100–110 °С, уменьшение продуктов побочных реакций и повышение селективности процесса. Продукты из реакционной массы выделяли методом вакуумной ректификации. Идентификация всех синтезированных тетраэфиров проведилась с использованием хроматомасс-спектрометрического анализа.*
Результаты. *В работе предложены варианты оптимизации условий термической этерификации пентаэритрита изомерными монокарбоновыми кислотами (изомасляной, изовалериновой, пивалевой, 2-этилгексановой), обладающими за счет своей структуры различной реакционной способностью. Разработаны методики выделения тетраэфиров пентаэритрита и соответствующих кислот. Получены характеристики основных серий ионов тетраэфиров пентаэритрита и алифатических изомерных кислот* C_4*–*C_8 *в масс-спектрах.*

Выводы. *В предложенных условиях проведения процесса выход тетраэфиров составил 95–96% от теоретического с чистотой не менее 99.6%. Полученные целевые продукты (тетраэфиры) характеризуются относительной цветостабильностью: максимальная степень окрашенности после очистки составляет не более 20 ед. по Хазену (для тетра-2-этилгексаноата – 180), что соответствует ГОСТ 29131-91 (ИСО 2211-73). Количественные выходы изомерных тетраэфиров при 100–110 °С достигаются: за 12–15 ч для изомасляной и изовалериановой кислоты, 25–27 ч для 2-этил-гексановой и ~40 ч для пивалевой кислоты.*

Ключевые слова: *пентаэритрит, карбоновые кислоты, сложные эфиры, этерификация, хромато-масс спектрометрия*

Для цитирования: Емельянов В.В., Красных Е.Л., Фетисов Д.А., Леванова С.В., Шакун В.А. Особенности синтеза сложных эфиров пентаэритрита и алифатических карбоновых кислот изомерного строения. *Тонкие химические технологии.* 2022;17(1):7–17. https://doi.org/10.32362/2410-6593-2022-17-1-7-17

INTRODUCTION

Pentaerythritol (PE) esters and carboxylic acids of aliphatic structure have a high flash point (>200°C) and attractive values of viscosity index (≥135) and flow temperature [1, 2]. An important feature of these compounds is their performance at low temperatures, including in Arctic conditions [3, 4]. The properties of tetraesters depend on the chemical nature of the acid residue and the possibility of combining various acid residues. It is known that solid PE esters of linear fatty acids C_{16}–C_{18} are recommended as components of technical lubricants, cosmetics, and pharmaceutical preparations [2]. PE tetraesters and aliphatic linear acids with an average chain length of the alkyl group (C_5–C_9) correspond to the scarce lubricating oils of the 5th group and have plasticizing properties [3, 5, 6].

Of particular interest are products obtained using isomeric acids for the esterification of PE. Isostructured tetraesters with a molecular weight from 300 to 900 g/mol have high thermal stability, and their plasticizing effect exceeds the effect of the most common industrial phthalate plasticizers by 1.5–2.0 times [2]. Unfortunately, information on the esterification of PE with isomeric carboxylic acids, which could be used to develop effective methods for obtaining esters with desired properties, is rather scarce.

Analysis of the raw material market showed that the existing natural gas-based oxosynthesis technologies in Russia are at the level of foreign analogs and are able to provide the production of esters with polyatomic alcohols and carboxylic acids as raw materials. The global production of PE in 2018–2021 amounted to ~500000 t/year, and 5% of which is produced in Russia. Unfortunately, the current main consumers of PE in Russia are the manufacturers of inexpensive paint and varnish products, whereas ~60% of Russia's PE is exported to Europe and Asia.[1]

It is important to note here that the process of oxosynthesis for the production of oxygen-containing compounds from natural gas is mainly focused on maximum regioselectivity for products with linear structure, which account for 70%–75% and the rest is isostructured aldehydes that can be used to produce isomeric carboxylic acids [7]. Thus, there is a need to develop new more technologically advanced options for the synthesis of PE tetraesters and aliphatic isomeric acids C_4–C_8.

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[1] *Godovoi otchet kompanii "Metafraks" (Annual report of the Metafrax company).* 2018. 124 p. (in Russ.). URL: https://metafrax.ru/files/disclosure_documents/10_RU_1597244243.pdf. Accessed December 10, 2022.

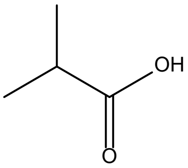
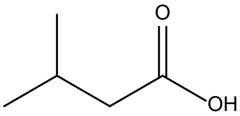
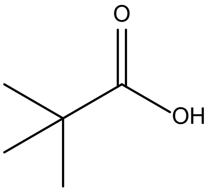
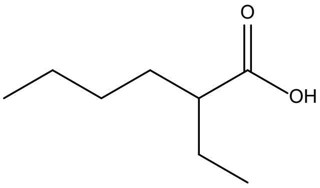
EXPERIMENTAL

Commercial samples of PE and isomeric aliphatic acids with a purity of at least 97 wt % (*Sigma-Aldrich*, USA and *Vekton*, Russia) were used as initial reagents (Table 1).

The design of the reaction units of the process depends on the type of the catalyst used. Three variants of the industrial esterification process are known: self-catalysis, homogeneous catalysis in the presence of mineral acids, and heterogeneous catalysis using ion-exchange resins [8]. The possibility of using any of the listed catalysis options is ambiguous, especially in the presence of fragments in the molecules of the initial compounds responsible for the appearance of steric and/or induction effects that affect the speed of the process [9].

In the conditions of self-catalysis, we are dealing with a slow reversible reaction proceeding by a carbonium-ion mechanism. The use of mineral acids can increase the reaction rate tenfold [9]. However, there are risks of adverse reactions such as dehydration and tarring, which lead to the formation of colored samples (Hazen color reaches 500 units at the maximum permissible according to GOST 29131-91[2] from 20 to 80–100 units for esters) [10, 11]. In this regard, it is necessary to conduct a set of measures for the purification of target products, which is characterized by the complexity of the technology and the use of expensive reagents [10, 11]. Heterogeneous catalysis using cation exchange resins has undeniable technological advantages of less corrosion, ease of separation from the reaction mass, and organization of continuous processes over homogeneous acid catalysis especially for low-molecular reagents [12, 13]. However, the disadvantage of this approach is the more stringent process conditions, where higher reaction temperature and amount of catalyst are required. This leads to tarring of the reaction mass and a decrease in the color stability

Table 1. Characteristics of the acids used

No.	Acid name	Formula	T_{bp}, °C	Dissociation constants pK
1	Isobutyric acid / 2-methylpropanoic		155.0	4.86
2	Isovaleric / 3-methylpropanoic		176.5	4.78
3	Pivalic / 2,2-dimethylpropanoic		163.8	5.05
4	2-Ethylhexanoic		227.0	–

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[2] GOST 29131-91 (ISO 2211-73) Liquid chemical products. Measurement of color in Hazen units (platinum-cobalt scale). Moscow: IPK Izd. standartov; 2004 (in Russ.).

of the target products, which sharply limit the possible areas of their applications.

Analysis of the available information and results of preliminary studies (conversion, reaction time, quality of the samples obtained, and stability of the reaction mass) resulted to the use of the self-catalysis mode for the esterification process. Table 1 shows that the acid strength values of isomeric acids are similar. Their pK values are comparable and are between the first and second stage of the dissociation of orthophosphoric acid (pK_1 = 2.12, pK_2 = 7.2), which is widely used in industrial homogeneous catalysis.

In the synthesis of isomeric PE tetraesters, the method of thermal esterification under self-catalytic conditions for linear carboxylic acids C4–C7 [5] served as the basis. To overcome thermodynamic limitations, the process was carried out in the presence of excess acids at a molar ration of 8:1 to achieve pseudo-zero order reaction and in the presence of a solvent (toluene) of ~30% of the reaction mass for uniform distillation of reaction water at a boiling point of azeotrope 100–110°C. The reaction proceeds without abrupt temperature increase and with high selectivity. The maximum degree of color of the reaction mass is 300–350 units according to Hazen [12].

The target products—tetraisobutyrate and tetrapivalate—are solid crystalline substances. After distillation of azeotrope (toluene + water) and excess acids (vacuum distillation), solid esters were isolated by recrystallization using methanol (for tetraisobutyrate) and acetonitrile (for tetrapivalate). The masterbatch solutions were partially distilled after filtration (fractional recrystallization method), which made it possible to reduce the loss of target products by up to 5%. The reaction mass was analyzed by standard chemical and physicochemical methods [5].

Purification of liquid tetraisovalerate was conducted by vacuum distillation (fraction selection at 290–298°C (26 mmHg)). Due to the high boiling point of tetra-2-ethylhexanoate, the methanol extraction method was used after distillation of unreacted carboxylic acids in vacuum. After the addition of methanol, the resulting mixture was stirred at elevated temperatures, while no side reaction of transesterification was observed. Then, the mixture was kept at negative temperatures for 12 h. After delamination, the product was separated by decantation followed by evaporation of the solvent residues. The last stage of purification of the target product, if necessary, was clarification on bentonite clay, according to the method we used by in our previous work [5]. The return of solvent and excess acids to the cycle helps to minimize losses during synthesis. The purity of the obtained tetraesters was >99%.

Identification of the obtained mixtures and purity of the products were determined by gas chromatography–mass spectrometry (GC–MS) using an Agilent 6850 gas chromatograph (*Agilent Technologies*, USA) that was equipped with an Agilent HP-5MS capillary column (30 m × 250 µm × 0.25 µm), an Agilent 5975C VL MSD mass selective detector, an ionizing voltage of 70 eV, and a NIST 2017 v. 2.3 spectra database.

The melting point was measured in accordance with GOST 33454-2015[3]. The crushed solid samples were driven into a capillary sealed on one side, which has an internal diameter of ~1 mm and a wall thickness of about 0.2–0.3 mm. The level of filling with the test substance was at the 3 mm. Temperature was fixed and monitored using a mercury thermometer (error ± 0.1°C). Temperature measurement was carried out in a container with a circulating coolant (polymethylsiloxane PMS-200), in which the tip of the thermometer containing a mercury ball was immersed. The heating rate was about 3°C/min until a temperature less than 10°C of the estimated melting point of the compound under study was reached. Afterwards, the heating rate was reduced to 1°C/min, while the capillary was immersed in the container so that it came in contact with the middle of the mercury bulb of the thermometer.

Liquid samples were loaded into a test tube and placed in a container with a refrigerant (methanol), and the mixture was subjected to constant stirring. An immersion Huber cryostat equipped with a cooling rate regulator was used to maintain the the tank temperature. The substance was constantly mixed. After crystallization, the compounds were slowly heated at a rate of 1°C/min.

The normal boiling point was determined by the Sivolobov method. The measured sample was loaded into a glass tube with a diameter of 0.5 cm and a capacity of 0.3–0.5 mL. A capillary sealed at one end with an internal diameter of 1 mm was immersed in the liquid. The installation was immersed in a container with a stirred coolant (PMS-200). Heating speed was 1°C/min, and temperature was measured using a mercury thermometer. Boiling point was measured upon the intense release of vapor bubbles from the capillary. Then, the installation was cooled, the test liquid was drawn into the capillary, and the temperature was recorded during this phenomenon. The adjusted boiling point was calculated as the average between the two values.

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[3] GOST 33454-2015. Interstate Standard. Testing of chemicals of environmental hazard. Determination of the melting point/melting range. Moscow: Standartinform; 2019 (in Russ.).

RESULTS AND DISCUSSION

Table 2 indicates the characteristics of all the synthesized PE tetraesters. Of all the compounds in the NIST 2017 database, only the mass spectrum for pentaerythritol tetrapivalate is available. Figure 1 shows the mass spectrum of the electron impact of the PE tetrapivalate obtained in this study. The mass spectrum available in the database is shown in Fig. 2.

As can be seen from the mass spectra in Figs. 1 and 2, the mass characteristic ions and radical ions are identical with a difference only in intensity, which is explained by the difference in the energy of ionizing electrons and the temperature regime of ionization.

The characteristics of the mass spectra of the tetraesters of PE and C_4–C_8 carboxylic acids synthesized in this study are given in Table 3. From the data presented, it can be seen that the mass spectra of the branched C_4–C_8 PE tetraesters and the previously studied mass spectra of linear C_4–C_7 carboxylic acid tetraesters [5] have the following characteristics:

- Absence of a molecular ion associated with rapid cleavage of fragments ($C_nH_{2n-1}O_2^\bullet$ and $C_nH_{2n-1}O^+$) and water molecules.
- An increase in ion intensity $\left[M^{+\bullet}-C_2H_{2n-1}O_2^\bullet\right]^+$ and $\left[M^{+\bullet}-C_nH_{2n-1}O_2^\bullet;-C_nH_{2n-2}O\right]^+$ with an increase in the number of carbon atoms in the carboxylic acid from C_4 to C_8.
- A relative intensity of 100% for $C_nH_{2n-1}O^+$ ion for all the considered compounds with the exception of tetrapivalate and tetra-2-ethylhexanoate in the mass spectra, where the intensity is weakened due to branching in the structure of the remainder of the carboxylic acid, in which there is a rupture of the C–C bonds with intense emission alkyl carbocations ($C_4H_9^+$ for tetrapivalate, $C_4H_9^+$ and $C_7H_{15}^+$ for tetra-2-ethylhexanoate).
- An increase in the intensity of $C_{n-1}H_{2n-1}^+$ in the spectrum due to the presence of branching in the carboxylic acid residue.
- Presence of the $\left[M^{+\bullet}-CH_3^\bullet\right]^+$ ion and the maximum intensity of the $C_4H_9^+$ ion in the tetrapivalate mass spectrum, which is explained by the energetically advantageous decay paths of a tertiary butyl substituent.

The data obtained in this work were used to estimate the rate of formation of esters in the presence of excess isomeric acids in the kinetic regime, which was provided by effective mixing of the reaction mass at a speed of ~1000 rpm and azeotropic removal of reaction water at a temperature of 100–110°C.

Figure 3 shows the experimental results illustrating the successive transformations of PE into mono-, di-, tri-, and tetraesters.

It is known that in the case of comparable acidity values, as in our case, the rate of esterification depends on the volume of alkyl residues associated with the carboxyl group and on the branching at the α-carbon atom of carboxylic acids [14, 15]. Figure 4 shows a comparison of the dependence of the change in the conversion of PE (the total share of unreacted OH groups) as a function time for isomeric acids.

Quantitative yields of isomeric tetraesters (96%) at 100–110°C are achieved in 12–15 h for isobutyric and isovaleric acids, 25–27 h for 2-ethyl-hexanoic acid, and ~40 h for pivalic acid. The esterification rates of normal valeric and isovaleric acids are comparable.

Table 2. Properties of the resulting products

PE tetraester	T_{bp}, °C	T_{cr}, °C	APHA color	Purity
Tetraisobutyrate	317 ± 2	56	20 ± 2	99.6
Tetraisovalerate	367	−7	18 ± 1	99.5
Tetrapivalate	265	129	19 ± 2	99.8
Tetra-2-ethylhexanoate	493*	−9	180 ± 10	99.6

Note: T_{bp} is the boiling point, T_{cr} is the crystallization temperature, * the temperature predicted is based on the logarithmic Kovacs retention indices obtained in [15].

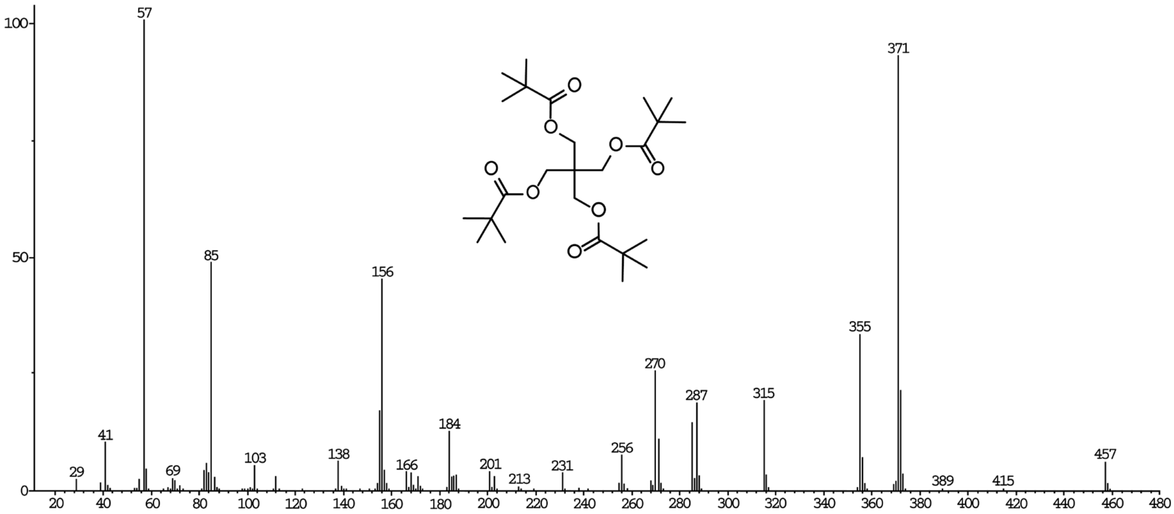


Fig. 1. GC–MS spectrum of the obtained pentaerythritol tetrapivalate.

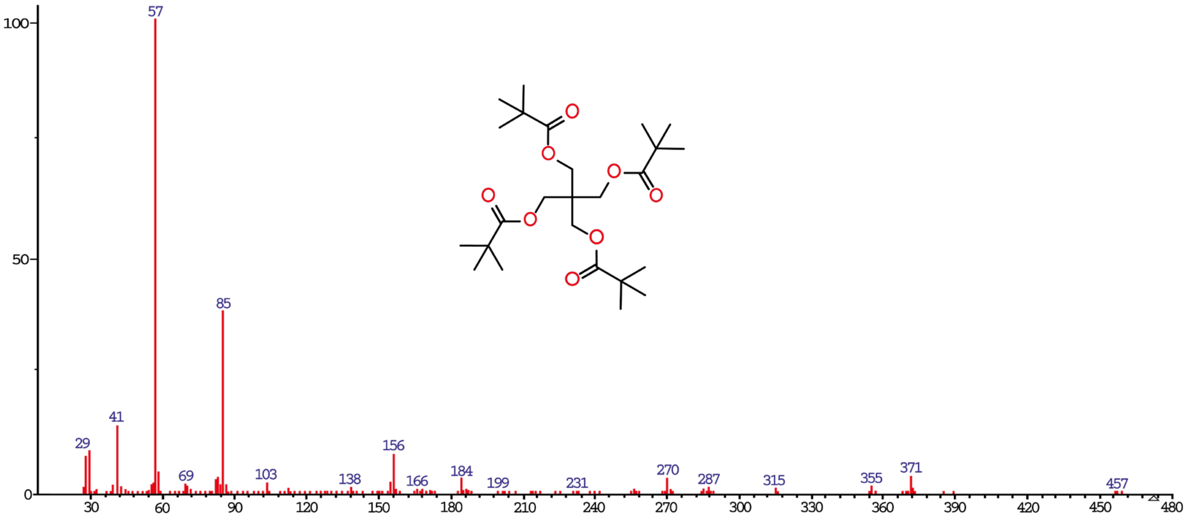


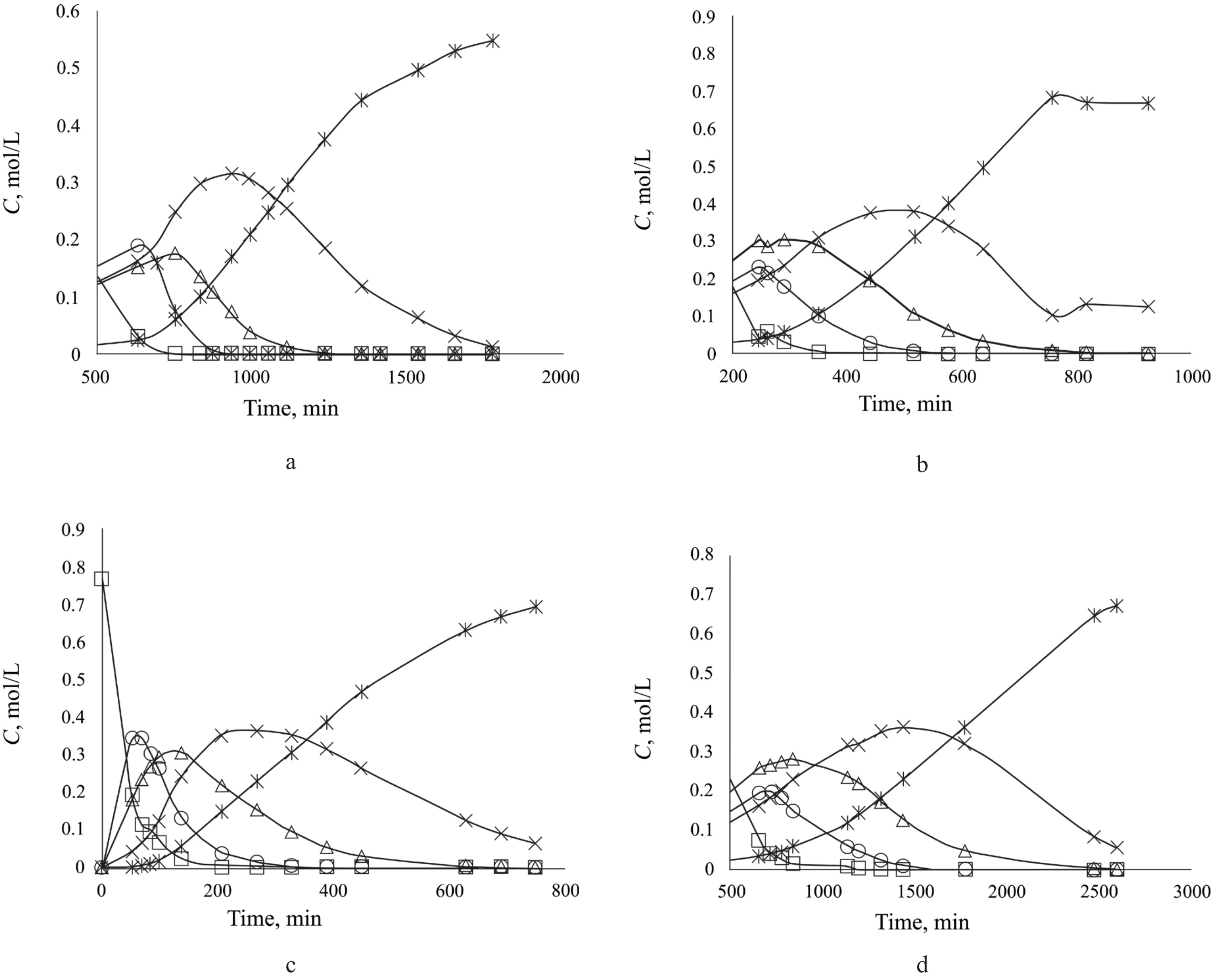
Fig. 2. GC–MS spectrum of pentaerythritol tetrapivalate according to the database.

Table 3. Characterization of the main series of ions in the mass spectra of tetraesters of PE and C_4–C_8 carboxylic acids

Compound	Main series of ions in the mass spectra, 70 eV, *m*/*z*, (structure, % rel.)
Tetraisobutyrate	**416** ($M^{+\bullet}$, 0); **398** ([$M^{+\bullet}$–H_2O]$^+$, 1); **329** ([$M^{+\bullet}$–$C_4H_7O_2^{\bullet}$]$^+$, 30); **313** ([$M^{+\bullet}$–$C_4H_7O_2^{\bullet}$;–CH_4]$^+$, 3); **300** ([$M^{+\bullet}$–$C_4H_7O_2^{\bullet}$; –$CHO^{\bullet}$]$^{+\bullet}$, 1); **259** ([$M^{+\bullet}$–$C_4H_7O_2^{\bullet}$;–C_4H_6O]$^+$, 5); **257** ([$M^{+\bullet}$–$C_4H_7O_2^{\bullet}$;–C_4H_8O]$^+$, 20); **228** ([$M^{+\bullet}$–$C_4H_7O_2^{\bullet}$;–C_4H_8O; –$CHO^{\bullet}$]$^{+\bullet}$, 10); **142** ([$M^{+\bullet}$–$C_4H_7O_2^{\bullet}$;–C_4H_8O; –$CHO^{\bullet}$;–$C_4H_6O_2$]$^{+\bullet}$, 44); **71** ($C_4H_7O^+$, 100); **43** ($C_3H_7^+$, 41)
Tetraisovalerate	**472**($M^{+\bullet}$, 0); 454 ([$M^{+\bullet}$–H_2O]$^+$, 1); **371** ([$M^{+\bullet}$–$C_5H_9O_2^{\bullet}$]$^+$, 73); **355** ([$M^{+\bullet}$–$C_5H_9O_2^{\bullet}$;–CH_4]$^+$, 47); **341** ([$M^{+\bullet}$–$C_5H_9O_2^{\bullet}$;–CH_2O]$^+$, 1); **287** ([$M^{+\bullet}$–$C_5H_9O_2^{\bullet}$;–C_5H_8O]$^+$, 63); **285** ([$M^{+\bullet}$–$C_5H_9O_2^{\bullet}$;–$C_5H_{10}O$]$^+$, 18); **256** ($M^{+\bullet}$–$C_5H_9O_2^{\bullet}$;–$C_5H_{10}O$; –$CHO^{\bullet}$]$^{+\bullet}$, 16); **156** ([$M^{+\bullet}$–$C_5H_9O_2^{\bullet}$;–$C_5H_{10}O$; –$CHO^{\bullet}$;–$C_5H_8O_2$]$^{+\bullet}$, 27); **85** ($C_5H_9O^+$, 100); **57** ($C_4H_9^+$, 41)

Table 3. Continued

Compound	Main series of ions in the mass spectra, 70 eV, *m*/*z*, (structure, % rel.)
Tetrapivalate	**472** ($M^{+\bullet}$, 0); 457 ($[M^{+\bullet}{-}CH_3^\bullet]^+$, 13); **371** ($[M^{+\bullet}{-}C_5H_9O_2^\bullet]^+$, 92); **355** ($[M^{+\bullet}{-}C_5H_9O_2^\bullet;{-}CH_4]^+$, 37); **341** ($[M^{+\bullet}{-}C_5H_9O_2^\bullet;{-}CH_2O]^+$, 0); **287** ($[M^{+\bullet}{-}C_5H_9O_2^\bullet;{-}C_5H_8O]^+$, 18); **285** ($[M^{+\bullet}{-}C_5H_9O_2^\bullet;{-}C_5H_{10}O]^+$, 14); **256** ($[M^{+\bullet}{-}C_5H_9O_2^\bullet;{-}C_5H_{10}O;{-}CHO^\bullet]^{+\bullet}$, 8); **156** ($[M^{+\bullet}{-}C_5H_9O_2^\bullet;{-}C_5H_{10}O;{-}CHO^\bullet;{-}C_5H_8O_2]^{+\bullet}$, 48); **85** ($C_5H_9O^+$, 51); **57** ($C_4H_9^+$, 100)
Tetra-2-ethylhexanoate	**640** ($M^{+\bullet}$, 0); **497** ($[M^{+\bullet}{-}C_8H_{15}O_2^\bullet]^+$, 100); **481** ($[M^{+\bullet}{-}C_8H_{15}O_2^\bullet;{-}CH_4]^+$, 2); **468** ($M^{+\bullet}{-}C_8H_{15}O_2^\bullet;{-}CH_2O]^+$, 16); **371** ($[M^{+\bullet}{-}C_8H_{15}O_2^\bullet;{-}C_8H_{14}O]^+$, 74); **369** ($[M^{+\bullet}{-}C_8H_{15}O_2^\bullet;{-}C_8H_{16}O]^+$, 12); **340** ($[M^{+\bullet}{-}C_8H_{15}O_2^\bullet;{-}C_8H_{16}O;{-}CHO^\bullet]^{+\bullet}$, 8); **198** ($[M^{+\bullet}{-}C_8H_{15}O_2^\bullet;{-}C_8H_{16}O;{-}CHO^\bullet;{-}C_8H_{14}O_2]^{+\bullet}$, 22); **127** ($C_8H_{15}O^+$, 34); **99** ($C_7H_{15}^+$, 26); **57** ($C_4H_9^+$, 50)



a

b

c

d

Fig. 3. Conversion of PE into monoesters (○), diesters (△), triesters (×), and tetraesters (⋇): (a) reaction of 2-ethylhexanoic acid and PE, (b) isobutyric acid and PE, (c) isovaleric acid and PE, and (d) pivalic acid and PE. *C* is the concentration.

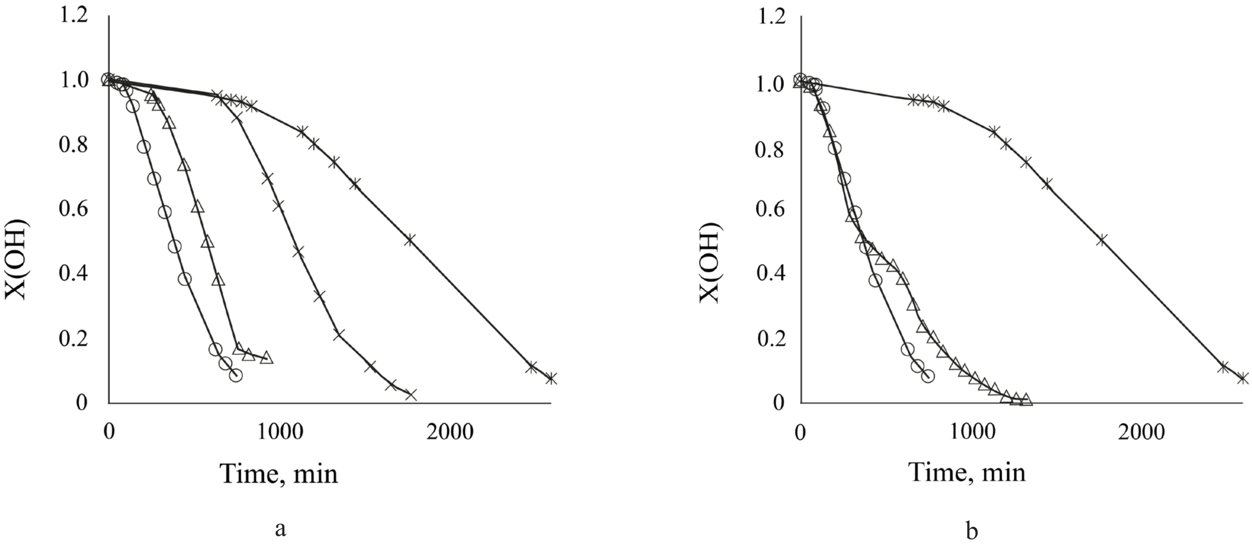


Fig. 4. Dependence of the change in the share of unreacted OH groups as a function of time.
(a) Comparison of the data from this study (for reactions of PE with isovaleric acid (○), pivalic acid (⋇), isobutyric acid (△), and 2-ethylhexanoic acid (×)); (b) comparison of the changes in the share of OH groups for the reactions of PE with valeric acid (△), isovaleric acid (○), and pivalic acid (⋇).

CONCLUSIONS

Methods of synthesis and isolation of complex tetraesters of pentaerythritol and isobutyric, isovaleric, pivalic, and 2-ethylhexanoic acids were developed. The purity of the obtained samples was at least 99.6% with a product yield of 95–96% from the theoretical value. For all the synthesized esters, the characteristics of the main series of PE tetraester ions in the mass spectra were obtained.

Kinetic regularities of the thermal esterification of pentaerythritol by isomeric carboxylic acids were investigated, and it was shown that the quantitative yields of isomeric tetraesters at 100–110°C were achieved in 12–15 h for isobutyric and isovaleric acids, 25–27 h for 2-ethyl-hexanoic acid, and ~40 h for pivalic acid.

The results obtained in this work can be used for predicting the rate of the esterification reaction in the case of using new reagents and as initial information for creating a flexible (complex) technology on a single installation. The transition to a particular product should be performed by replacing raw materials and/or adjusting the operating parameters. This approach makes it possible to diversify the range of products, thus adapting to market conditions.

Acknowledgments

The study was supported by the Russian Foundation for Basic Research, project No. 20-38-90141.

Authors' contribution

V.V. Emelyanov – conducting the experiment, data processing, and analysis of the results;

E.L. Krasnykh – analysis of the experimental data and writing the article;

D.A. Fetisov – conducting the experiment, data processing, and analysis of the results;

S.V. Levanova – analysis of the experimental data and writing the article;

V.A. Shakun – performance of chromato-mass-spectrometry research and analysis of the results.

The authors declare no conflicts of interest.

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About the authors:

Vladimir V. Emelyanov, Postgraduate Student, Technology of Organic and Petrochemical Synthesis Department, Samara State Technical University (244, Molodogvardeyskaya ul., Samara, 443100, Russia). E-mail: dragonage2rus@mail.ru. http://orcid.org/0000-0002-6228-5713

Eugen L. Krasnykh, Dr. Sci. (Chem.), Associate Professor, Head of the Technology of Organic and Petrochemical Synthesis Department, Samara State Technical University (244, Molodogvardeyskaya ul., Samara, 443100, Russia). E-mail: ekras73@mail.ru. http://orcid.org/0000-0002-3886-1450

Dmitriy A. Fetisov, Master Student, Technology of Organic and Petrochemical Synthesis Department, Samara State Technical University (244, Molodogvardeyskaya ul., Samara, 443100, Russia). E-mail: fetis.dim@gmail.com. http://orcid.org/0000-0002-5438-2919

Svetlana V. Levanova, Dr. Sci. (Chem.), Professor, Technology of Organic and Petrochemical Synthesis Department, Samara State Technical University (244, Molodogvardeyskaya ul., Samara, 443100, Russia). E-mail: kinterm@mail.ru. http://orcid.org/0000-0003-2539-8986

Vladimir A. Shakun, Cand. Sci. (Chem.), Associate Professor, Technology of Organic and Petrochemical Synthesis Department, Samara State Technical University (244, Molodogvardeyskaya ul., Samara, 443100, Russia). E-mail: shakyh@mail.ru. http://orcid.org/0000-0003-2682-3024

Об авторах:

Емельянов Владимир Владимирович, аспирант кафедры «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» (443100, Россия, г. Самара, ул. Молодогвардейская, д. 244.). E-mail: dragonage2rus@mail.ru. http://orcid.org/0000-0002-6228-5713

Красных Евгений Леонидович, д.х.н, доцент, заведующий кафедрой «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» *(*443100, Россия, г. Самара, ул. Молодогвардейская, д. 244.). E-mail: ekras73@mail.ru. http://orcid.org/0000-0002-3886-1450

Фетисов Дмитрий Александрович, магистрант кафедры «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» *(*443100, Россия, г. Самара, ул. Молодогвардейская, д. 244.). E-mail: fetis.dim@gmail.com. http://orcid.org/0000-0002-5438-2919

Леванова Светлана Васильевна, д.х.н., профессор кафедры «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» *(*443100, Россия, г. Самара, ул. Молодогвардейская, д. 244.). E-mail: kinterm@mail.ru. http://orcid.org/0000-0003-2539-8986

Шакун Владимир Андреевич, к.х.н., доцент кафедры «Технология органического и нефтехимического синтеза» ФГБОУ ВО «Самарский государственный технический университет» *(*443100, Россия, г. Самара, ул. Молодогвардейская, д. 244.). E-mail: shakyh@mail.ru. http://orcid.org/0000-0003-2682-3024

The article was submitted: August 18, 2021; approved after reviewing: October 27, 2021; accepted for publication: February 07, 2022.

Translated from Russian into English by N. Isaeva
Edited for English language and spelling by Enago, an editing brand of Crimson Interactive Inc.

Tonkie Khimicheskie Tekhnologii = Fine Chemical Technologie. 2022;17(1):18–29

CHEMISTRY AND TECHNOLOGY OF ORGANIC SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ОРГАНИЧЕСКИХ ВЕЩЕСТВ

ISSN 2686-7575 (Online)

https://doi.org/10.32362/2410-6593-2022-17-1-18-29

UDC 665.662.2

RESEARCH ARTICLE

Purification of benzene fractions and benzene from unsaturated and sulfur compounds using a novel modified natural clay-based adsorbent

Boris Yu. Malyshkin, Ivan P. Semenov✉, Dmitry S. Sazonov, Igor O. Putenikhin, Elizaveta Yu. Semenikhina

United Catalyst Technologies, Moscow, 117292 Russia
✉Corresponding author, e-mail: i.semenov@united-catalyst.com

Abstract

Objectives. *This study aimed to create a method for purifying benzene fractions using a modified natural clay-based adsorbent, which removes both unsaturated and sulfur compounds from benzene or benzene fractions obtained by pyrolysis of petrochemical raw materials.*
Methods. *Chemical and chromatographic methods were used to conduct flow analyses before and after purification. Testing was conducted under conditions that were similar to industrial conditions. The functional characteristics of the adsorbents (moisture resistance and bulk density) were evaluated by strength tests after wetting with water and by weighing batches of the adsorbents fixed in volume.*
Results. *Three clay-based adsorbent samples were developed, and tested under laboratory conditions. Thereafter, the CS-Sorb-6890 (M) sample—an Ni-modified adsorbent—was tested under experimental industrial conditions. A positive effect was obtained, and a method for purifying benzene fractions (benzene) from sulfur compounds and olefins is proposed.*
Conclusions. *The obtained results revealed that the modified active clay-based adsorbent successfully removed sulfur and unsaturated compounds from the benzene fraction simultaneously. The total sulfur concentration was reduced to 0.00004 wt % after 90% of it was removed. The conversion of the unsaturated compounds reached 100%.*

Keywords: *benzene, benzene fraction, adsorption, purification from impurities, modified clay-based adsorbent*

For citation: Malyshkin B.Yu., Semenov I.P., Sazonov D.S., Putenikhin I.O., Semenikhina E.Yu. Purification of benzene fractions and benzene from unsaturated and sulfur compounds using a novel modified natural clay-based adsorbent. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(1):18–29 (Russ., Eng.). https://doi.org/10.32362/2410-6593-2022-17-1-18-29

НАУЧНАЯ СТАТЬЯ

Очистка бензольной фракции и бензола от непредельных и сернистых соединений новым модифицированным адсорбентом на основе природной глины

Б.Ю. Малышкин, И.П. Семёнов✉, Д.С. Сазонов, И.О. Путенихин, Е.Ю. Семенихина

United Catalyst Technologies, Москва, 117292 Россия
✉Автор для переписки, e-mail: i.semenov@united-catalyst.com

Аннотация

Цели. *Создание способа очистки бензольной фракции (бензола) с помощью модифицированного адсорбента на основе природной глины, который позволит одновременно удалять непредельные и сернистые соединения из бензола или бензольной фракции, полученных пиролизом нефтехимического сырья.*
Методы. *Анализы потоков до и после очистки выполняли химическими и хроматографическими методами. Тестирование проводили в условиях, приближенных к промышленным. Функциональные характеристики адсорбентов (влагостойкость, насыпная плотность) оценивали с помощью испытаний на прочность после смачивания водой и методом взвешивания фиксированных по объему партий адсорбентов.*
Результаты. *Разработаны три образца адсорбента на основе глины, проведено их тестирование в лабораторных условиях, после чего образец CS-Sorb-6890 (M) – адсорбент с нанесенным Ni – прошел испытания в опытно-промышленных условиях. Получен положительный эффект, предложен способ очистки бензольной фракции (бензола) от сернистых соединений и олефинов.*
Выводы. *Достигнутые результаты свидетельствуют о том, что созданный модифицированный адсорбент на основе активной глины успешно удаляет одновременно сернистые и непредельные соединения из бензольной фракции. Удаление общей серы максимально составило 90%, и ее концентрация минимизирована до 0.00004 мас. %. Конверсия непредельных соединений достигла 100%.*

Ключевые слова: *бензол, бензольная фракция, адсорбция, очистка от примесей, модифицированный адсорбент на основе глины*

Для цитирования: Малышкин Б.Ю., Семёнов И.П., Сазонов Д.С., Путенихин И.О., Семенихина Е.Ю. Очистка бензольной фракции и бензола от непредельных и сернистых соединений новым модифицированным адсорбентом на основе природной глины. *Тонкие химические технологии.* 2022;17(1):18–29. https://doi.org/10.32362/2410-6593-2022-17-1-18-29

INTRODUCTION

Benzene is one of the most sought-after substances in the chemical industry, and it is widely used in organic synthesis. Benzene can be obtained via several methods, including pyrolysis of gasoline fractions and separation of pyrocondensate, processing of catalytic reforming products, and coking of coal.

Benzene is mainly produced from petrochemical raw materials, and the volume produced is about 1.1–1.2 mln t/year. *ExxonMobil Chemical* (USA), *Dow Chemical* (USA), and *Shell Chemicals* (USA) are the leading chemical companies in the world. *Angarsk Polymer Plant*, *Gazprom Neftekhim Salavat*, and *Nizhnekamskneftekhim* are the three largest benzene producers in Russia [1].

The benzene–toluene–xylene (BTX) fractions of liquid pyrolysis products are mainly hydrogenated to obtain benzene as the main commercial product [2]. The scheme for petrochemical benzene production (Fig. 1) includes BTX fraction separation, sequential two-stage hydrotreatment for the removal of unsaturated and sulfur compounds, catalytic or thermal hydrodealkylation, product separation in a system of distillation columns, and contact purification of the benzene fraction from unsaturated compounds and resins [3].

The adsorber is the most interesting in terms of the research task. Clay is loaded into this apparatus to separate the benzene fraction from the residual unsaturated and sulfur compounds.

According to GOST 58415-2019, the total sulfur concentration in benzene should not exceed 0.00005 wt %. Simultaneously, the concentration of unsaturated compounds in petrochemical benzene is not directly regulated; only the “sulfuric acid color” indicator and, upon consumer request, the “bromine number” indicator are normalized, both of which indicate the unsaturated compound concentrations.[1]

Petrochemical raw materials contain mercaptans, sulfides, thiophenes, and other sulfur-containing compounds. In most cases, up to 10% of the total amount of initial sulfur remains in the benzene fraction. The most difficult substances to remove are thiophene derivatives. They are concentrated in the benzene fraction because their boiling point coincides with that of gasoline.[2]

Although the benzene production scheme includes a hydrotreating stage for sulfur removal, sulfur compounds can still be found in benzene and benzene fractions, which compromises the commercial product quality. This is due to the fact that hydrogen sulfide present in the benzene fraction after hydrotreatment interacts with olefins and paraffins to form mercaptans under hydrodealkylation reactor conditions:

$$\mathrm{RCH{=}CH_2{+}H_2S \leftrightarrow RCH(SH)CH_3}$$

This nucleophilic addition reaction is reversible, but the equilibrium is predominantly shifted to the right because hydrogen sulfide has a high reactivity [4]. A fine posttreatment of benzene is required because of the newly formed mercaptans, which cause deviations in the total sulfur content, jeopardizing the stable sale of marketable products by the enterprise.

Absorption (extraction) and adsorption methods are used to capture poisons and impurities. The absorption or extraction method is used when the concentration of the absorbed substance in the initial mixture is significant, such as in the case of purifying benzene from thiophene [5]. Since there were minor unsaturated and sulfur compound impurities in the benzene fraction in our study, adsorption—the process of absorbing a substance from a gas or liquid using a solid adsorbent surface layer—was the most appropriate method.

The standard adsorbent for purifying the benzene fraction from unsaturated compounds is active clay, which undergoes alkylation and oligomerization reactions, resulting in unsaturated compounds being converted to alkyl-substituted aromatic compounds or heavy resinous compounds, which are then adsorbed by clay or separated in a benzene separation column.

Attempts have been made to modify clay-based adsorbents in order to purify the benzene fraction. For example, carbon disulfide can be removed from CaA zeolites, while thiophene can be removed from Ni- and Cu-substituted CaX and CaA zeolites according to the following reaction:

$$\text{Zeolite–Ca} + \mathrm{NiSO_4} \rightarrow \text{Zeolite–Ni} + \mathrm{CaSO_4}\downarrow.$$

When the adsorbent is treated with nickel salt, the effectiveness of thiophene purification increases from 4% to 21.3%, while sulfuric acid modification does not have a positive effect [6]. However, there is no evidence that these adsorbents extract both unsaturated compounds and sulfur compounds simultaneously.

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[1] GOST 58415-2019. National Standard of the Russian Federation. Petrochemical Benzene. Specifications. Moscow: Standartinform; 2019.

[2] Glotov A.P. *Obesserivayushchie dobavki k katalizatoram krekinga neftyanogo syr’ya* (*Desulfurizing additives to catalysts for the cracking of petroleum feedstock*): Cand. Sci. Thesis. Moscow: M.V. Lomonosov Moscow State University; 2016. 23 p. (in Russ).

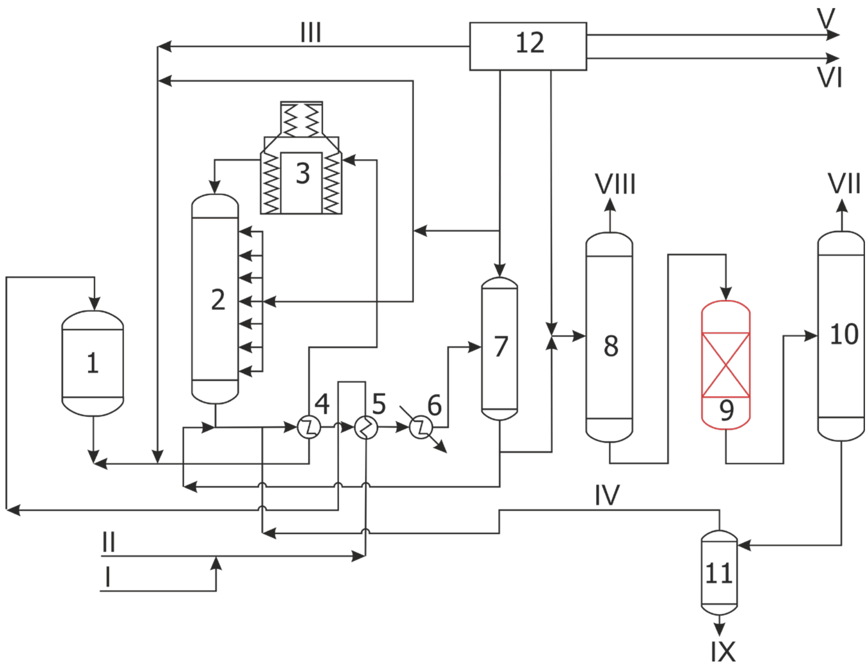

Fig. 1. Schematic of the petrochemical benzene production plant.
(1) Hydrogenation reactor, (2) hydrodealkylation reactor, (3) tubular furnace, (4 and 5) heat exchangers, (6) refrigerator, (7) gas separator, (8) stabilizer, (9) adsorber, (10) benzene recovery column, (11) toluene and biphenyl recovery column, and (12) hydrogen concentration unit.
(I) Raw materials, (II) fresh hydrogen, (III) purified hydrogen, (IV) toluene and diphenyl, (V) methane-enriched gas, (VI) C_{2+} hydrocarbons, (VII) fuel gas, (VIII) benzene, and (IX) resins and heavy hydrocarbons.

There are several reported clay-based adsorbents [7–9], which were modified in an aluminum sulfate solution. Although the adsorbent samples had a high adsorption capacity for unsaturated compounds, they did not remove sulfur compounds from the purified flow of benzene and benzene fractions.

This study aimed to develop a clay-based adsorbent and an application method that will allow it to remove both unsaturated and sulfur compounds from the benzene fraction using one apparatus.

EXPERIMENTAL

Adsorbent preparation

The standard adsorbent for the post-purification of benzene and the benzene fraction was made by drying natural clay, calcining it, isolating the target fraction, and activating it with acid solutions.

Active natural clay was impregnated to prepare the modified adsorbent for sulfur compound removal. Active clays are clays that have been subjected to the complete production cycle, which includes drying, granulation, activation, and calcination. A batch of active natural clay-based adsorbents with a grain size of 0.2–2.5 mm was loaded into an impregnating container. A solution was prepared using soluble inorganic (e.g., nitrates) or organic (e.g., oxalates or lactates) salts of copper, zinc, and nickel to impregnate the adsorbent. The solutions were prepared using distilled water. The concentration of the solutions was selected based on the desired active metal content in the developed adsorbent. The concentrations of the impregnating aqueous solutions of organic and/or inorganic salts of copper, zinc, and nickel ranged from 5 to 400 g per 100 mL, and the ratio of the impregnating solution to the clay mass ranged from 1:2 to 1:10. The salts were selected such that when heated, the acid residue decomposes as the metal or metal oxide is deposited on the adsorbent surface.

The adsorbent batch was impregnated in an impregnating container for 1–2 h at temperatures of 20–80°C. Afterward, the impregnating solution was drained, and the adsorbent was then discharged from the drum. Subsequently, the adsorbent was dried and calcined in an oven at temperatures ranging from 250 to 550°C for 0.5–4.0 h. During calcination at this temperature, the excess of the impregnating solution was removed, while the active metal or its oxide remained on the adsorbent surface. The target adsorbent fraction with a grain size of 0.2–2.5 mm was released after sieving the calcined adsorbent through sieves. This granule size ensured that the adsorbent had an optimal specific surface area and a low pressure drop, increasing the effectiveness of using the adsorbent when it was loaded into the adsorber.

Prepared adsorbent sample test

Laboratory tests of the active clay samples were conducted in a flow unit (Fig. 2).

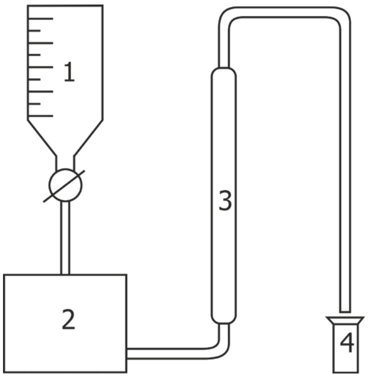

Fig. 2. Diagram of the laboratory setup for testing the adsorbent samples: (1) The model solution container, (2) a pump, (3) an adsorption column, and (4) a receiver.

The setup consists of a receptacle under the model solution (1), a pump (2), a glass adsorption column (3) with an inner diameter of 14 mm and a SCHOTT filter at the bottom of the inert material to fill the column in the form of a glass nozzle with a fraction size of 2–3 mm, and bottles receivers (4) with a sampling volume of 10 mL. The tests were conducted at room temperature (23 ± 2°C). The loaded sample had a volume of 5 mL and a particle size of 0.5–1.0 mm. The sample was precalcined at a temperature of 195°C for 6 h and heated for 30 min to eliminate moisture. The flow rate at the outlet was 0.55 ± 0.05 mL/min. Sampling was carried out for every 8 mL of the solution that passed through the adsorbent. The analyses were performed using titrimetric and gas chromatographic methods. The initial mixture was a mixture of benzene with hexene and propanethiol. Hexene and propanethiol were chosen as representative components for unsaturated and sulfur compound impurities, respectively.

Figure 3 shows the scheme of the installation that was used to test the adsorbent under experimental industrial conditions.

The prepared clay-based adsorbent (550 mL) was loaded into a direct-flow adsorber (1), which was then fed with a hot flow of benzene fraction at a temperature of 170–230°C and pressure of 7.5–28.0 kgf/cm^2. A shut-off valve (2a) was installed on the flow supply line to the adsorber, allowing the supply of the benzene fraction to the reactor to be shut off. The shut-off valve (2b) was used for sampling the initial benzene fraction. Residual resins, unsaturated compounds, and sulfur compounds were removed from the flow of the benzene fraction as it passed through the clay layer. The purified flow from the adsorber (1) was cooled in an air heat exchanger (3). The flow rate was regulated by a control valve (4), which was installed on the outlet line after the heat exchanger. The purified benzene fraction was drained into a canister tank (5). The drain tank (5) was replaced with a measuring tank (6) during sampling or flow measurement.

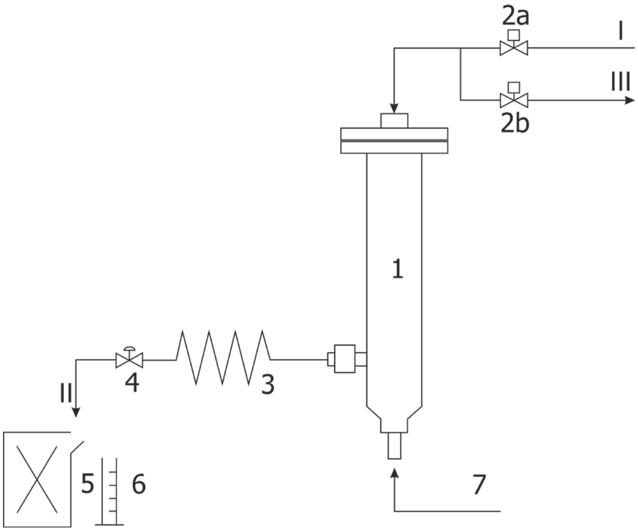

Fig. 3. Pilot installation of adsorbent testing. (1) Adsorber, (2a) shut-off valve in adsorber flow line, (2b) shut-off valve in sampling line, (3) air cooler, (4) valve, (5) drain tank, (6) measuring tank, and (7) inner pocket for thermocouple. (I) The flow from the BTX fraction extraction unit, (II) the purified flow of the benzene fraction, and (III) the flow for sampling the initial BTX fraction.

RESULTS AND DISCUSSION

Laboratory test results

Three samples were created for laboratory studies:

1. CS-Sorb-6891 (S), which is an adsorbent based on active clay with deposited Cu and Zn metals;
2. CS-CL200X, which is an adsorbent based on active clay without metals;
3. CS-Sorb-6890 (M), which is an adsorbent based on active clay with deposited Ni metal.

Table 1 shows the characteristics of the tested adsorbent samples.

Table 2 presents the initial composition of the flow.

Table 3 shows the results obtained under laboratory conditions when the benzene flow was purified with the adsorbents.

As shown in Table 3, the samples demonstrated different abilities in removing sulfur and unsaturated compounds from the model mixture. The CS-Sorb-6891 (S) sample exhibited the highest activity in removing sulfur compounds but did not

Table 1. Characteristics of the adsorbent samples

Indicators	CS-Sorb-6891 (S)	CS-CL200X	CS-Sorb-6890 (M)
Base metals	Cu, Zn	–	Ni
Metal content, %	10	–	10
Free moisture content (calcination at 105°C), wt %	1.0	2.5	4.9
Mass fraction of water (calcination at 195°C), wt %	6.4	5.4	5.4
Bulk density, g/cm^3	0.76	0.81	0.81
Fractional composition, %			
>2.0 mm	8.5	18.4	1.9
2.0–0.25 mm	90.6	81.0	90.2
<0.25 mm	0.9	0.6	7.9

Table 2. Composition of the initial flow of benzene (benzene fraction)

Component	Concentration
Benzene	98.99 wt %
Hexene	1 wt %
2-Propanethiol	21–28 ppm

Table 3. Performance indicators of the adsorbent samples

Sample	Mass of passed raw materials, g	Concentration of sulfur compounds, ppm	Concentration of unsaturated compounds, wt %	Number of removed sulfur compounds, ppm	Number of removed unsaturated connections, wt %
CS-Sorb-6891 (S)	0.00	27.30	0.23	–	–
	98.5	0.65	0.22	26.65	0.02
	150.8	0.53	0.22	26.77	0.02
	216.3	0.57	0.23	26.73	0.00
CS-CL200X	0.00	22.99	0.20	–	–
	85.0	10.95	0.08	12.04	0.12
	98.0	12.26	0.10	10.73	0.10
	131.4	16.72	0.14	6.27	0.06
CS-Sorb-6890 (M)	0.00	28.04	0.34	–	–
	98.4	1.24	0.22	26.80	0.12
	150.1	2.56	0.24	25.49	0.10
	196.4	3.93	0.21	24.11	0.10

affect the concentration of unsaturated compounds. As expected, the CS-CL200X sample (clay without metals) was the least effective at removing sulfur compounds. The CS-Sorb-6890 (M) sample exhibited the best results; it effectively removed both the unsaturated and sulfur compounds. However, it had a slightly lower unsaturated compound removal activity than the CS-CL200X sample and a slightly lower degree of purification from sulfur compounds than the CS-Sorb-6891(S) sample at temperature 170–230°C.

Pilot test results

Since the CS-Sorb-6890 (M) adsorbent showed good cleaning results during the laboratory studies, the decision was made to use it for pilot tests at one of the industrial enterprises. The sulfur compound concentration in the incoming benzene fraction ranged from 0.1 to 3.2 ppm. The adsorbent sample was compared with industrial R-01 and R-02 adsorbents under less favorable conditions to confirm its effectiveness. Table 4 shows the operation parameters of the pilot plant and industrial adsorbents.

Pilot tests were conducted for 7 days (3 days for the debugging mode and 4 days for the stabilized mode), and the obtained data (the stabilized mileage and averaged data marked in gray) are presented in Table 5.

Figures 4–6 compare the activities of the pilot and industrial adsorbers toward the removal of unsaturated and sulfur compounds.

The test results showed that the CS-Sorb-6890 (M) adsorbent removed the sulfur compounds and unsaturated hydrocarbons stably throughout the entire test period. The total sulfur concentration was reduced to an average concentration of 0.41 ppm. The industrial R-01 and R-02 adsorbers had an average sulfur compound concentration of 1.86 and 0.61 ppm at the output, respectively. The unsaturated compound concentration at the outlet of the adsorber was determined by the iodine number indicator. The iodine number indicator ranged from 40 to 180 mg/100 g (with an average value of 100 mg/100 g) at the output. When compared to the industrial R-01 and

Table 4. Parameters during active clay testing

No.	Parameter	In the industrial adsorber R-01/R-02	In the pilot adsorber R-1
1	Consumption of benzene fraction per adsorber	7500 kg/h	1200–1500 mL/h (20–25 mL/min)
2	Adsorbent volume in one adsorber	22.7 m^3	550 cm^3
3	Volumetric flow rate	0.4 h^{-1}	2.2–2.7 h^{-1}
4	Temperature in the adsorber	≥170°C	35–45°C
5	Pressure in the adsorber	7.5–28 kgf/cm^2	7.5–8.5 kgf/cm^2

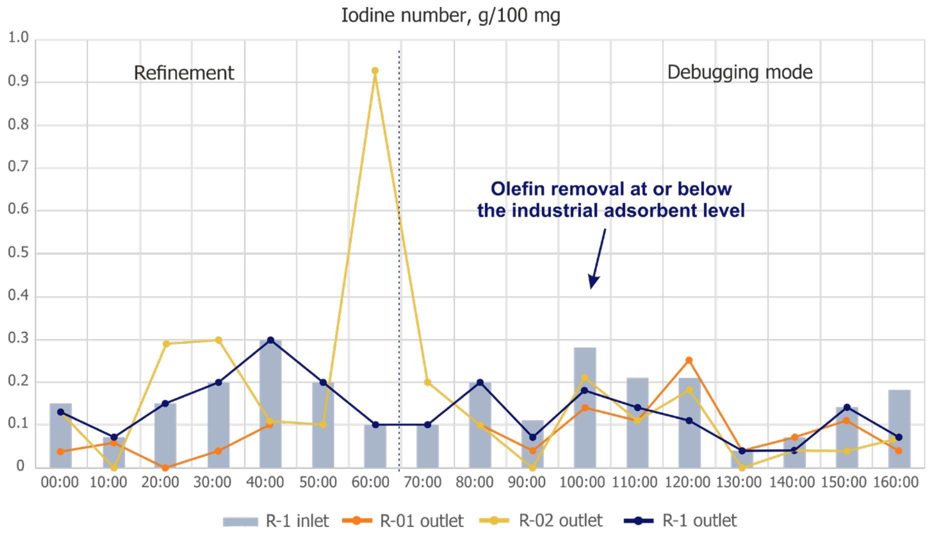

Fig. 4. Iodine number in the flow at the inlet and outlet of the adsorbers.

Table 5. Pilot test results of the adsorbers

Selection point	Initial benzene fraction (entrance to the adsorber R-1)		Output of the pilot adsorber R-1		Output of industrial adsorber R-01		Output of industrial adsorber R-02	
Indicator/time, h	**Iodine number, g/100 g**	**Sulfur, ppmw**	**Iodine number, g/100 g**	**Sulfur, ppmw**	**Iodine number, g/100 g**	**Sulfur, ppmw**	**Iodine number, g/100 g**	**Sulfur, ppmw**
00:00	0.15	2.60	0.13	1.70	0.04	0.50	0.13	0.20
10:00	0.07	3.50	0.07	2.20	0.06	6.30	0.00	0.40
20:00	0.15	2.60	0.15	0.90	0.00	1.20	0.29	0.30
30:00	0.20	2.00	0.20	1.00	0.04	0.60	0.30	2.70
40:00	0.30	1.60	0.30	4.80	0.10	5.00	0.11	1.50
50:00	0.20	3.40	0.20	2.70	0.10	8.10	0.10	0.90
60:00	0.10	3.30	0.10	2.00	0.92	1.30	0.92	0.40
70:00	0.10	2.90	0.10	0.30	0.20	0.80	0.20	0.60
80:00	0.20	2.70	0.20	1.70	0.10	1.90	0.10	0.70
90:00	0.11	3.20	0.07	1.00	0.04	2.10	0.00	1.00
100:00	0.28	0.10	0.18	0.30	0.14	1.00	0.21	1.00
110:00	0.21	0.30	0.14	0.20	0.11	1.00	0.11	0.20
120:00	0.21	2.00	0.11	0.40	0.25	0.20	0.18	0.50
130:00	0.04	2.00	0.04	0.30	0.04	0.30	0.00	0.80
140:00	0.07	2.00	0.04	0.50	0.07	3.00	0.04	0.10
150:00	0.14	1.00	0.14	0.30	0.11	3.00	0.04	0.30
160:00	0.18	2.60	0.07	0.30	0.04	4.30	0.07	1.00
Minimum	**0.04**	**0.10**	**0.04**	**0.20**	**0.04**	**0.20**	**0.00**	**0.10**
Maximum	**0.28**	**3.20**	**0.18**	**1.00**	**0.25**	**4.30**	**0.21**	**1.00**
Average	**0.16**	**1.65**	**0.10**	**0.41**	**0.10**	**1.86**	**0.08**	**0.61**

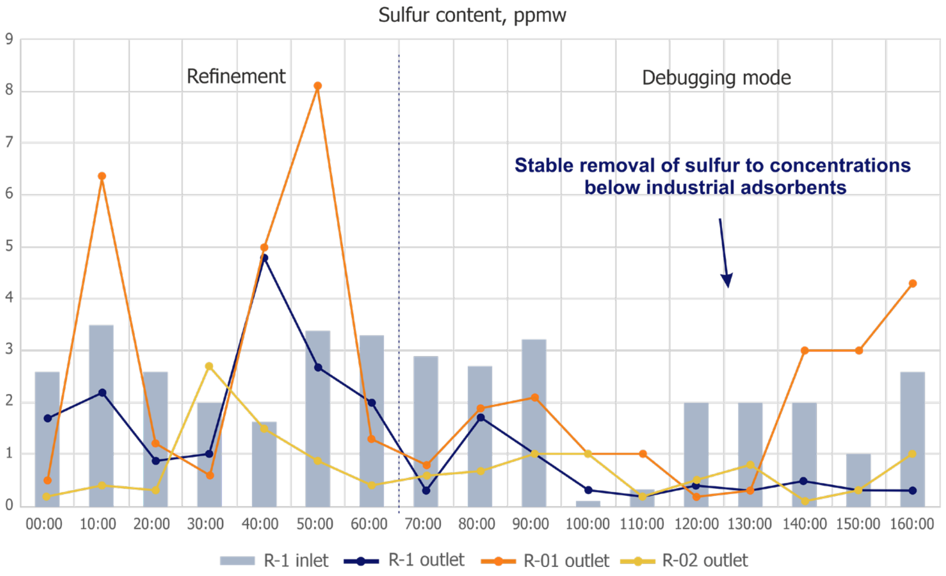

Fig. 5. Sulfur content in the flow at the inlet and outlet of the adsorbers.

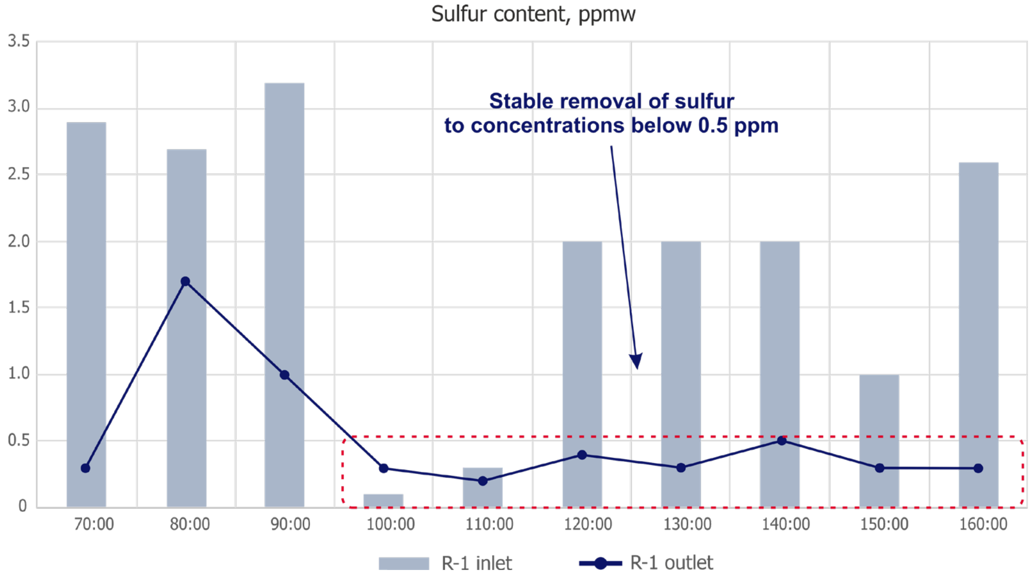

Fig. 6. Removal of sulfur by the CS-Sorb-6890 (M) sample after regime stabilization.

Table 6. Achieved adsorbent indicators during pilot tests

Indicator	Results for the CS-Sorb-6890 (M) sample in the R-1 pilot adsorber		Results for a standard adsorbent in an industrial adsorber			
			R-01		R-02	
	Average	Range	Average	Range	Average	Range
Content of unsaturated compounds (iodine number), mg/100 mL	100	40–180	100	40–250	80	40–210
Total sulfur content, ppmw	0.41	0.2–1.0	1.86	0.2–4.3	0.61	0.1–1.0

R-02 adsorbers (with a volume velocity that is 5.5–6 times higher and a temperature of ~130°C below than those of the CS-Sorb-6890 (M) adsorbent), the CS-Sorb-6890 (M) adsorbent showed similar efficiency in the removal of unsaturated compounds and higher efficiency in the removal of sulfur compounds under less favorable conditions.

CONCLUSIONS

A modified active clay-based adsorbent, CS-Sorb-6890 (M), was created and tested under laboratory and pilot-industrial conditions. According to the laboratory test results, the studied samples had different sorption capacities for sulfur and unsaturated compounds. The CS-Sorb-6890 (M) adsorbent successfully removed olefins and sulfur compounds from the benzene fraction simultaneously under pilot testing conditions. The benzene flow had a total sulfur content of 0.41 ppm after purification, and the iodine number had a minimum value of 40 mg/100 g.

The results indicate that it is possible to purify the benzene fraction from sulfur and unsaturated compounds in only one apparatus, allowing commercial benzene of specific quality to be obtained without changing the technological production scheme and with only existing equipment.

Authors' contribution

B.Yu. Malyshkin – development of the concept of scientific work, the chemical composition of the adsorbent, advice on methodology and research;

I.P. Semenov – development of the concept of scientific work, consultation on methodology and research, editing the text of the article;

D.S. Sazonov – advice on methodology and research;

I.O. Putenikhin – development of the concept of scientific work, consultation on methodology and research;

E.Yu. Semenikhina – collection and processing of material, writing the text of the article.

The authors declare no conflicts of interest.

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About the authors:

Boris Yu. Malyshkin, General Director, United Catalyst Technologies (719, 3, Profsoyuznaya ul., Moscow, 117292, Russia). E-mail: b.malyshkin@united-catalyst.com. https://orcid.org/0000-0002-2183-7091

Ivan P. Semenov, Cand. Sci. (Eng.), Deputy General Director, Director of the Scientific and Technical Center, United Catalyst Technologies (719, 3, Profsoyuznaya ul., Moscow, 117292, Russia). E-mail: i.semenov@united-catalyst.com. https://orcid.org/0000-0002-6408-3285

Dmitrii S. Sazonov, Cand. Sci. (Chem.), Manager for Personnel Training, Sales and Technical Service of Synthesis Gas Catalysts, United Catalyst Technologies (719, 3, Profsoyuznaya ul., Moscow, 117292, Russia). E-mail: d.sazonov@united-catalyst.com. https://orcid.org/0000-0002-5175-9055

Igor O. Putenikhin, Leading Process Engineer, United Catalyst Technologies (719, 3, Profsoyuznaya ul., Moscow, 117292, Russia). E-mail: i.putenikhin@united-catalyst.com. https://orcid.org/0000-0001-5643-595X

Elizaveta Yu. Semenikhina, Process Engineer, United Catalyst Technologies (719, 3, Profsoyuznaya ul., Moscow, 117292, Russia). E-mail: e.semenikhina@united-catalyst.com. https://orcid.org/0000-0003-3633-8946

Об авторах:

Малышкин Борис Юрьевич, генеральный директор ООО «United Catalyst Technologies» (117292, Россия, Москва, Профсоюзная ул., д. 3, офис 719). E-mail: b.malyshkin@united-catalyst.com. https://orcid.org/0000-0002-2183-7091

Семёнов Иван Павлович, к.т.н., заместитель генерального директора – директор НТЦ ООО «United Catalyst Technologies» (117292, Россия, Москва, Профсоюзная ул., д. 3, офис 719). E-mail: i.semenov@united-catalyst.com. https://orcid.org/0000-0002-6408-3285

Сазонов Дмитрий Станиславович, к.т.н., менеджер по обучению персонала, продажам и техническому сервису катализаторов синтез-газа ООО «United Catalyst Technologies» (117292, Россия, Москва, Профсоюзная ул., д. 3, офис 719). E-mail: d.sazonov@united-catalyst.com. https://orcid.org/0000-0002-5175-9055

Путенихин Игорь Олегович, ведущий инженер-технолог ООО «United Catalyst Technologies» (117292, Россия, Москва, Профсоюзная ул., д. 3, офис 719). E-mail: i.putenikhin@united-catalyst.com. https://orcid.org/0000-0001-5643-595X

Семенихина Елизавета Юрьевна, инженер-технолог ООО «United Catalyst Technologies» (117292, Россия, Москва, Профсоюзная ул., д. 3, офис 719). E-mail: e.semenikhina@united-catalyst.com. https://orcid.org/0000-0003-3633-8946

The article was submitted: November 29, 2021; approved after reviewing: January 24, 2022; accepted for publication: February 17, 2022.

Translated from Russian into English by N. Isaeva
Edited for English language and spelling by Enago, an editing brand of Crimson Interactive Inc.

CHEMISTRY AND TECHNOLOGY OF ORGANIC SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ОРГАНИЧЕСКИХ ВЕЩЕСТВ

ISSN 2686-7575 (Online)

https://doi.org/10.32362/2410-6593-2022-17-1-30-38

UDC 665.642

RESEARCH ARTICLE

Coking of high-viscosity water-containing oil

Alexander I. Nikolaev✉, Boris V. Peshnev, Ekaterina V. Egorova

MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia
✉Corresponding author, e-mail: nikolaev_a@mirea.ru

Abstract

Objectives. *A characteristic feature of oil production is an increase in the volume of high-viscosity bituminous oil. In Russia, technologies based on the use of water vapor are used for their extraction. The use of such technologies leads to a large amount of water in the product stream from the production well. Preparation of oil for processing involves its stabilization, desalination, and dewatering. Since the densities of the extracted oil and the water contained in it are comparable, traditional preparation schemes for processing of high-viscosity bituminous oil are ineffective. One of the possible solutions to the problem involving such oil in the fuel, energy, and petrochemical balance is to use a coking process at the first stage of its processing. This aim can be achieved by studying the influence of the process conditions of coking high-viscosity water-containing oil on the yield and characteristics of the resulting products.*
Methods. *Coking of oil with a density of 1.0200 g/cm^3 at 50°C and with 18 wt% water content was carried out in a laboratory installation in a "cube." A hollow cylindrical apparatus was used as a reactor and was placed in a furnace. The temperature and pressure in the reactor were maintained at 500–700°C and 0.10–0.35 MPa, respectively.*
Results. *An increase in the coking process temperature results in an increase in the amount of gaseous products, a decrease in the amount of the coke generated, and a higher dependence of the amount of liquid products on temperature with a maximum yield at 550–600°C. The process temperature also affects the composition of liquid products. At a lower temperature, the amount of gasoline and kerosene fractions in liquid products is higher. With an increase in pressure, a higher amount of gaseous products, coke, and low-molecular-weight hydrocarbon fractions in liquid products could also be obtained. The characteristics of the coke produced in the coking process are similar to those of commercially produced grades. It is noted that when coking water-containing oil, up to 98% of the emulsion water goes with liquid products, and the remaining amount of water remains in the formed coke.*

Conclusions. *Results showed the possible application of the coking process at the initial stage of processing high-viscosity bituminous oil. In this case, the dewatering stage is significantly simplified since the technological scheme of delayed coking allows the separation of the gasoline fraction from water.*

Keywords: *coking, high-viscosity bituminous oil, watered oil, oil refining, oil refining method*

For citation: Nikolaev A.I., Peshnev B.V., Egorova E.V. Coking of high-viscosity water-containing oil. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(1):30–38 (Russ., Eng.). https://doi.org/10.32362/2410-6593-2022-17-1-30-38

НАУЧНАЯ СТАТЬЯ

Коксование высоковязкой обводненной нефти

А.И. Николаев✉, Б.В. Пешнев, Е.В. Егорова

МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия
✉Автор для переписки, e-mail: nikolaev_a@mirea.ru

Аннотация

Цели. *Возрастание доли высоковязкой и битуминозной нефти является характерной особенностью современной нефтедобычи. В России при ее добыче применяют технологии, основанные на использовании водяного пара. Применение таких технологий приводит к тому, что продуктовый поток, выходящий из добывающей скважины, может содержать большое количество воды. Подготовка нефти к переработке предполагает ее стабилизацию, обессоливание и обезвоживание. Вследствие того, что плотность добываемой нефти и содержащейся в ней воды сопоставимы, традиционные схемы подготовки к переработке высоковязкой и битуминозной нефти являются малоэффективными. Одним из возможных решений проблемы вовлечения такой нефти в топливно-энергетический и нефтехимический баланс является использование на первом этапе ее переработки процесса коксования. Для реализации этой идеи необходимо изучить влияние условий коксования высоковязкой обводненной нефти на выход и характеристики образующихся продуктов.*

Методы. *Объектом исследования была нефть с плотностью при 50 °С 1.0200 г/см³, содержащая 18 мас. % воды. Коксование проводили на лабораторной установке в «кубе». В качестве реактора использовался пустотелый цилиндрический аппарат, размещаемый в печи. Температура в реакторе варьировалась от 500 до 700°С, давление от 0.10 до 0.35 Мпа.*

Результаты. *Проведенные исследования показали, что при возрастании температуры коксования выход газообразных продуктов увеличивается, образование кокса уменьшается, а зависимость выхода жидких продуктов имеет экстремальный характер с максимумом в области температур 550–600 °С. Температура процесса влияет на состав жидких продуктов. При более низкой температуре в жидких продуктах выше содержание бензиновой и керосиновой фракций. Повышение давления приводит к возрастанию выхода газообразных продуктов, кокса и содержания в жидких продуктах низкомолекулярных фракций углеводородов. Образующийся в процессе кокс по своим характеристикам близок к промышленно выпускаемым маркам. Отмечено, что при коксовании обводненной нефти до 98% водной эмульсии уходит с жидкими продуктами коксования, и лишь небольшое количество воды остается в образовавшемся коксе.*

Выводы. *Представленные результаты показывают возможность использования процесса коксования на начальном этапе переработки высоковязкой и битуминозной нефти. В этом случае существенно упрощается проведение стадии ее обезвоживания, так как в технологической схеме замедленного коксования предусмотрено отделение бензиновой фракции от воды.*

Ключевые слова: *коксование, высоковязкие и битуминозные нефти, обводненные нефти, переработка нефти, способ переработки нефти*

Для цитирования: Николаев А.И., Пешнев Б.В., Егорова Е.В. Коксование высоковязкой обводненной нефти. *Тонкие химические технологии*. 2022;17(1):30–38. https://doi.org/10.32362/2410-6593-2022-17-1-30-38

INTRODUCTION

In recent years, a characteristic feature of oil production is an increase in the total volume of high-viscosity bituminous oil, which contains a high amount of resin–asphaltene substances (RAS) and has high density and viscosity values. The technologies of extracting such oil include (1) the use of solvents, such as water, to displace fossil hydrocarbons (also known as cold recovery) and (2) in situ combustion where oil viscosity is reduced as a result of increasing the temperature and creating the pressure needed to displace the formed oil through gaseous combustion products [1–11]. In Russia, technologies based on the use of water vapor are used in the extraction of high-viscosity bituminous oil [8–11]. However, the use of water or water vapor to displace oil results to the inclusion of up to 95% water in the product stream from the production well.

Preparation of oil for processing involves its stabilization, desalination, and dehydration [12, 13]. Dehydration is based on the difference in the densities of petroleum hydrocarbons and water. However, due to the comparable densities of resin–asphaltene substances and water, their separation by gravitational method is almost impossible, and the high viscosity of RAS prevents the effective use of demulsifiers for the destruction of oil–water emulsions. As a result, traditional preparation schemes for processing of high-viscosity bituminous sands are ineffective [14].

A possible solution to the problem of involving such oil in the fuel, energy, and petrochemical balance is the use of a coking process at the first stage of its processing [15]. Currently, this process is widely used to increase the extent of oil refining, thereby obtaining distillate fractions from heavy oil residues (fuel oil, cracking residues, and tar). At the same time, the main components of such residues are RAS, and the technology involves the use of water vapor to prevent coking of the tubular furnace.

MATERIALS AND METHODS

Herein, a stable, high-viscosity oil–water emulsion (not amenable to dehydration) was subjected to a coking process, and its characteristics are presented in Table 1. The effects of the coking process conditions on the yield and characteristics of the resulting products were also investigated.

The density and paraffin content of the oil–water emulsion correspond to the fifth type of oil (bituminous) and to the first type (low paraffin) based on the classification in GOST 31378-2009[1] and OST 38.01197-80[2], respectively. However, the amount of water (more than the 1.0 wt % standard for the third type) and solids (more than 0.05 wt %) in the emulsion does not make it possible to be considered as a commodity product (GOST 31378-2009) for processing.

Coking was carried out in a laboratory installation in a “cube”[3] [16]. A hollow cylindrical

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[1] GOST 31378-2009. Interstate Standard. Crude Petroleum. General Specifications. Moscow: Standartinform; 2019.

[2] OST 38.01197-80. Industry standard. Oil of the USSR. Technological Indexing. Moscow: Ministry of Oil Refining and Petrochemical Industry of the USSR; 1980.

[3] Bikbulatova A.M. *Etapy stanovleniya i razvitiya otechestvennogo proizvodstva neftyanogo koksa metodom zamedlennogo koksovaniya: Na primere Novo-Ufimskogo NPZ* (*Stages of formation and development of domestic production of petroleum coke by the method of delayed coking: a case study of the Novo-Ufimsky refinery*): Cand. Sci. Thesis. Ufa; 2002. 104 p. (in Russ.).

Table 1. Characteristics of oil-water emulsion

Characteristics	Value
Density, 50°C, g/cm^3	1.0200
Dynamic viscosity at 50°C, MPa·s	22557
Molecular weight, g/mol	520
Content of mechanical impurities, wt %	0.72
Water content, wt %	18.0
Resin and asphaltene content, wt %	42.0
Paraffin content, wt %	1.0

apparatus was used as a reactor, which was equipped with a "pocket" for a chromel–alumel thermocouple and a nozzle for installing a pressure gauge. The raw materials were loaded into the reactor, and the connections of the components of the installation were checked for tightness. The reactor was heated to a set temperature using an electric furnace. The coking process temperature and pressure were varied from 500 to 700°C and from 0.10 to 0.35 MPa, respectively. During the experiment, the temperature and pressure in the reactor were monitored, as well as the volume of waste gas, which was recorded using a GSB-400 gas meter (*NII Electromera*[4], Russia). At the end of the experiment, the amount of the liquid products and coke formed was determined.

The hydrocarbon content in waste gas was determined by gas adsorption chromatography using a 3700 chromatograph (*Chromatec*, Yoshkar-Ola, Russia) that was equipped with a thermal conductivity detector. Conditions of the analysis are as follows: the current of the detector bridge was 90 mA, the carrier gas was nitrogen with a flow rate of 25 mL/min, the temperature of the column thermostat was at 70°C; the column length and diameter were 7 m and 2 mm, respectively, and the chromatographic phase was Al_2O_3 with a fraction of 0.15–0.25 mm and promoted with a 5% NaOH solution. To increase the sensitivity and simplify the calibration and processing of chromatograms, a heated reaction column for the conversion of hydrocarbons to hydrogen was installed in the gas line of the chromatograph, which was between the chromatographic column and the detector. The temperature, length, diameter, and nozzle of the reaction column were 850°C, 0.2 m, 5 mm, and copper oxide and iron chips (arranged sequentially), respectively. Registration of the detector signal and processing of chromatograms were carried out using the hardware and software complex EKOKHROM.

For liquid products, their fractional composition and pycnometric density were determined using an ARNP-1 apparatus (*Promkhimpribor*, Moscow, Russia) according to the GOST 2177-99[5] and GOST 3900-85[6] methods, respectively. Furthermore, the ash content of the carbon material was determined according to GOST 22692-77[7], and the mass fraction of the volatile substances was measured in accordance with GOST 22898-78[8].

RESULTS AND DISCUSSION

The output indicators of the coking process are shown in Table 2.

It can be seen that with an increase in temperature, the yield of gaseous products increases, the formation of coke decreases, and the dependence of the amount of liquid products on temperature increases with a maximum yield at 550–600°C. An increase in the pressure leads to an increase in the yield of gaseous products and coke but a decrease in the yield of liquid products.

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[4] https://electromera.ru/. Accessed October 23, 2021.

[5] GOST 2177-99. Interstate Standard. Petroleum products. Methods for determination of distillation characteristics. Moscow: Kodeks; 2001 (in Russ.).

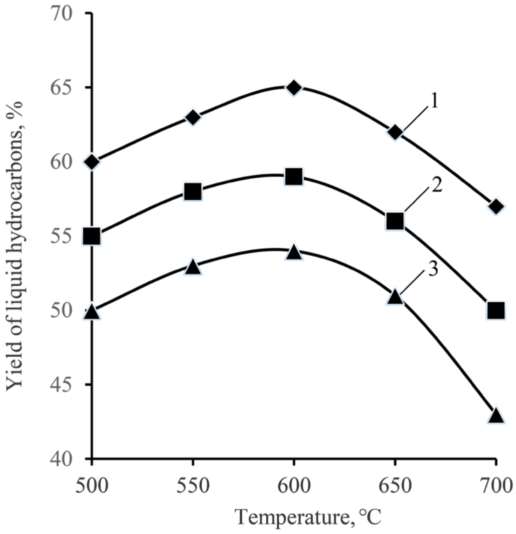
[6] GOST 3000-85. Interstate Standard. Petroleum and petroleum products. Methods for determination of density. Moscow: Standartinform; 2006 (in Russ.).

[7] GOST 22692-77. Interstate Standard. Carbon materials. Method for determination of ash. Moscow: IPK Izd. standartov; 2001 (in Russ.).

[8] GOST 22898-78. Interstate Standard. Low-sulphur petroleum cokes. Specifications. Moscow: IPK Izd. standartov; 2004 (in Russ.).

It is noted that ~98% of the emulsion water goes with liquid products and was subsequently easily separated by gravity, and the rest (~2%) was "encapsulated" by the resulting coke.

The effect of the coking process conditions on the yield of liquid hydrocarbons is shown in the figure.



Effect of the coking process conditions on the yield of liquid products. Coking pressure is at (1) 0.10 MPa, (2) 0.20 MPa, and (3) 0.35 MPa.

The characteristics of the products were only determined for those obtained under conditions where maximum yield was achieved, i.e., at 500°C (maximum coke yield) and 600°C (maximum yield of liquid products). In addition, the density of liquid products (hydrocarbons) varied from 0.8977 to 0.9346 g/cm^3, and it increased with an increase in temperature (from 500 to 600°C) and a decrease in pressure. The change in density is due to a change in the fractional composition of liquid hydrocarbons (Table 3).

It can be seen that at a lower temperature and a higher pressure, the amount of gasoline and kerosene fractions in liquid products is higher, which correlates with the densities of these products. The characteristics of the coke residue from the coking process are presented in Table 4.

In terms of density and amount of volatile substances and moisture, the resulting residues meet the GOST 22898-78 "Low-sulfur petroleum cokes. Technical specifications" requirements for coke. Due to a high amount of impurities in the raw materials, as well as the fact that they have not been desalted, the ash content of the resulting coke is significantly higher than that allowed for cokes used for structural purposes (no more than 0.8 wt %).

Table 2. Influence of coking process conditions on product yield

Process conditions		Output, wt %		
Temperature, °C	**Pressure, MPa**	**Gas**	**Liquid**	**Coke**
500	0.10	1.7	79.2	19.1
	0.20	6.5	72.8	20.7
	0.35	8.4	68.5	23.1
550	0.10	2.2	82.8	15.0
	0.20	7.0	76.4	16.6
	0.35	8.9	72.1	19.0
600	0.10	2.9	85.2	11.9
	0.20	7.7	79.0	13.3
	0.35	9.7	74.9	15.4
650	0.10	5.1	83.2	11.7
	0.20	11.4	75.8	12.8
	0.35	14.6	70.9	14.5
700	0.10	10.3	78.4	11.3
	0.20	19.9	67.8	12.3
	0.35	25.5	60.7	13.8

Table 3. Influence of the coking process conditions on the fractional composition of liquid products

Conditions of carbonization		Fraction content, vol %			
Temperature, °C	Pressure, MPa	Petrol (T_{bp} – 180°C)*	Kerosene (180–240°C)	Diesel (240–350°C)	Residue
500	0.10	12.4	34.3	28.8	24.5
	0.20	14.7	38.9	27.7	18.7
	0.35	25.0	40.0	25.2	9.8
600	0.10	11.3	26.4	30.3	32.0
	0.20	13.9	30.0	29.3	26.8
	0.35	22.3	31.5	27.3	18.9

* T_{bp} is the initial boiling point.

Table 4. Influence of the coking process conditions on the characteristics of the coke residue

Conditions of carbonization		Density of coke calcined at 1300°C, g/cm^3	Ash content, wt %	Mass fraction of volatile substances and moisture, wt %
Temperature, °C	Pressure, MPa			
500	0.10	2.10	2.51	10
	0.20	2.11	2.54	9
	0.35	2.12	2.57	8
600	0.10	2.11	2.82	9
	0.20	2.12	2.85	8
	0.35	2.13	2.87	7

Coking gases contained hydrogen (20 ± 5 vol %), methane (45 ± 5 vol %), and C_2–C_4 hydrocarbons. An increase in the temperature and pressure during the coking process led to an increase in the amount of hydrogen in the gas and a decrease in the amount of methane. The amount of the remaining components did not change significantly.

A characteristic feature of the resulting gas is the significantly low amount of alkenes. In the coking gases of residues from straight runs, the amount of unsaturated hydrocarbons can reach 50%, whereas in our case, it did not exceed 7 vol %. Obviously, this is due to the composition of the raw materials: low content of alkanes and high content of resins and asphaltenes that have polycyclic aromatic structures.

CONCLUSIONS

The results show the possible application of the coking process at the initial stage of processing high-viscosity bituminous oil. In this case, the dehydration stage is greatly simplified because the technological scheme of delayed coking allows the separation of the gasoline fraction from water. Also, the results have shown that with an increase in the coking process temperature, the yield of gaseous products increases, the formation of coke decreases, and the dependence of the amount of liquid products on temperature increases with a maximum yield at 550–600°C. The coking process temperature also affects the composition of liquid products. At a lower temperature, the amount of gasoline and kerosene fractions in liquid products is higher. In addition, an increase in pressure leads to an increase in the yield of gaseous products and coke and to an increase in the amount of low-molecular-weight fractions of hydrocarbons in liquid products. The characteristics of the coke formed from the coking process carried out in this study are comparable to those that are commercially produced. It is noted that during coking of water-containing oil, up to 98% of emulsion water goes with liquid products, and the remaining amount of water remains in the formed coke.

Authors' contributions

A.I. Nikolaev – formulation of the problem, planning and conducting experimental studies, determination of the physicochemical characteristics of the research objects and resulting products, processing the data obtained, preparation of the data obtained for publication.

B.V. Peshnev – formulation of the problem, planning and conducting experimental studies, processing the data obtained, preparation of the data obtained for publication.

E.V. Egorova – determination of the physicochemical characteristics of the research objects and the resulting products, processing the data obtained, preparation of the data obtained for publication.

The authors declare no conflicts of interest.

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About the authors:

Alexander I. Nikolaev, Dr. Sci. (Tech.), Professor, A.N. Bashkirov Department of Petrochemical Synthesis and Artificial Liquid Fuel Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: nikolaev_a@mirea.ru. https://orcid.org/0000-0001-8594-2985

Boris V. Peshnev, Dr. Sci. (Tech.), Professor, A.N. Bashkirov Department of Petrochemical Synthesis and Artificial Liquid Fuel Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: peshnevbv@mail.ru. https://orcid.org/0000-0002-0507-2754

Ekaterina V. Egorova, Cand. Sci. (Tech.), Associate Professor, A.N. Bashkirov Department of Petrochemical Synthesis and Artificial Liquid Fuel Technology, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: egorova1412@mail.ru. https://orcid.org/0000-0002-7520-832X

Об авторах:

Николаев Александр Игоревич, д.т.н., профессор кафедры технологии нефтехимического синтеза и искусственного жидкого топлива им. А.Н. Башкирова Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: nikolaev_a@mirea.ru. https://orcid.org/0000-0001-8594-2985

Пешнев Борис Владимирович, д.т.н., профессор кафедры технологии нефтехимического синтеза и искусственного жидкого топлива им. А.Н. Башкирова Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: peshnev@mirea.ru. https://orcid.org/0000-0002-0507-2754

Егорова Екатерина Владимировна, к.т.н., доцент кафедры технологии нефтехимического синтеза и искусственного жидкого топлива им. А.Н. Башкирова Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: egorova1412@mail.ru. https://orcid.org/0000-0002-7520-832X

The article was submitted: October 23, 2020; approved after reviewing: December 11, 2020; accepted for publication: February 04, 2022.

Translated from Russian into English by N. Isaeva
Edited for English language and spelling by Enago, an editing brand of Crimson Interactive Inc.

CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

ISSN 2686-7575 (Online)

https://doi.org/10.32362/2410-6593-2022-17-1-39-49

UDC 543.066

RESEARCH ARTICLE

Quantitation of polysorbate 80 in recombinant protein formulation using high-performance liquid chromatography

Aleksandr D. Askretkov[1,✉], **Denis O. Shatalov**[1], **Natalya V. Orlova**[2], **Dmitry I. Zybin**[1], **Valeriya V. Nikolaeva**[2], **Anatoly A. Klishin**[2], **Elena S. Tuzova**[2], **Dmitry S. Minenkov**[3], **Stanislav A. Kedik**[1], **Yuri A. Seregin**[4]

[1]*MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia*
[2]*Scientific Center "Kurchatov Institute," Research Institute for Genetics and Selection of Industrial Microorganisms, Moscow, 117545 Russia*
[3]*Ishlinsky Institute for Problems in Mechanics, Russian Academy of Sciences, Moscow, 119526 Russia*
[4]*PHARMAPARK, Moscow, 117246 Russia*
✉*Corresponding author, e-mail: askretkov.a.d@gmail.com*

Abstract

Objectives. *Polysorbate 80 (PS80) quantification in biopharmaceutical products has always been challenging owing to its minute content, absorption to the protein backbone, lack of specific chromophoric PS80 groups, and heterogenic nature. This work is aimed at developing an express method for PS80 analysis in biopharmaceutical products using hydrolysis and subsequent high-performance liquid chromatography analysis with ultraviolet detection that does not consume substantial amounts of sample (≥35 µL).*
Methods. *Five therapeutic protein formulations were chosen as model proteins. Alkaline hydrolysis formulation was applied, without protein precipitation and with a range of precipitation techniques to remove protein from the test solution and hydrolyze PS80, to free fatty acids. The obtained hydrolysate was analyzed using reverse-phase high-performance liquid chromatography.*
Results. *As a result of the high protein content of monoclonal antibody formulations, preliminary protein removal was required, which was achieved by precipitation with organic solvents. A specific*

precipitant ethanol–isopropanol mixture (1:1 volumetric ratio) was developed to efficiently remove antibodies while keeping PS80 in the solution. The PS80 quantification method was developed for monoclonal antibody drugs. For three monoclonal antibody drug products (adalimumab, infliximab, and eculizumab), method validation was performed according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, the United States Pharmacopeia, and the State Pharmacopeia of the Russian Federation guidelines. ***Conclusions.*** *The optimal assay conditions for each group of recombinant monoclonal antibody substances were chosen. Protein precipitation with ethanol or ethanol–isopropanol mixtures before hydrolysis was introduced, allowing for a substantial reduction of sample to 35 µL or even less if PS80 content is higher than 0.05 mg/ mL. Accelerated hydrolysis (90 min) is preferable to slow hydrolysis (4–18 h). Method validation for protein products such as adalimumab, infliximab, and eculizumab was demonstrated for the first time. Both methods were validated for each drug product. The coefficients of variation for method specificity and high precision were ≤6.0% for 3 analyses. The accuracy of the methods ranged from 96% to 109% for all of the tested drug products.*

Keywords: *polysorbate 80, hydrolysis, HPLC, oleic acid, therapeutic proteins, spectrophotometric detection*

For citation: Askretkov A.D., Shatalov D.O., Orlova N.V., Zybin D.I., Nikolaeva V.V., Klishin A.A., Tuzova E.S., Minenkov D.S., Kedik S.A., Seregin Y.A. Quantitation of polysorbate 80 in recombinant protein formulation using high-performance liquid chromatography. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(1):39–49. https://doi.org/10.32362/2410-6593-2022-17-1-39-49

НАУЧНАЯ СТАТЬЯ

Методика ВЭЖХ для определения полисорбата 80 в препаратах рекомбинантных терапевтических белков

А.Д. Аскретков[1,✉], Д.О. Шаталов[1], Н.В. Орлова[2], Д.И. Зыбин[1], В.В. Николаева[2], А.А. Клишин[2], Е.С. Тузова[2], Д.С. Миненков[3], С.А. Кедик[1], Ю.А. Серегин[4]

[1]*МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия*
[2]*Государственный научно-исследовательский институт генетики и селекции промышленных микроорганизмов национального исследовательского центра «Курчатовский институт», Москва, 117545 Россия*
[3]*Институт проблем механики им. А.Ю. Ишлинского РАН, Москва, 119526 Россия*
[4]*ФАРМАПАРК, Москва, 117246 Россия*
✉*Автор для переписки, e-mail: askretkov.a.d@gmail.com*

Аннотация

Цели. *Определение полисорбата 80 в препаратах терапевтических рекомбинантных белков всегда являлось трудной задачей, ввиду низкого содержания, гетерогенной природы, присутствия белка в препарате, а также отсутствия хромофорных групп у данного аналита. Целью данной работы являлась разработка экспрессной и* *экономичной методики определения полисорбата 80 в препаратах рекомбинантных моноклональных антител с использованием гидролиза с последующим определением высвобожденной олеиновой кислоты методом высокоэффективной жидкостной хроматографии (ВЭЖХ) с УФ детектированием.*

***Методы.** В качестве модельных образцов выбраны пять терапевтических рекомбинантных белков. Использован щелочной гидролиз без удаления белка и с его удалением различными способами осаждения для выделения свободных жирных кислот. Полученный гидролизат проанализирован методом ВЭЖХ.*

***Результаты.** Для субстанций моноклональных антител, ввиду высокого содержания белка, требовалось его удаление. В качестве наиболее простого способа удаления выбрана денатурация и последующая преципитация белка, что достигалось путем осаждения антитела органическим растворителем. Был выбран универсальный осадитель (смесь этанола и изопропанола в объемном соотношении 1:1), использование которого позволяло эффективно удалять моноклональное антитело, но в то же время не допускать потерь полисорбата 80. Была разработана экспрессная методика определения полисорбата 80 для субстанций моноклональных антител. Методика определения полисорбата 80 валидирована согласно требованиям International Council for Harmonisation, United States Pharmacopeia и Государственной фармакопеи Российской Федерации.*

***Выводы.** Были проведены испытания условий пробоподготовки для моноклональных антител. Впервые было внедрено осаждение белка этанолом или смесью этанол-изопропанол перед проведением гидролиза и анализом полисорбата 80. Это позволило значительно уменьшить требуемое количество образца для анализа до 35 мкл при концентрации полисорбата 80 0.05 мг/мл или еще меньше при его большем содержании. Ускоренный гидролиз полисорбата 80 в течение 90 мин является более предпочтительным при проведении анализа в сравнении с продолжительным гидролизом в течение 4–18 ч, описанным в литературе. Впервые была проведена валидация методики пробоподготовки и анализа для моноклональных антител адалимумаб, экулизумаб и инфликсимаб. Высокая прецизионность методики (среднеквадратичное отклонение ≤6.0%), специфичность и удовлетворительные значения правильности (фактор отклика от 96 до 109%), говорят о пригодности методики для определения полисорбата 80 в лекарственных средствах на основе рекомбинантных моноклональных антител.*

***Ключевые слова:** полисорбат 80, гидролиз, высокоэффективная жидкостная хроматография, олеиновая кислота, рекомбинантные терапевтические белки, спектрофотометрическое детектирование*

Для цитирования: Askretkov A.D., Shatalov D.O., Orlova N.V., Zybin D.I., Nikolaeva V.V., Klishin A.A., Tuzova E.S., Minenkov D.S., Kedik S.A., Seregin Y.A. Quantitation of polysorbate 80 in recombinant protein formulation using high-performance liquid chromatography. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(1):39–49. https://doi.org/10.32362/2410-6593-2022-17-1-39-49

INTRODUCTION

PSs consist of sorbitol core bound to oxyethylene units, with one molecule of sorbitol containing one molecule of oleic (PS80) or lauric (PS20) acid. Its heterogenic nature [8], lack of chromophoric groups, and a tendency to bond with proteins present in formulation make it difficult to analyze [9]. Thus, several analytical approaches have been developed, including spectrophotometric detection, which is based on the extraction of PSs complexes with transition metals thiocyanates into organic solvent [10, 11] or inclusion of a fluorescent dye into PS micelles, followed by fluorescence detection and quantification [12, 13] and gas chromatography [14, 15]. The given methods are relatively free of systematic error owing to differences of PSs lot and manufacturer, but their laboriousness and low precision make them unsuitable for routine quality control.

High-performance liquid chromatography (HPLC) is another approach. There are multiple methods, each with its level of sensitivity, sample pretreatment, and detection. Reversed-phase (RP) HPLC of native PSs is conducted using evaporative light scattering detection (ELSD), and PS chromatograms appear as a collection of peaks [9, 16]. The detection of one of the PS components, mostly commonly liberated fatty acid, is based on HPLC with mass spectrometric [17, 18], fluorometric [19], or spectrophotometric [20–22] detection, or gas chromatography with flame ionization detector [23]. Although sample pretreatment is required, most of these approaches are less laborious than other quantitation methods. Currently, the presented methods require a substantial amount of sample for analysis or a prolonged hydrolysis time. Both of these conditions complicate routine PS80 analysis in TPs, which should be solved.

It should be noted that not every laboratory has the necessary equipment for analysis, thus HPLC with spectrophotometric detection is the most preferred and available, despite the following disadvantages:

Oleic acid (OA) extraction methods described in [21, 22, 24–26] require a substantial amount of sample (200–300 µL), which can be problematic in downstream technology development or drug product stability estimation.

Poor sensitivity, prolonged incubation time, or inability to quantify PS80 in high protein content formulations [20, 25].

Thus, the development of the low-demanding PS80 quantitation method is of interest.

In this work, a modified HPLC method for PS80 quantification was developed. The method begins with a protein precipitation stage using ethanol–isopropanol mixture, followed by fatty acid hydrolysis and ultraviolet spectroscopy with HPLC analysis. The developed procedure uses 5 to 6 times fewer samples than others presented in scientific literature and can quantify PS80 concentrations as low as 0.005 mg/mL. Monoclonal antibody (MAb) precipitation was performed in an ethanol–isopropanol mixture. The method was approbated for three recombinant MAb formulations with a protein content of about 10 mg/mL or more, validation was performed according to the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use[1], the United States Pharmacopeia (USP), the United States Food and Drug Administration[2], and the State Pharmacopeia of the Russian Federation[3].

MATERIALS AND METHODS

Materials

PS80 [the USP and the National Formulary (NF)], OA (65.0%–88.0%), formic acid (98%–100%), phosphoric acid (85%), and potassium hydroxide (≥85%) were purchased from *Sigma-Aldrich* (USA). Acetonitrile and isopropanol (UHPLC grade) were purchased from *PanReac AppliChem* (Spain). HPLC-grade water (18.2 MΩ/cm) was obtained using the Millipore Milli-Q Advantage A 10 system (USA). The monoclonal antibodies, eculizumab (ECZB), adalimumab (ADMB), and infliximab (INFL), were manufactured by *Pharmapark* (Russia); 15.1 mg/mL for ECZB and INFL and 60.5 mg/mL for ADMB.

Method optimization

Method optimization was performed using the central composite design, which was done using the design of the Minitab19 experiment software (*Minitab*, USA).

Volume V_1 of precipitation reagent [X, % (v/v) isopropanol solution in ethanol] was mixed with 35 µL of ECZB substance with a 0.22 mg/mL PS80 content and Milli-Q water. After 10 min incubation at 80°C, volume V_2 of supernatant was added to 35 µL of 0.5 M potassium hydroxide and incubated for 1.5 h at 80°C. After the reaction was stopped with 35 µL of 4% formic acid in acetonitrile, 40 µL of the sample was injected. Input varied parameters (factors) are shown in Table 1.

All other parameters remained constant.

As criteria, recovery of PS80 in ECZB and signal to noise (S/N) ratio of the OA postpeak was chosen.

Sample preparation

PS80 standard solutions in Milli-Q water were prepared in seven concentrations ranging from 50% to 150% of the nominal PS80 concentration (NC) for each drug product.

ECZB (NC 0.22 mg/mL), ADMB (NC 1.00 mg/mL), and INFL (NC 0.05 mg/mL) formulations were prepared as follows. Followed by vortexing, sample incubation at 80°C for 10 min, and centrifugation for 10 min at RT, 35 µL of standard or test sample were added to 20 µL of 1/1 (v/v) isopropanol/ethanol mixture. Twenty µLof obtained supernatant was mixed with 35 µL of 0.5 M potassium hydroxide solution. Subsequently, the mixture was incubated at 80°C for 90 min, followed by addition of 35 µL of 4% formic acid in acetonitrile. All mixtures were transferred into chromatographic vials.

Chromatography

HPLC was performed on the Ultimate 3000 system (*Thermo Fisher Scientific*, USA), which included a quaternary gradient pump (LPG-3400SD), a split loop autosampler (WPS-3000), a column oven (TCC-3000), and an ultraviolet detector (DAD-3000). A C18 stationary

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Table 1. Design of experiment variable parameters to optimize method

Input parameter	Value	
	Low level	High level
X (isopropanol concentration in ethanol), %	25	65
V_1 (volume of precipitation reagent), μL	20	40
V_2 (volume of supernatant), μL	20	40

HPLC column [YMC-Pack ODS-AQ, 150 × 4.6 mm, 3 μm particle diameter (*YMC*, Japan)] with end-capping was used. The mobile phase consisted of an 80:20 (v/v) mixture of acetonitrile and 0.85% phosphoric acid. The analysis was performed using isocratic elution for 13 min at a flow rate of 1.2 mL/min, a column temperature of 30°C, and a detection wavelength of 195 nm (the choice of that wavelength was based on low absorption at high wavelengths). The injection volume was set at 40 μL.

Each injection in process of analysis or validation was derived from a separate vial containing a sample that had been prepared separately.

All validation procedures followed the ICH Q2 (R1), ICH, and USP guidelines. Selectivity, linearity, analytical range, precision, accuracy, limit of detection (LOD), and limit of quantification (LOQ) were evaluated.

Specificity

Specificity was evaluated by analyzing the pre-formulated PS80-free drug product, PS80 spiked drug product, Milli-Q water, standards of PS80, and OA.

Linearity

Linearity was analyzed in triplicate by preparing seven PS80 standards in Milli-Q water: 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, and 1.2 mg/mL. Linear regression was used to plot the OA peak area against PS80 concentration, and the correlation coefficient (R^2) was determined.

Accuracy

For the estimation of accuracy, each PS80-free recombinant protein solution was spiked with PS80 to obtain a final concentration of 100% and, at least 80% and 120% of the nominal PS80 concentration while containing protein at the level present in the substance. Sample pretreatment and analysis were performed in triplicate for each concentration level. Following PS80 quantification, the recovery (R, %) at every concentration level was calculated for each replica using the formula:

$$R = \frac{C_0}{C_t} \times 100,$$

where C_0 is the obtained PS80 concentration and C_t is the calculated PS80 concentration.

Repeatability and precision

The repeatability of the analytical technique was assessed using the accuracy assessment results ($n = 3$). The coefficient of variation (CV, %) was calculated for each concentration level. For evaluation of the intermediate precision, the same analyses were conducted in two additional days, and the CV values of the overall PS80 concentration for each sample were compared.

LOD and LOQ

LOD and LOQ values were determined using consecutive injections of standard sample dilutions and estimation of the S/N ratio.

RESULTS AND DISCUSSION

Method development

This study aimed at developing a simple and reproducible PS80 quantification method for biopharmaceutical formulations of recombinant monoclonal antibodies protein products that require a relatively small amount of tested sample. The approbation of the method [18] showed relatively accurate PS80 quantification results, although it possessed certain drawbacks such as a large sample amount (200 μL) and difficulty in phase separation after hydrolysis.

The use of RP chromatography in analyzing nonhydrolyzed PS80 with spectrophotometric detection at 234 nm revealed multiple PS80 peaks, as indicated in previous works that used HPLC ELSD detection [8, 13]. PS80 quantification using a sum of multiple peak areas demonstrated reasonable method accuracy, but PS80 concentration had gradually increased over long-term TP stability assessment, making the method unfit for quantifying PS80 in long-term storage [20].

To develop the method, OA, which was the main fatty acid component, was chosen as the analyte, and hydrolysis with potassium hydroxide at a final concentration of 0.1 M was carried out without protein precipitation, followed by neutralization of the solution with 4% formic acid in acetonitrile. MAb preparation showed a tailing peak over all chromatograms owing to high concentration (≥10 mg/mL) and high tendency to aggregate in the presence of organic solvents, without protein removal (Fig. 1), resulting in OA quantification errors and column degradation with the MAb precipitate.

To remove MAb from test solutions, multiple methods, such as precipitation with organic solvents and heat denaturation, or both, were used. Heat denaturation of the test solution at 80°C for 10 min resulted in protein precipitation, although further assessment the accuracy of the method revealed a decrease in PS80 content from 20% for ECZB and ADMB to 40% for INFL. For MAb precipitation, ethanol, isopropanol, and a 20% 1-butanol solution in ethanol were used at an initial volumetric 1:1 ratio (Fig. 2).

Chromatograms revealed the presence of close-eluting to the OA postpeak for all samples (standard PS80 solution, protein formulation, and water) with 20% butanol precipitation and, to a lesser extent, isopropanol, resulting in a loss of specificity and misestimation of PS80 content. The OA postpeak was due to the extraction of leachables from the Eppendorf tube. There was no close-eluting peak for the ethanol when compared to OA. The preliminary results of the accuracy assessment are shown in Table 2.

Using ethanol precipitation, the method demonstrated satisfactory accuracy for ADMB, but not for ECZB or INFL.

The central composite design method was used to optimize the method for ECZB, resulting in 15 experiments with 3 variables. Contour plots were used to assess the optimum recovery (95%−105%), and the absence of OA postpeak (S/N = 0) was determined. The results of each experiment are depicted in Table 3.

The most ideal conditions, according to the obtained data, were $X = 50\%$ and $V_1 = V_2 = 20$ µL.

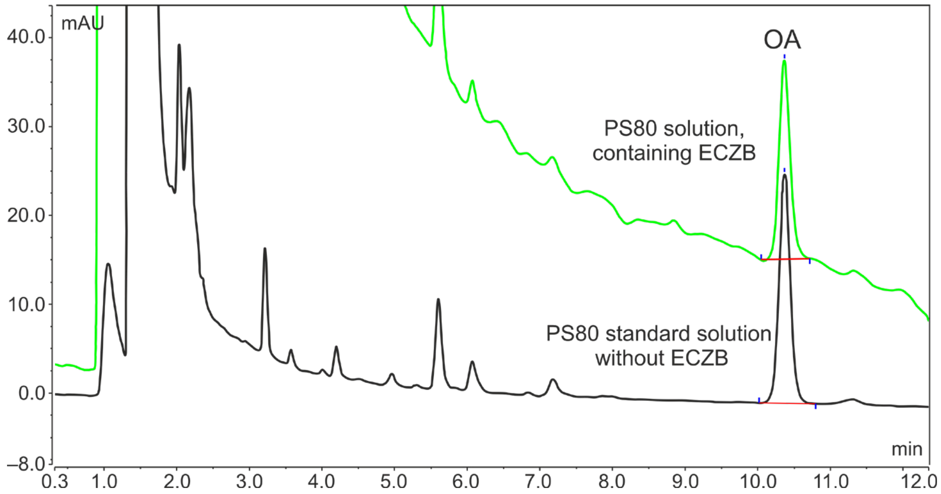

Fig. 1. Representative chromatogram of a 0.22 mg/mL PS80 solution. The OA retention time is 10.3 min.

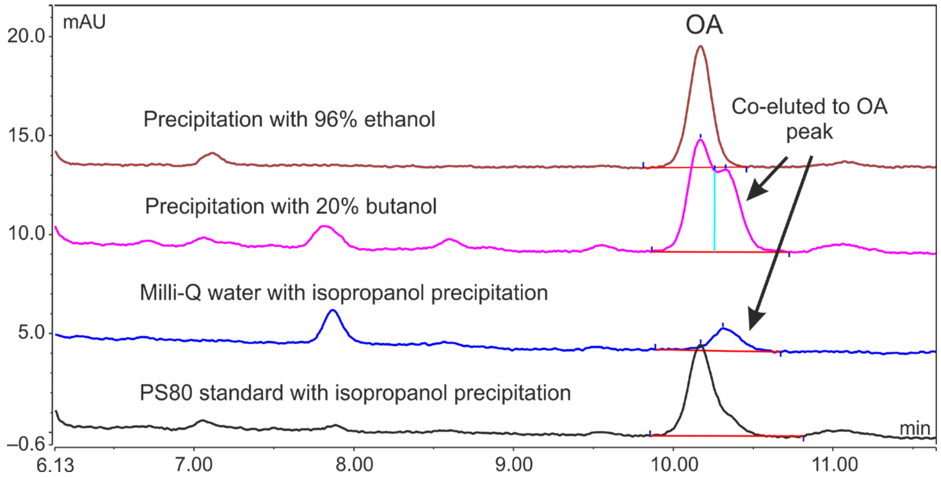

Fig. 2. Chromatograms obtained after PS80 solution hydrolysis and protein precipitation with organic solvents.

Table 2. Preliminary testing results of different precipitation reagents

Precipitation reagent	Recovery, %			OA postpeak presence
	ECZB	ADMB	INFL	
Ethanol 96%	84	102	82	–
Isopropanol	103	105	112	+
20% 1-butanol solution in ethanol	–*	–*	–*	+

*The results were incorrect owing to interference from a large postpeak presence.

Under the given conditions, recovery was about 99%, and there was no OA postpeak.

Under the given conditions, INFL substance testing demonstrated the same level of accuracy.

Method validation

The developed method demonstrated specificity. No peaks with OA retention time were observed in the Milli-Q water and PS80-free protein product. ECZB specificity assessments are shown in Fig. 3.

The method used for other drug products also demonstrated specificity. The correlation coefficient, R^2, of the regression line was 0.996, obtained R^2 values were ≥0.99, and the linearity of the methods was demonstrated. Accuracy estimation results for each biopharmaceutical are depicted in Table 4.

As a result, the recovery results for each biopharmaceutical were narrowly scattered around the 100% value, and no sample exceeded the 90%–110% recovery range limit. If the same PS80 lot was used as standard, the obtained values are considered free of systematic error and give actual PS80 concentration for the tested sample.

Repeatability and intermediate precision assessment results are presented in Table 5.

No sample exceeded the repeatability limit of 5% or the intermediate precision limit of 8%. In the one-day and day-to-day analyses, results obtained using both methods demonstrated narrow result distribution across the calibration range. Positive linearity, accuracy, and precision assessment results indicate that both methods are capable of persistently producing correct results in the range of 80% to 120% of nominal PS80 concentration. The LOQ was found to be 0.005 mg/mL (S/N = 3.4) while the LOD was found to be 0.002 mg/mL (S/N = 11.2).

Table 3. Method condition screening results

Experiment	Isopropanol content in ethanol (v/v), %	Volume of precipitation reagent (V_1), µL	Volume of supernatant for hydrolysis (V_2), µL	Criteria	
				Recovery, %	S/N of OA postpeak
1	25.0	20.0	20.0	84	0.0
2	25.0	20.0	40.0	85	0.0
3	25.0	40.0	20.0	92	0.0
4	25.0	40.0	40.0	93	0.0
5	65.0	20.0	20.0	99	0.0
6	65.0	20.0	40.0	98	3.2
7	65.0	40.0	20.0	102	5.2
8	65.0	40.0	40.0	104	6.1
9	11.4	30.0	30.0	85	0.0
10	78.6	30.0	30.0	103	15.2
11	45.0	13.2	30.0	98	0.0
12	45.0	46.8	30.0	99	5.2
13	45.0	30.0	13.2	97	0.0
14	45.0	30.0	46.8	96	0.0
15	45.0	30.0	30.0	96	0.0

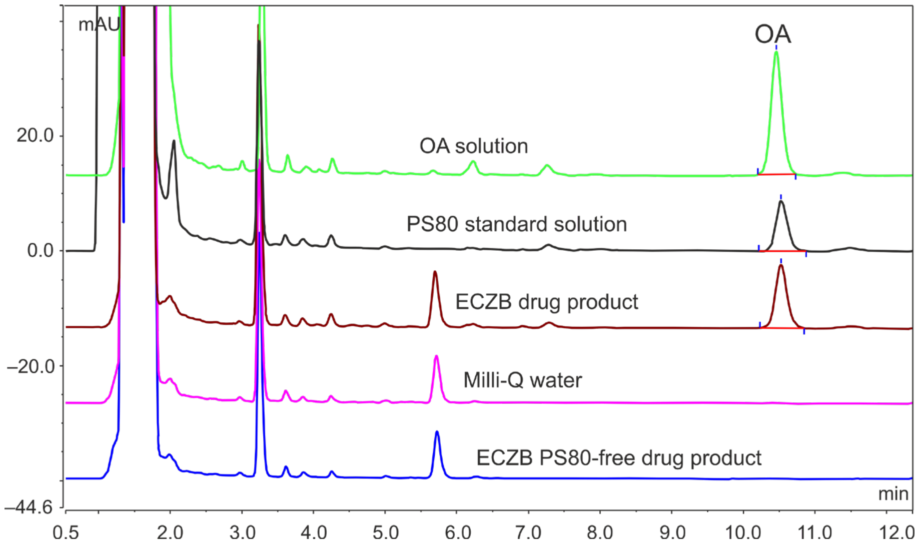

Fig. 3. Chromatograms of specificity assessment of PS80 determination in the ECZB substance.

Table 4. Accuracy estimation results

PS80 content from nominal concentration*, %	**Recovery, %**		
	ADMB	**ECZB**	**INFL**
NC, mg/mL	1.00	0.22	0.05
50	99.9	104.1	96.7
100	98.0	103.8	98.7
150	99.6	106.6	100.5

*Accuracy, precision, and repeatability for INFL and ECZB were assessed in the range of 40% to 160% and 80% to 120%, respectively.

Table 5. Repeatability assessment

Parameter	**PS80 content from nominal concentration*, %**	**CV, %**		
		ADMB	**ECZB**	**INFL**
Repeatability (*n* = 3)	50	2.6	1.0	3.0
	100	0.5	0.5	1.2
	150	2.5	3.9	2.9
Intermediate precision (*n* = 3)	50	5.4	4.3	3.5
	100	2.7	3.4	1.9
	150	4.8	5.6	2.3

*Accuracy, precision, and repeatability for INFL and ECZB were assessed in the range of 40% to 160% and 80% to 120%, respectively.

CONCLUSIONS

An HPLC method with spectrophotometric detection was developed for PS80 determination in TPs. The method is based on the hydrolysis of PS80 to free fatty acids, with OA as the main constituent being detected using RP HPLC. For monoclonal antibody removal, an additional step with organic solvent mixture precipitation was developed, while PS80 remained in solution, ensuring method accuracy. The method was approbated and validated for 3 therapeutic monoclonal antibody substances. The accuracy assessment demonstrated recovery ranging from 96% to 109%. The repeatability and intermediate precision values (*n* = 3) were less than 4.0% and 6.0%, respectively. The LOQ was 0.005 mg/mL. The current method requires minor quantities of protein products (≤35 µL). The method is also dependent on PS80 lot-to-lot variability, although the PS80 lots from a single manufacturer within two years of manufacture can be used as a standard to determine its content in drug formulation. Since the method was only tested on 3 monoclonal antibody drug products, others may require sample pretreatment optimization, which can be achieved by varying the isopropanol/ethanol ratio or adding precipitants, such as sulfosalicylic acid, which was tested in another method for filgrastim analysis.

Authors' contributions

A.D. Askretkov – development of analytical methods, conducting experimental studies and methods validation, writing the text of the article;

D.O. Shatalov – writing the article, developing of the research methodology, editing the text of an article;

N.V. Orlova – development of the research methodology, experimental data processing, adjustment of experimental studies;

D.I. Zybin – data visualization, writing the text of the article;

V.V. Nikolaeva – conceptualization of the research methodology;

A.A. Klishin – conceptualization of the research methodology;

E.S. Tuzova – correction of the text of the article, conceptualization of the article metodology;

D.S. Minenkov – editing the text of the article, development of research methodology;

S.A. Kedik – writing an article, developing of the research methodology, editing the text of an article, conceptualizing of the article;

Yu.A. Seregin – analysis of literary sources, writing and editing the text of the article, conceptualization of the article.

The authors declare no conflicts of interest.

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About the authors:

Aleksandr D. Askretkov, Postgraduate Student, Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: askretkov.a.d@gmail.com. https://orcid.org/0000-0003-0110-8323

Denis O. Shatalov, Cand. Sci. (Pharm.), Associate Professor, Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: shat-05@mail.ru. https://orcid.org/0000-0003-4510-1721

Natalya V. Orlova, Cand. Sci. (Biol.), Head of Research Laboratory, State Research Institute of Genetics and Selection of Industrial Microorganisms of NRC "Kurchatov Institute" (1, 1st Dorozhnyi pr., Moscow, 117545, Russia). E-mail: orlova.chemist@gmail.com. https://orcid.org/0000-0003-4161-5880

Dmitry I. Zybin, Senior Analytical Chemist, PHARMAPARK LLC (8, b. 1, Nauchnyi pr., Moscow, 117246, Russia). E-mail: zybin@pharmapark.ru. ResearcherID P-8049-2016, https://orcid.org/0000-0002-5542-982X

Valeriya V. Nikolaeva, Cand. Sci. (Biol.), Senior Specialist of Research Laboratory, State Research Institute of Genetics and Selection of Industrial Microorganisms of NRC "Kurchatov Institute" (1, 1st Dorozhnyi pr., Moscow, 117545, Russia). E-mail: leroffka@mail.ru. https://orcid.org/0000-0002-0431-5304

Anatoly A. Klishin, Specialist of Research Laboratory, State Research Institute of Genetics and Selection of Industrial Microorganisms of NRC "Kurchatov Institute" (1, 1st Dorozhnyi pr., Moscow, 117545, Russia). E-mail: anatolii-klishin@bk.ru. https://orcid.org/0000-0002-5497-6688

Elena S. Tuzova, Postgraduate Student, State Research Institute of Genetics and Selection of Industrial Microorganisms of NRC "Kurchatov Institute" (1, 1st Dorozhnyi pr., Moscow, 117545, Russia). E-mail: shaggy.crew.cut@gmail.com. https://orcid.org/0000-0002-5191-9354

Dmitry S. Minenkov, Cand. Sci. (Phys.-Math.), Senior Researcher, Ishlinsky Institute for Problems in Mechanics, Russian Academy of Sciences (101-1, Vernadskogo pr., Moscow, 119526, Russia). E-mail: minenkov.ds@gmail.com. https://orcid.org/0000-0001-6432-8134

Stanislav A. Kedik, Dr. Sci. (Eng.), Professor, Head of the Department of Biotechnology and Industrial Pharmacy, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: kedik@mirea.ru. https://orcid.org/0000-0003-2610-8493

Yuri A. Seregin, Cand. Sci. (Biol.), Head of Research and Development Department, Pharmapark LLC (8, b. 1, Nauchnyi pr., Moscow, 117246, Russia). E-mail: yuriy.seregin@pharmapark.ru. https://orcid.org/0000-0002-2161-3960

Об авторах:

Аскретков Александр Дмитриевич, аспирант кафедры биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: askretkov.a.d@gmail.com. https://orcid.org/0000-0003-0110-8323

Шаталов Денис Олегович, к.фарм.н, доцент кафедры биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: shat-05@mail.ru. https://orcid.org/0000-0003-4510-1721

Орлова Наталья Владимировна, к.б.н, заведующий испытательной лаборатории Национального исследовательского центра «Курчатовский институт» – ГосНИИгенетика (117545, Россия, Москва, 1-й Дорожный проезд, д. 1). E-mail: orlova.chemist@gmail.com. https://orcid.org/0000-0003-4161-5880

Зыбин Дмитрий Игоревич, старший химик-аналитик ООО «Фармапарк» (117246, Россия, Москва, Научный проезд, д. 8, стр. 1). E-mail: zybin@pharmapark.ru. https://orcid.org/0000-0002-5542-982X

Николаева Валерия Валерьевна, к.б.н, старший специалист испытательной лаборатории Национального исследовательского центра «Курчатовский институт» – ГосНИИгенетика (117545, Россия, Москва, 1-й Дорожный проезд, д. 1). E-mail: leroffka@mail.ru. https://orcid.org/0000-0002-0431-5304

Клишин Анатолий Анатольевич, специалист испытательной лаборатории Национального исследовательского центра «Курчатовский институт» – ГосНИИгенетика (117545, Россия, Москва, 1-й Дорожный проезд, д. 1). E-mail: anatolii-klishin@bk.ru. https://orcid.org/0000-0002-5497-6688

Тузова Елена Сергеевна, аспирант Национального исследовательского центра «Курчатовский институт» – ГосНИИгенетика (117545, Россия, Москва, 1-й Дорожный проезд, д. 1). E-mail: shaggy.crew.cut@gmail.com. https://orcid.org/0000-0002-5191-9354

Миненков Дмитрий Сергеевич, к.ф.-м.н., старший научный сотрудник Институт проблем механики им. А.Ю. Ишлинского РАН (119526, Россия, Москва, пр-т Вернадского, д. 101, корп. 1). E-mail: minenkov.ds@gmail.com. https://orcid.org/0000-0001-6432-8134

Кедик Станислав Анатольевич, д.т.н., профессор, заведующий кафедрой биотехнологии и промышленной фармации Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: kedik@mirea.ru. https://orcid.org/0000-0003-2610-8493

Серегин Юрий Александрович, к.б.н., начальник отдела, ООО «Фармапарк» (117246, Россия, Москва, Научный проезд, д. 8, стр. 1). E-mail: yuriy.seregin@pharmapark.ru. https://orcid.org/0000-0002-2161-3960

The article was submitted: January 13, 2021; approved after reviewing: February 16, 2022; accepted for publication: February 21, 2022.

The text was submitted by the author in English.
Edited for English language and spelling by Enago, an editing brand of Crimson Interactive Inc.

CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

ISSN 2686-7575 (Online)

https://doi.org/10.32362/2410-6593-2022-17-1-50-64

UDC 577.115.083; 577.112.345

RESEARCH ARTICLE

Synthesis of diethanolamine-based amino acid derivatives with symmetric and asymmetric radicals in their hydrophobic domain and potential antimicrobial activity

Maxim D. Korotkin[1],✉, Svetlana M. Filatova[1], Zaret G. Denieva[2], Ulyana A. Budanova[1], Yury L. Sebyakin[1]

[1]MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia
[2]A.N. Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, Moscow, 119071 Russia
✉Corresponding author, e-mail: maks.korotkin.99@mail.ru

Abstract

Objectives. *Resistance to antibiotics and other antimicrobial drugs is an acute problem in the world today. Therefore, the chemical and pharmaceutical industries are still in search of new antibacterial agents that can overcome the resistance of pathogenic bacterial strains. To date, it has been established that molecules with antimicrobial activity must have an amphiphilic nature, a small size, one or more positive charges, and the required degree of hydrophobicity, that is, a significant hydrophilic–lipophilic balance (HLB) value. Some examples of such structures are antimicrobial peptides or peptidomimetics. This study aimed to develop a universal scheme for synthesizing several amino acid derivatives based on diethanolamine diesters with symmetric and asymmetric radicals in a hydrophobic block and potential antibacterial activity.*

Methods. *The progression of chemical reactions was analyzed using thin-layer chromatography (TLC) on Sorbfil plates. The obtained compounds were isolated and purified using preparative TLC on Kieselgel (Merck) 60 F254 plates and column chromatography on Merck silica gel 0.040–0.063 mm. The TLC method was used to detect substances using a 3% ninhydrin solution, followed by heating to 70°C. The structures of the obtained compounds were confirmed by hydrogen-1 nuclear magnetic resonance (^1H NMR) spectroscopy on a Bruker WM-300 pulse NMR spectrometer, with hexamethyldisiloxane serving as the internal standard.*

Results. *The HLB values of the diethanolamine derivatives were calculated, and samples were selected for subsequent synthesis. A scheme was developed for preparing amino acid derivatives based on diethanolamine diesters with symmetric and asymmetric radicals in the hydrophobic domain, and five new compounds were synthesized. The hydrophilic blocks of these compounds included residues of amino acids such as glycine, β-alanine, L-ornithine, and L-lysine.*

Conclusions. *The potential antimicrobial activity of the synthesized peptidomimetics was assessed by their HLB values using the ACD/Labs Log P program. New amphiphiles were synthesized using amino acids and diethanolamine, and their structures were confirmed by ^{1}H NMR spectroscopy data. The synthesized compounds were prepared for antibacterial activity analysis.*

Keywords: *antimicrobial peptides, antibacterial agents, resistance, hydrophilic-lipophilic balance, amphiphiles, amino acids, diethanolamine esters*

For citation: Korotkin M.D., Filatova S.M., Denieva Z.G., Budanova U.A., Sebyakin Y.L. Synthesis of diethanolamine-based amino acid derivatives with symmetric and asymmetric radicals in their hydrophobic domain and potential antimicrobial activity. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(1):50–64 (Russ., Eng.). https://doi.org/10.32362/2410-6593-2022-17-1-50-64

НАУЧНАЯ СТАТЬЯ

Синтез производных аминокислот на основе диэтаноламина с симметричными и асимметричными радикалами в гидрофобном домене с потенциальной антимикробной активностью

М.Д. Короткин[1,✉], С.М. Филатова[1], З.Г. Дениева[2], У.А. Буданова[1], Ю.Л. Себякин[1]

[1] *МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия*

[2] *Институт физической химии и электрохимии им. А.Н. Фрумкина Российской академии наук, Москва, 119071 Россия*

✉*Автор для переписки, e-mail:* maks.korotkin.99@mail.ru

Аннотация

Цели. *Резистентность к антибиотикам и другим антимикробным препаратам является острой проблемой современности. Поиск новых антибактериальных агентов, преодолевающих резистентность патогенных штаммов бактерий, является востребованным в химико-фармацевтической промышленности. На сегодняшний день известно, что молекулы, обладающие антимикробной активностью, должны быть амфифильной природы, иметь небольшой размер, нести один или несколько положительных зарядов, а также обладать необходимой степенью гидрофобности, выраженной величиной гидрофильно-липофильного баланса. Такими структурами могут выступать антимикробные пептиды или пептидомиметики. Целью данного исследования была разработка универсальной схемы и проведение синтеза ряда производных аминокислот на основе диэфиров диэтаноламина с симметричными и асимметричными радикалами в гидрофобном блоке с потенциальной антибактериальной активностью.*

Методы. *Анализ химических реакций, выделение и очистку полученных соединений проводили с помощью тонкослойной и колоночной хроматографии. Обнаружение веществ осуществляли методом тонкослойной хроматографии с использованием нингидриновой реакции для их визуализации на пластинах. Структуры полученных соединений подтверждали методом ^{1}H-ЯМР спектроскопии.*

Результаты. *Проведен расчет величин гидрофильно-липофильного баланса производных диэтаноламина и выбраны образцы для последующего синтеза. Разработаны схемы получения производных аминокислот на основе диэфиров диэтаноламина с симметричными и асимметричными радикалами в гидрофобном домене и проведен синтез пяти новых соединений, в состав гидрофильных блоков которых входят остатки таких аминокислот, как глицин, β-аланин, L-орнитин и L-лизин.*

Выводы. *Произведена оценка потенциальной антимикробной активности синтезированных пептидомиметиков по величине их гидрофильно-липофильного баланса с помощью программы ACD/Labs Log P. Синтезированы новые амфифилы на основе аминокислот и диэтаноламина, структуры которых подтверждены данными ^{1}H-ЯМР спектроскопии.*

Ключевые слова: *антибактериальные агенты, антимикробные пептиды, резистентность, гидрофильно-липофильный баланс, амфифилы, аминокислоты, диэфиры диэтаноламина*

Для цитирования: Короткин М.Д., Филатова С.М., Дениева З.Г., Буданова У.А., Себякин Ю.Л. Синтез производных аминокислот на основе диэтаноламина с симметричными и асимметричными радикалами в гидрофобном домене с потенциальной антимикробной активностью. *Тонкие химические технологии*. 2022;17(1):50–64. https://doi.org/10.32362/2410-6593-2022-17-1-50-64

INTRODUCTION

Multiple drug-resistant strains of pathogenic microorganisms pose a serious threat to public health. The dynamics of the spread of antibiotic-resistant bacteria have demonstrated the importance of developing new antibacterial drugs [1, 2]. Although numerous research and experiments are being conducted globally to find novel biologically active compounds that can treat various bacterial infections and fungal diseases, the number of newly approved drugs has decreased significantly in the last 20 years [3–5].

Endogenous antimicrobial peptides are an essential part of innate immunity [6]. They have high bactericidal efficiency, as well as antiviral, antifungal, antitumor, and antioxidant properties [7, 8]. However, their low selectivity, high in vivo toxicity, potential immunogenicity, high cost, and complex large-scale industrial preparation have precluded them from being widely used in medical practice [9].

These shortcomings have prompted the development of synthetic strategies to produce antimicrobial low-molecular-weight peptidomimetics [10–13] that mimic the physical properties of the prototypes. The most important structural features of a molecule with antimicrobial activity are its amphiphilic nature, its degree of hydrophobicity, the presence of one or more positive charges, and its small size.

The action of cationic peptidomimetics is to destroy the cell membrane through pore formation [14]. When the integrity of the bacterial membrane is compromised, it results in intracellular content leakage and subsequent cell lysis [15, 16]. In addition, peptidomimetics can enhance the action of other antibiotics when used together [17]. There is evidence that threshold hydrophobicity is required for high antibacterial activity, but an uncontrolled increase in hydrophobicity causes an increase in toxicity [12].

The new class of cationic amphiphiles has a uniform structural design, with a hydrophobic domain that typically represents saturated or unsaturated aliphatic chains, aromatic compounds, and a hydrophilic component that bears one or more positive charges. Many natural amino acids or their sequences are used as hydrophilic blocks [18, 19]. An amide bond represents the spacer fragment that connects both domains, and its presence determines the high bioavailability of molecules.

According to research, the value of the minimum inhibitory concentration is influenced by the structure and length of hydrocarbon radicals in the hydrophobic domain to a certain extent [20].

This work aimed to synthesize several derivatives of glycine, β-alanine, L-lysine, and L-ornithine using symmetrical and asymmetric diethanolamine diesters in the hydrophobic block and investigate their biological activity.

EXPERIMENTAL

Several glycine, β-alanine, L-lysine, and L-ornithine derivatives were synthesized, isolated, and purified using diethanolamine, sodium hydroxide, sodium sulfate, citric acid, potassium carbonate, potassium iodide, 1-bromooctane, trifluoroacetic acid, di-*tert*-butyl dicarbonate, dimethylaminopyridine (DMAP), dicyclohexylcarbodiimide (DCC), octanoic acid, octyl bromide, and thionyl chloride (puriss. grade) (*Component Reaktiv*, Russia).

The hydrophilic–lipophilic balance (HLB) of the structures was calculated using the ACD/Labs Log P program (version 14.0.1.11391). The hydrogen-1 nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterated chloroform ($CDCl_3$) on a WM-300 pulse NMR spectrometer (*Bruker*, Germany) with a 300 MHz operating frequency and hexamethyldisiloxane as an internal standard. Thin-layer chromatography (TLC) was performed on Sorbfil plates (*IMID*, Russia) with particle sizes of 0.005–0.015 mm. Preparative TLC was performed on Kieselgel plates 60 F_{254} (*Merck*, Germany). Column chromatography was performed on silica gel 60 Å (0.040–0.063 mm) with 230–400 mesh particle size (*Merck*, Germany). The solvents used were of puriss. and p.a. grades (*Component Reaktiv*, Russia). The eluent systems were as follows:

(A) chloroform/methanol = 1:1
(B) toluene/ethyl acetate = 1:1
(C) hexane/diethyl ether = 4:3
(D) toluene/ethyl acetate = 20:1
(E) toluene/ethyl acetate = 5:1
(F) hexane/diethyl ether = 2:1
(G) toluene/ethyl acetate = 10:1
(H) chloroform/methanol = 20:1
(I) hexane/diethyl ether = 15:1

Substances were detected by TLC using a 3% ninhydrin solution (*Acros Organics*, Belgium), followed by heating to 70°C. The solvents were distilled off using an RV 3 vacuum rotary evaporator (*IKA*, Germany).

N-*tert*-butoxycarbonyl-diethanolamine (2) [21]

A solution of 2.34 g (10.7 mmol) of di-*tert*-butyl dicarbonate in 35 mL of tetrahydrofuran (THF) was added dropwise to a solution of 0.75 g (7.14 mmol) of diethanolamine **1** in 20 mL of THF for 1 h, maintaining the pH at 8. The reaction mass was stirred for 3 h at room temperature. The reaction progress was monitored using TLC in the (A) eluent system. After the reaction, the solvent was removed in a vacuum, and the resultant mixture was acidified with a 20% citric acid solution before being extracted with ethyl acetate (three times by 75 mL). The organic phase was dried over anhydrous sodium sulfate and then filtered. Product **2** had a yield of 0.77 g (52.6%).

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.48 (s, 9H, $C\underline{H}_3$), 3.31 (t, 4H, $NHC\underline{H}_2CH_2$), 3.86 (t, 4H, $NHCH_2C\underline{H}_2$).

N-(*tert*-butoxycarbonyl)-*O*,*O′*-dioctyldiethanolamine (3) and *N*-*tert*-butoxycarbonyl-*O*-octyldiethanolamine (13)

Furthermore, 0.42 g (2.2 mmol) of 1-bromooctane, 0.40 g (2.9 mmol) of potassium carbonate, and a catalytic amount of potassium iodide were added to a solution of 0.15 g (0.73 mmol) of **2** in 20 mL of THF. The reaction mass was stirred for 24 h at 80°C. The reaction progress was monitored using TLC in the (B) and (C) eluent systems. The solvent was subsequently removed in a vacuum, and the resultant mixture was extracted with ethyl acetate (three times by 75 mL). The organic phase was dried over anhydrous sodium sulfate and subsequently filtered. Ethyl acetate was evaporated using a rotary evaporator. Compounds **3** and **13** were isolated from the mixture by column chromatography, with the polarity of the (D) eluent system gradually increasing to that of the (E) system. Compound **3** had a yield of 39 mg (12.5%), while compound **13** had a yield of 92 mg (39.7%).

^{1}H NMR spectrum of compound **3** ($CDCl_3$, δ, ppm): 0.88 (6H, t, $CH_2C\underline{H}_3$); 3.40 (4H, t, $^{\alpha}C\underline{H}_2$); 1.54 (4H, p, $^{\beta}C\underline{H}_2$); 1.27 (20H, m, $C\underline{H}_2$); 3.40 (2H, t, $NC\underline{H}_2CH_2O$); 3.51 (2H, t, $NC\underline{H}_2CH_2O$); 3.51 (4H, t, $NCH_2C\underline{H}_2O$); 1.48 (9H, s, $C(C\underline{H}_3)_3$).

^{1}H NMR spectrum of compound **13** ($CDCl_3$, δ, ppm): 0.87 (3H, t, $CH_2C\underline{H}_3$); 3.44 (2H, m, $^{\alpha}C\underline{H}_2$); 1.57 (2H, p, $^{\beta}C\underline{H}_2$); 1.27 (10H, m, $C\underline{H}_2$); 3.44 (4H, t, $NC\underline{H}_2CH_2O$); 3.69 (4H, t, $NCH_2C\underline{H}_2O$); 1.45 (9H, s, $C(C\underline{H}_3)_3$); 3.57 (1H, s, $O\underline{H}$).

O,*O′*-dioctyl-diethanolamine trifluoroacetate (4)

Here, 1 mL of trifluoroacetic acid was added to a solution of 39 mg (0.09 mmol) of compound **3**, which had been preliminarily cooled to 0°C in 10 mL of chloroform, and the reaction mixture was stirred for 20 min. The reaction progress was monitored using TLC in the (E) eluent system. The solvent and residual trifluoroacetic acid were then removed in a vacuum. Thus, 37 mg of compound **4** was obtained, with a 92.3% yield.

N-(*tert*-butoxycarbonyl)-glycine (6a)

A solution of 5.81 g (26.66 mol) of di-*tert*-butyl dicarbonate in 30 mL of isopropanol was added dropwise to a solution of 1.00 g (13.33 mmol) of glycine (**5a**) in 20 mL of distilled water for 1 h, maintaining pH 8 with 4 M sodium hydroxide solution. The reaction mass was stirred for 3 h at room temperature. The reaction progress was monitored by TLC in the (A) eluent system. The solvents were removed under a vacuum after the reaction was completed. The resultant mixture was acidified with a 20% citric acid solution and extracted with ethyl acetate (three times by 50 mL). The organic phase was dried over anhydrous sodium sulfate. Ethyl acetate was distilled off using a rotary evaporator, and 2.13 g of product **6a** was obtained with a 91.4% yield.

^{1}H NMR spectrum of compound **6a**: 1.48 (9H, s, $C(C\underline{H}_3)_3$); 12.26 (1H, s, COOH); 6.85 (1H, t, $N\underline{H}C(R)CO$); 4.33 (2H, d, $NC\underline{H}_2CO$).

N-(*tert*-butoxycarbonyl)-β-alanine (6b)

A similar procedure was used to prepare **6b**, and 1.85 g of product **6b**, with an 87.1% yield, was obtained from 1 g (11.24 mmol) of β-alanine **5b**.

^{1}H NMR spectrum of compound **6b**: 1.49 (9H, s, $C(C\underline{H}_3)_3$); 12.21 (1H, s, COOH); 6.80 (1H, t, $N\underline{H}C(R)CO$); 3.21 (2H, s, $NC\underline{H}_2CH_2CO$); 2.35 (2H, s, $NCH_2C\underline{H}_2CO$).

*N*α,*N*δ-bis(*tert*-butoxycarbonyl)-L-ornithine (10a)

A similar procedure was used to prepare **10a**, and 1.96 g (5.90 mmol) of product **10a**, with a 77.8% yield, was obtained from 1 g (7.58 mmol) of L-ornithine **9a**.

^{1}H NMR spectrum of compound **10a**: 1.47 (9H, s, $C(C\underline{H}_3)_3$); 12.27 (1H, s, COOH); 5.12 (1H, t, $N\underline{H}C(R)CO$); 4.01 (1H, d, $NC\underline{H}(R)CO$); 3.02 (2H, k, $NC\underline{H}_2CH_2CH_2C$); 1.62 (2H, p, $NCH_2C\underline{H}_2CH_2C$); 1.84 (2H, p, $NCH_2CH_2C\underline{H}_2C$); 4.21 (1H, k, $N\underline{H}CH(R)CO$).

*N*α,*N*ε-bis(*tert*-butoxycarbonyl)-L-lysine (10b)

A similar procedure was used to prepare **10b**, and 1.99 g (5.75 mmol) of product **10b** with an 83.9% yield, was obtained from 1 g (6.85 mmol) of L-lysine **9b**.

^{1}H NMR spectrum of compound **10b**: 1.48 (9H, s, $C(C\underline{H}_3)_3$); 12.25 (1H, s, COOH); 5.14 (1H, t, $N\underline{H}C(R)CO$); 4.03 (1H, d, $NC\underline{H}(R)CO$); 3.09 (2H, k, $NC\underline{H}_2CH_2CH_2CH_2C$); 1.63 (2H, p, $NCH_2C\underline{H}_2CH_2CH_2C$); 1.32 (2H, p, $NCH_2CH_2C\underline{H}_2CH_2C$); 1.83 (2H, m, $NCH_2CH_2CH_2C\underline{H}_2C$); 4.76 (1H, k, $N\underline{H}CH(R)CO$).

N-((*tert*-butoxycarbonyl)-glycyl)-*O*,*O'*-dioctyl-diethanolamine (7a)

A catalytic amount of DMAP, 28 mg (0.16 mmol) of **6a**, and 49 mg (0.24 mmol) of DCC were added to a solution of 37 mg (0.08 mmol) of compound **4** in 20 mL of chloroform, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 48 h at room temperature. The reaction progress was monitored using TLC in the (E) eluent system. The resultant mixture was centrifuged, and the solution was decanted. The precipitate was washed with chloroform and centrifuged again, and the solution was subsequently decanted. The resultant solutions were combined, and then chloroform was distilled off using a rotary evaporator. Compound **7a** was isolated from the mixture by preparative TLC in the (G) eluent system, resulting in 22 mg of byproduct **7a** with a yield of 53.6%.

^{1}H NMR spectrum of compound **7a**: 0.86 (6H, t, $CH_2C\underline{H}_3$); 3.74 (4H, t, $^{\alpha}C\underline{H}_2$); 1.65 (4H, p, $^{\beta}C\underline{H}_2$); 1.26 (20H, m, $C\underline{H}_2$); 3.74 (4H, t, $NC\underline{H}_2CH_2O$); 4.17 (4H, t, $NCH_2C\underline{H}_2O$); 1.50 (9H, s, $C(C\underline{H}_3)_3$); 4.48 (2H, s, $NC\underline{H}_2CO$); 5.23 (1H, s, $CON\underline{H}CH_2CO$).

Glycyl-*O*,*O'*-dioctyl-diethanolamine trifluoroacetate (8a)

Trifluoroacetic acid (1 mL) was added to a solution of 22 mg (0.05 mmol) of compound **7a** preliminarily cooled to 0°C in 10 mL of methylene chloride. The reaction mass was stirred for 20 min. The solvent and trifluoroacetic acid residue were removed under vacuum. 21 mg of compound **8a** with a yield of 93.3% was obtained.

N-(*tert*-butoxycarbonyl)-*O*-octyl-*O'*-octanoyl-diethanolamine (14)

A catalytic amount of DMAP, 0.13 g (0.87 mmol) of octanoic acid, and 0.12 g (0.58 mmol) of DCC were added to a solution preliminarily cooled to 0°C of 92 mg (0.29 mmol) of compound **13** in 20 mL of chloroform. The reaction mass was stirred for 48 h. Then the resultant mixture was filtered, the solvent was distilled off in a vacuum, and the resultant mixture was extracted with ethyl acetate (three times by 50 mL). The organic phase was dried over anhydrous sodium sulfate. Ethyl acetate was distilled off using a rotary evaporator. Compound **14** was isolated from the mixture by preparative TLC in the (E) eluent system, resulting in 103 mg of byproduct **14** with a yield of 80.3%.

^{1}H NMR spectrum of compound **14**: 0.89 (6H, t, $CH_2C\underline{H}_3$); 3.42 (2H, t, $^{\alpha}C\underline{H}_2$); 1.56 (2H, p, $^{\beta}C\underline{H}_2$); 2.31 (2H, t, $^{\alpha}C\underline{H}_2$); 1.63 (2H, p, $^{\beta}C\underline{H}_2$); 1.28 (18H, m, $C\underline{H}_2$); 3.42 (2H, t, $NC\underline{H}_2CH_2O$); 3.51 (2H, t, $NC\underline{H}_2CH_2O$); 3.51 (4H, t, $NCH_2C\underline{H}_2O$); 1.48 (9H, s, $C(CH_3)_3$).

O-octyl-*O'*-octanoyl-diethanolamine trifluoroacetate (15)

Trifluoroacetic acid (1 mL) was added to a solution of 103 mg (0.23 mmol) of compound **14** in 25 mL of methylene chloride, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 20 min. The solvent and trifluoroacetic acid residue were removed in a vacuum. Compound **15** had a yield of 99 mg (93.1%).

N-((*tert*-butoxycarbonyl)-glycyl)-*O*-octyl-*O'*-octanoyl-diethanolamine (16)

A catalytic amount of DMAP, 77 mg (0.44 mmol) of compound **6a**, and 136 mg (0.66 mmol) of DCC were added to a solution of 99 mg (0.22mmol) of compound 15 in 25 mL of chloroform, which had been cooled to 0°C. The reaction mass was stirred for 48 h. The reaction progress was monitored using TLC in the (C) eluent system. The resultant mixture was centrifuged, and the solution was decanted. The precipitate was washed with chloroform, and centrifuged again. The resultant solutions were combined, and then chloroform was evaporated using a rotary evaporator. Compound **16** was isolated from the mixture by column chromatography in the (G) eluent system, resulting in 72 mg of byproduct **16** with a yield of 66.4%.

^{1}H NMR spectrum of compound **16**: 0.87 (6H, t, $CH_2C\underline{H}_3$); 3.78 (2H, t, $^{\alpha}C\underline{H}_2$); 1.53 (2H, p, $^{\beta}C\underline{H}_2$); 2.35 (2H, t, $^{\alpha}C\underline{H2}$); 1.63 (2H, p, $^{\beta}C\underline{H}_2$); 1.25 (18H, m, $C\underline{H}_2$); 3.78 (4H, m, $NC\underline{H}_2CH_2O$); 4.11 (4H, m, $NCH_2C\underline{H}_2O$); 1.51 (9H, s, $C(C\underline{H}_3)_3$); 4.34 (2H, s, $NC\underline{H}_2CO$); 5.23 (1H, s, $CON\underline{H}CH_2CO$).

Glycyl-*O*-octyl-*O'*-octanoyl-diethanolamine trifluoroacetate (17)

Trifluoroacetic acid (1 mL) was added to a solution of 72 mg (0.14 mmol) of compound **16** in 20 mL of methylene chloride, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 20 min. The reaction progress was monitored using TLC in the (C) eluent system. The solvent and trifluoroacetic acid residue were removed in a vacuum. Compound **17** had a yield of 67 mg (90.3%).

N,*N*-di(2-chloroethyl)amine (18)

A solution of 1.50 g (14.29 mmol) of compound **1** in 40 mL of methylene chloride was added dropwise to a solution of 5.10 g (42.9 mmol) of thionyl chloride in 10 mL of methylene chloride for 1 h at 0°C. Then the reaction mass was stirred at room temperature for 48 h. The reaction progress was monitored using TLC in the (A) eluent system. The solvent and the rest of the thionyl chloride were removed in a vacuum. The resultant mixture was alkalized with a 15% potassium carbonate solution to pH 7–8, and then extracted with ethyl acetate (three times by 50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and the solvent was distilled off using a rotary evaporator. Compound **18** had a yield of 1.30 g (64.0%).

^{1}H NMR spectrum of compound **18**: 1.7 (1H, s, $N\underline{H}$); 2.92 (4H, m, $NHC\underline{H}_2$); 3.55 (4H, m, $NHCH_2C\underline{H}_2$).

O,*O'*-dioctyl-diethanolamine (19)

A catalytic amount of potassium iodide, 3.89 g (28.16 mmol) of potassium carbonate, and 4.5 mL of 1-octanol were added to a solution of 1.00 g (7.04 mmol) of compound **18** in 40 mL of acetonitrile. The reaction mass was stirred for 24 h at 80°C. The reaction progress was monitored using TLC in the (H) eluent system. The solution was filtered, and then the acetonitrile was removed in a vacuum. The residue was extracted with ethyl acetate (three times by 50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and the solvent was distilled off using a rotary evaporator. Compound **19** had a yield of 1.6 g (69.1%).

^{1}H NMR spectrum of compound **19**: 0.99 (6H, t, $CH_2C\underline{H}_3$); 0.99 (1H, s, $N\underline{H}$); 1.32 (20H, m, $C\underline{H}_2CH_3$); 1.53 (4H, m, $OCH_2C\underline{H}_2$); 2.81 (4H, t, $NHC\underline{H}_2CH_2$); 3.40 (4H, t, $OC\underline{H}_2CH_2$); 3.52 (4H, m, $NHCH_2C\underline{H}_2$).

N-((*tert*-butoxycarbonyl)-glycyl)-*O*,*O'*-dioctyl-diethanolamine (20a)

A catalytic amount of DMAP, 0.26 g (1.46 mmol) of compound **6a**, and 0.45 g (2.19 mmol) of DCC were added to a solution of 0.24 g (0.73 mmol) of compound **19** in 30 mL of methylene chloride, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 24 h. The reaction progress was monitored using TLC in the (C) eluent system. The methylene chloride was then removed in a vacuum. The resultant mixture was washed with 20 mL of hexane, and then the solution was centrifuged and decanted. The precipitate was repeatedly washed with hexane, and then the solution was centrifuged and decanted again. The resultant solutions were combined, and then the solvent was evaporated using a rotary evaporator. Compound **20a** was isolated from the mixture by column chromatography, gradually increasing the polarity of the (I) system to (E) system, resulting in 0.31 g of byproduct **20a** with a yield of 87.4%.

^{1}H NMR spectrum of compound **20a**: 0.87 (6H, t, $CH_2C\underline{H}_3$); 3.62 (4H, t, $^{\alpha}C\underline{H}_2$); 1.55 (4H, p, $^{\beta}C\underline{H}_2$); 1.26 (20H, m, $C\underline{H}_2$); 3.62 (4H, t, $NC\underline{H}_2CH_2O$); 4.11 (4H, t, $NCH_2C\underline{H}_2O$); 1.49 (9H, s, $C(C\underline{H}_3)_3$); 4.48 (2H, s, $NC\underline{H}_2CO$); 5.23 (1H, s, $CON\underline{H}CH_2CO$).

N-((*tert*-butoxycarbonyl)-β-alanyl)-*O*,*O'*-dioctyl-diethanolamine (20b)

A similar procedure was used to prepare **20b**, and 0.267 g of byproduct **20b**, with a yield of a 73.2%, was obtained from 0.24 g (0.73 mmol) of compound **19**.

^{1}H NMR spectrum of compound **20b**: 0.87 (6H, t, $CH_2C\underline{H}_3$); 3.62 (4H, t, $^{\alpha}C\underline{H}_2$); 1.60 (4H, p, $^{\beta}C\underline{H}_2$); 1.25 (20H, m, $C\underline{H}_2$); 3.62 (4H, t, $NC\underline{H}_2CH_2O$); 4.06 (4H, t, $NCH_2C\underline{H}_2O$); 1.41 (9H, s, $C(CH_3)_3$); 2.49 (2H, t, $NCH_2C\underline{H}_2CO$); 3.35 (2H, k, $NC\underline{H}_2CH_2CO$); 5.02 (1H, s, $CONHCH_2CH_2CO$).

***N*α,*N*δ-(bis(*tert*-butoxycarbonyl)-L-ornithyl)-*O*,*O*'-dioctyl-diethanolamine (22a)**

A similar procedure was used to prepare **22a**, and 0.34 g of byproduct **22a**, with a yield of 72.5%, was obtained from 0.24 g (0.73 mmol) of compound **19**.

^{1}H NMR spectrum of compound **22a**: 0.84 (6H, t, $CH_2C\underline{H}_3$); 3.42 (4H, t, $^{\alpha}C\underline{H}_2$); 1.50 (4H, p, $^{\beta}C\underline{H}_2$); 1.26 (20H, m, $C\underline{H}_2$); 3.42 (4H, t, $NC\underline{H}_2CH_2O$); 4.08 (4H, t, $NCH_2C\underline{H}_2O$); 1.40 (18H, s, $C(C\underline{H}_3)_3$); 4.23 (1H, k, $NC\underline{H}(R)CO$); 5.07 (1H, s, $CON\underline{H}CH(R)CO$); 3.10 (2H, k, $NC\underline{H}_2CH_2CH_2C$); 1.60 (2H, m, $NCH_2C\underline{H}_2CH_2C$); 1.79 (2H, m, $NCH_2CH_2C\underline{H}_2C$); 4.61 (1H, s, $N\underline{H}(CH_2)_3C$).

***N*α,*N*δ-(bis(*tert*-butoxycarbonyl)-L-lysyl)-*O*,*O*'-dioctyl-diethanolamine (22b)**

A similar procedure was used to prepare **22b**, and 0.282 g of byproduct **22b**, with a yield of 58.8%, was obtained from 0.24 g (0.73 mmol) of compound **19**.

^{1}H NMR spectrum of compound **22b**: 0.87 (6H, t, $CH_2C\underline{H}_3$); 3.46 (4H, t, $^{\alpha}C\underline{H}_2$); 1.48 (4H, m, $^{\beta}C\underline{H}_2$); 1.25 (20H, m, $C\underline{H}_2$); 3.46 (4H, t, $NC\underline{H}_2CH_2O$); 4.10 (4H, t, $NCH_2C\underline{H}_2O$); 1.42 (18H, s, $C(C\underline{H}_3)_3$); 4.24 (1H, k, $NC\underline{H}(R)CO$); 5.08 (1H, s, $CON\underline{H}CH(R)CO$); 3.09 (2H, k, $NC\underline{H}_2CH_2CH_2CH_2C$); 1.61 (2H, m, $NCH_2C\underline{H}_2CH_2CH_2C$); 1.36 (2H, p, $NCH_2CH_2C\underline{H}_2CH_2C$); 1.78 (2H, m, $NCH_2CH_2CH_2C\underline{H}_2C$); 4.58 (1H, s, $N\underline{H}(CH_2)_4C$).

Glycyl-*O*,*O*'-dioctyl-diethanolamine trifluoroacetate (21a)

Trifluoroacetic acid (1 mL) was added to a solution of 0.310 g (0.64 mmol) of compound **20a** in 30 mL of methylene chloride, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 20 min. The reaction progress was monitored using TLC in the (C) eluent system. The solvent and trifluoroacetic acid residue were removed in a vacuum. Target product **21a** had a yield of 0.296 g (92.8%).

Triftoracetate β-alanil-*O*,*O*'-dioctyl-diethanolamine (21b)

A similar procedure was used to prepare **21b**, and 0.248 g of target product **21b**, with a yield of 90.3%, was obtained from 0.267 g (0.53 mmol) of compound **20b.**

Trifluoroacetate L-ornithyl-*O*,*O*-dioctyl-diethanolamine (23a)

A similar procedure was used to prepare **23a**, and 0.316 g of target product **23a**, with a yield of 89.0%, was obtained from 0.340 g (0.53 mmol) of compound **22a.**

L-lysyl-*O*,*O*'-dioctyl-diethanolamine trifluoroacetate (23b)

A similar procedure was used to prepare **23b**, and 0.259 g of target product **23b**, with a yield of 88.1%, was obtained from 0.282 g (0.429 mmol) of compound **22b**.

RESULTS AND DISCUSSION

The potential antimicrobial activity of peptidomimetics can be preliminarily assessed by their HLB value [22]. This parameter largely determines the possible electrostatic interactions and hydrogen bond formation between the molecule and the bacterial cell wall components.

To select the most effective structures, we calculated the HLB values of the diethanolamine (DEA) derivatives and several amino acids, such as glycine (Gly), β-alanine (βAla), L-phenylalanine (Phe), L-tyrosine (Tyr), γ-aminobutyric acid (GABA), L-tryptophan (Trp), L-lysine (Lys), and L-ornithine (Orn), with alkyl radical lengths of C_6–C_{12} carbon atoms (Fig.).

Most of the diethanolamine diester-based amino acid derivatives had the desired HLB range of 5–8. Table shows the structures of the target compounds.

Glycine and β-alanine derivatives were chosen to investigate the effect of carbon skeleton length on antibacterial activity, while L-ornithine and L-lysine derivatives were chosen to investigate the effect of the number of methylene groups of the side radical of amino acids on biological activity.

Scheme 1 was developed to synthesize the selected compounds.

Compound **2** was treated with octyl bromide in the presence of potassium carbonate and a catalytic amount of potassium iodide in THF to create a hydrophobic block. The TLC and ^{1}H NMR spectroscopy analyses of the products revealed that monoester **13** containing a free hydroxyl group and one alkyl radical was predominantly formed by the developed method. Compounds **3** and **13**, which had yields of 12.5% and 39.7%, respectively, were isolated from the mixture by column chromatography.

The protecting group of compound **3** was removed by the action of trifluoroacetic acid. After the reaction, the solvent and acid residue were removed under a vacuum, affording salt **4** with a 92.3% yield.

The carbodiimide method was used to conjugate the polar part (**6a**) and the hydrophobic block (**4**) in the presence of DMAP. After the protecting group was removed, the target amphiphile (**7a**) was obtained, with a yield of 53.6%. The structures of the byproduct and target compounds were confirmed by ^{1}H NMR spectroscopy.

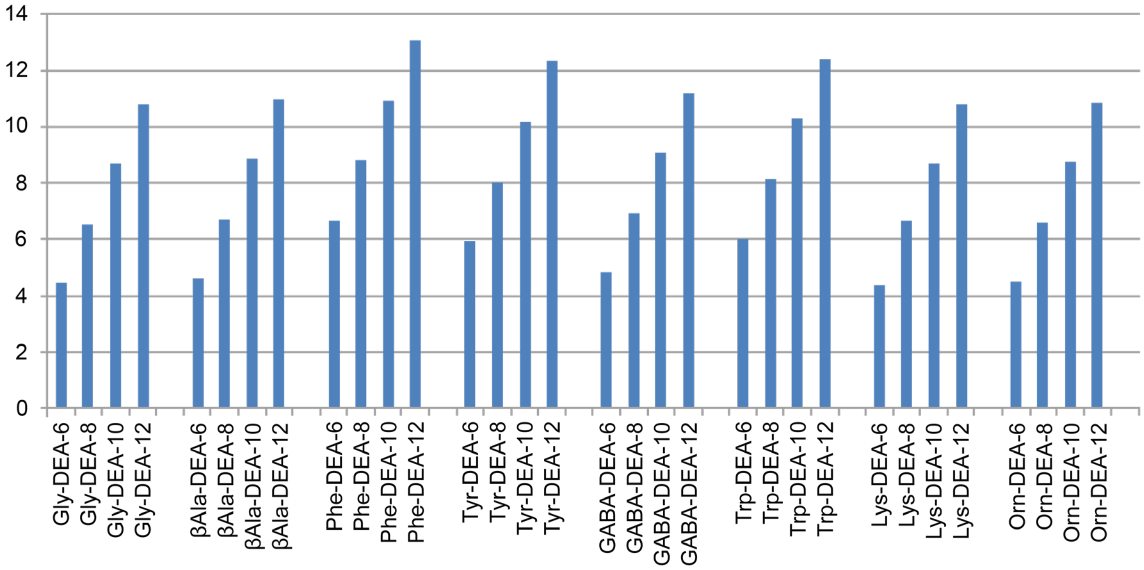
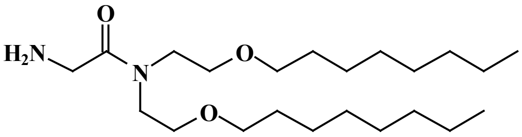
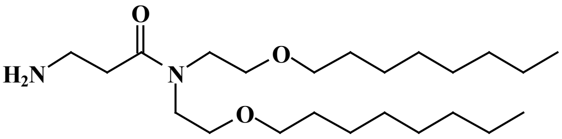
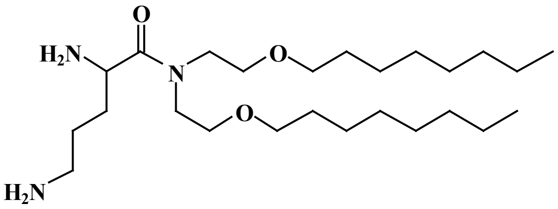
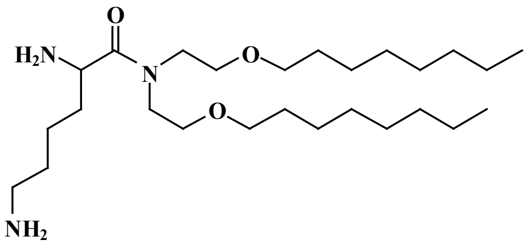
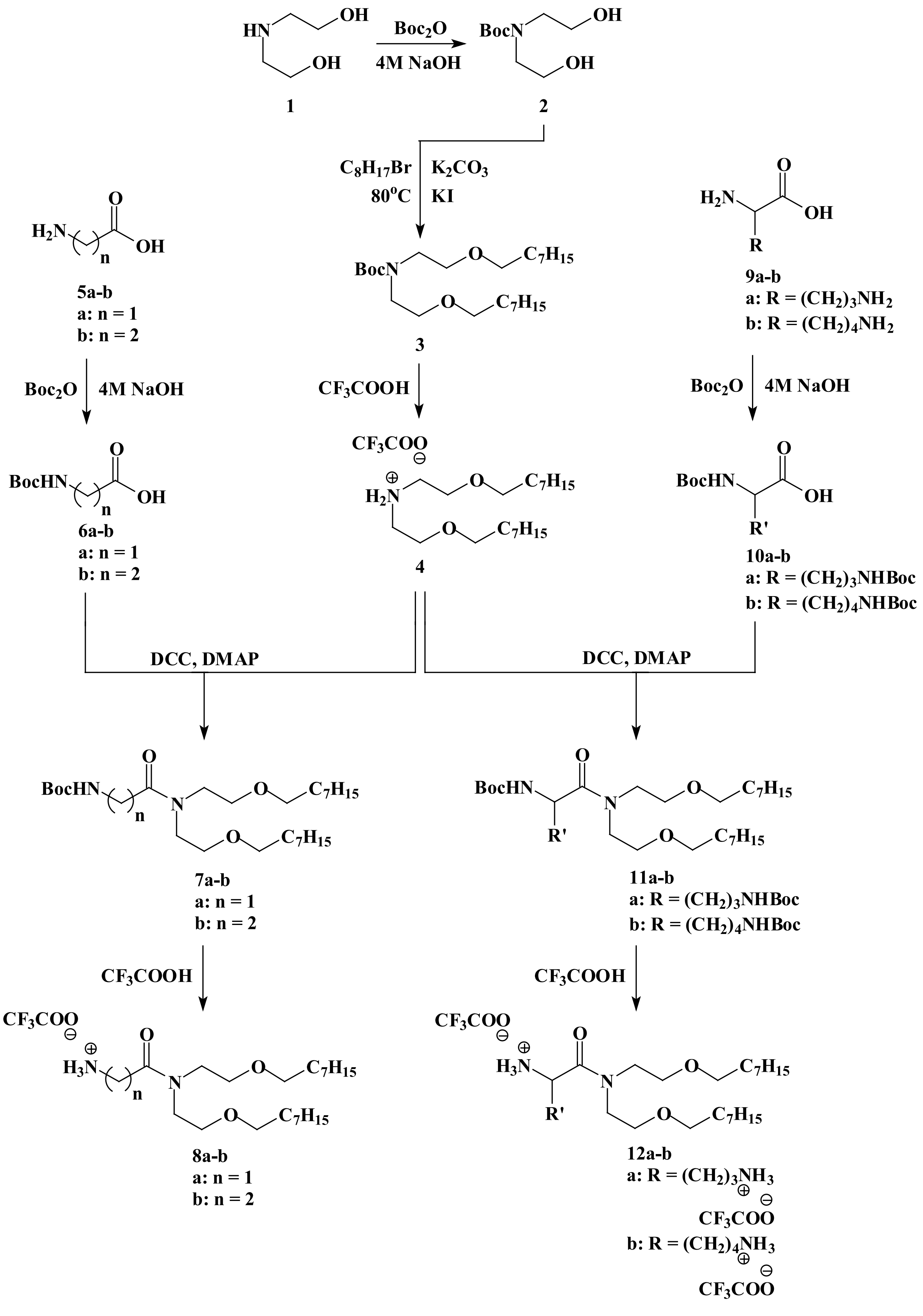


Figure. Dependence of HLB values on the structure of amphiphiles with symmetrical alkyl substituents in the nonpolar block. DEA stands for diethanolamine, while 6, 8, 10, and 12 represent the number of carbon atoms in the saturated aliphatic chains.

Table. HLB value of the selected compounds

Compound	Structure	HLB value
8a (**21a**)		6.56
8b (**21b**)		6.73
12a (**23a**)		6.62
12b (**23b**)		6.65



Scheme 1. Preparation of the diethanolamine diester-based amino acid derivatives. DCC is the *N*,*N*'-dicyclohexylcarbodiimide, DMAP is the 4-dimethylaminopyridine, Boc is the *tert*-butoxycarbonyl protecting group.

As shown in Scheme 2, the **13** byproduct obtained during the synthesis, which accounted for 39.7% of the total reaction mass, was used to produce an amphiphilic diethanolamine derivative (**17**) containing hybrid alkyl-acyl radicals in the hydrophobic block.

Compound **13** was reacted with octanoic acid in the presence of DCC and DMAP in chloroform. Byproduct **14** was isolated from the mixture using preparative TLC, resulting in an 80.3% yield. The structure of compound **14** was confirmed by ^{1}H NMR spectroscopy.

The *tert*-butoxycarbonyl group of the alkyl-acyl derivative of diethanolamine (**14**) was removed by the action of trifluoroacetic acid in methylene chloride. Compound **15** had a 93.1% yield.

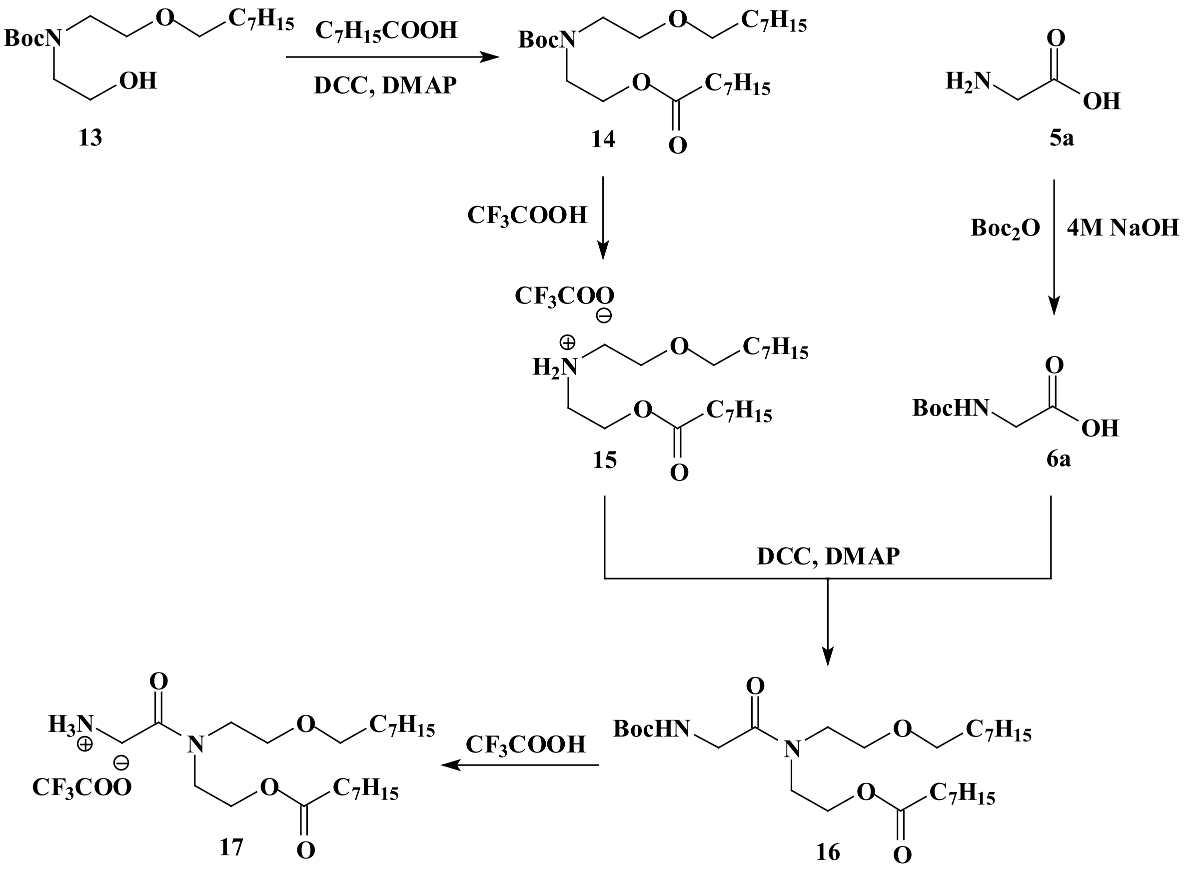
The carbodiimide method was used to produce amphiphile (**16**) in the presence of DMAP in chloroform for 48 h, similar to the conjugation reaction shown in Scheme 1. The solvent was removed under a vacuum when the interaction was completed. Product **16** was obtained with a 66.4% yield using silica gel column chromatography. The structure was confirmed by ^{1}H NMR spectroscopy.

After the *tert*-butoxycarbonyl group was removed, trifluoroacetic salt (**17**) was obtained with a 90.3% yield.

The preparation of the target diethanolamine diester derivatives (**8a–b** and **12a–b**) using Scheme 1 was inefficient because of the predominant generation of a side product, monoester **13**. Scheme 3 was developed to solve this problem; it differs from Scheme 1 in that it produces relatively high yields of the byproducts because of an increase in the reactivity of diethanolamine and the nonnecessity for a *tert*-butoxycarbonyl protecting group, significantly simplifying the synthesis.

A solution of 1 in chloroform was added dropwise to thionyl chloride. *N*,*N*-di(2-chloroethyl)-amine (**18**) had a 64.0% yield. Octanol-1 was added to di-(2-chloroethyl)-amine **18** in the presence of potassium carbonate and potassium iodide in acetonitrile at 80°C. After purification, product **19** was obtained with a 69.1% yield.

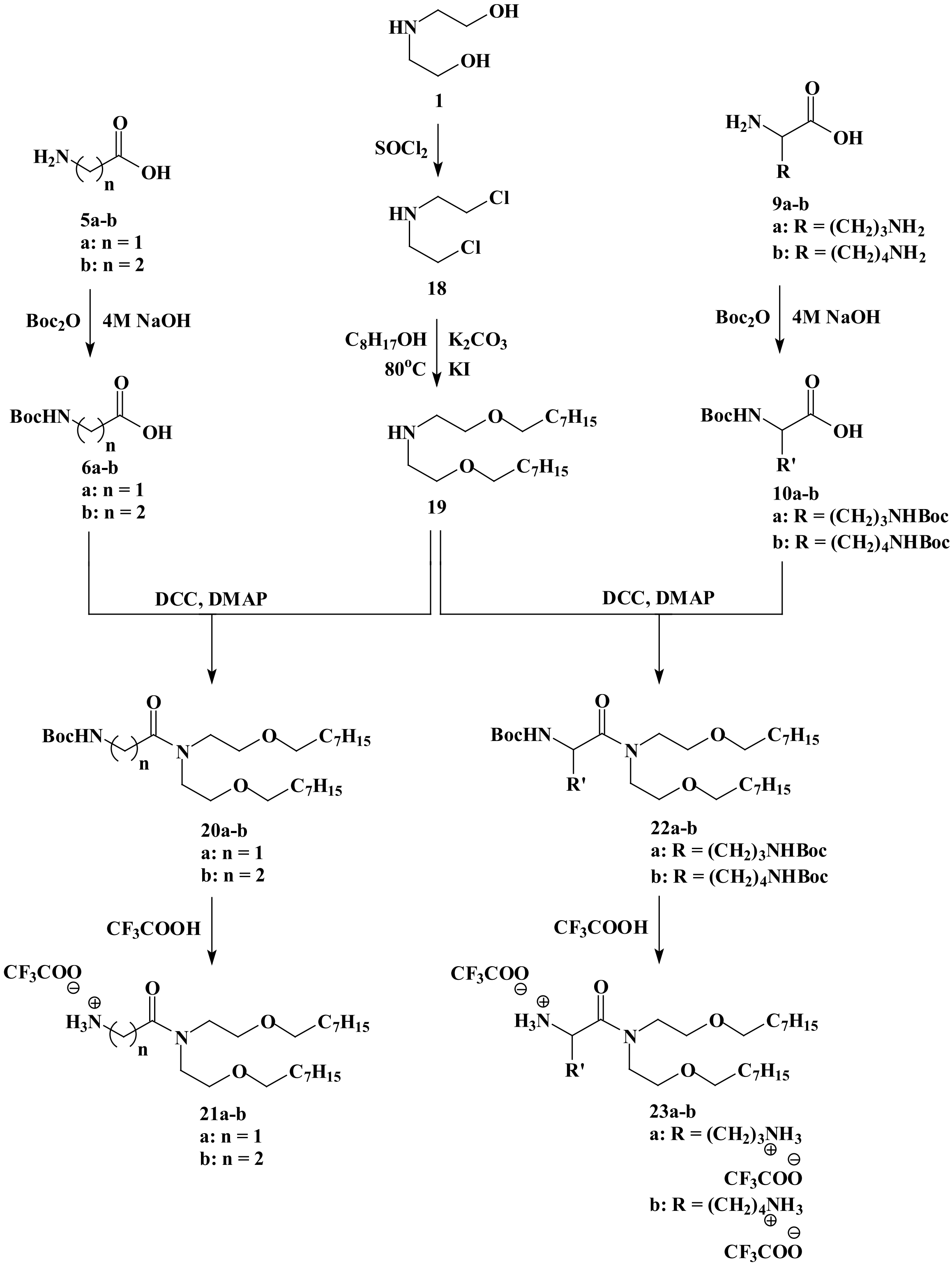
Tert-butoxycarbonyl-protected amino acids **6a–b** and **10a–b** and compound **19** were conjugated similarly to the transformation described in Schemes 1 and 2. The reaction products **20a–b** and **22a–b**, which



Scheme 2. Preparation of compound **17** with asymmetric radicals in the hydrophobic block. DCC is the *N*,*N*'-dicyclohexylcarbodiimide, DMAP is the 4-dimethylaminopyridine, Boc is the *tert*-butoxycarbonyl protecting group.

had yields of 87.4%, 73.2%, 72.5%, and 58.8%, respectively, were isolated from the mixtures by column chromatography on silica gel. The structures of the byproducts and target compounds were confirmed by ^{1}H-NMR spectroscopy data.

Cationic amphiphiles, **21a–b** and **23a–b**, with yields 92.8%, 90.3%, 89.0%, and 88.1%, respectively, were obtained by treating compounds **20a–b** and **22a–b** with trifluoroacetic acid and removing the solvent under a vacuum.



Scheme 3. Preparation of the target derivatives of diethanolamine diesters. DCC is the *N,N'*-dicyclohexylcarbodiimide, DMAP is the 4-dimethylaminopyridine, Boc is the *tert*-butoxycarbonyl protecting group.

CONCLUSIONS

A scheme was developed for preparing amino acid derivatives based on diethanolamine diesters. Five new compounds were synthesized, and their hydrophilic blocks included residues of amino acids such as glycine, β-alanine, L-ornithine, and L-lysine. The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy. The synthesized compounds were prepared in order to analyze their antibacterial activity against gram-positive and gram-negative strains. The safety of the leading antibacterial compounds in terms of general and hemolytic toxicity will be investigated in future studies.

Acknowledgments

This work was performed using the equipment of the Shared Science and Training Center for Collective Use of RTU MIREA and supported by the Ministry of Science and Higher Education of the Russian Federation. This work was supported by the Russian Foundation for Basic Research, project No. 20-04-00672.

Authors' contribution

M.D. Korotkin – conducting the study, collection and provision of the material, writing the article;

S.M. Filatova – conducting the study, collection and provision of the material, writing the article;

Z.G. Denieva – conducting the study, collection and provision of the material, writing the article;

U.A. Budanova – consultation on conducting individual stages of the study, scientific editing;

Y.L. Sebyakin – development of the research idea and literature analysis.

The authors declare no conflicts of interest.

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[Original Russian Text: Filatova S.M., Denieva Z.G., Budanova U.A., Sebyakin Y.L. Synthesis of low-molecular-weight antibacterial peptide mimetics based on dialkyl- and diacylamines, *Vestnik Moskovskogo universiteta. Seriya 2. Khimiya = Moscow Univ. Chem. Bull.*2020;61(6):405–413 (in Russ.).]

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About the authors:

Maxim D. Korotkin, Master Student, N.A. Preobrazhensky Department of Chemistry and Technology of Biologically Active Compounds, Medicinal and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: maks.korotkin.99@mail.ru. https://orcid.org/0000-0002-4730-1244

Svetlana M. Filatova, Master Student, N.A. Preobrazhensky Department of Chemistry and Technology of Biologically Active Compounds, Medicinal and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: svetochka9806@mail.ru. https://orcid.org/0000-0002-5066-9074

Zaret G. Denieva, Engineer of the 1st category, Laboratory of Bioelectrochemistry, A.N. Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences (IPCE RAS) (31/4, Leninsky pr., Moscow, 119071, Russia). E-mail: zaret03@mail.ru. Scopus Author ID 57203550055, ResearcherID T-5756-2019, https://orcid.org/0000-0001-5388-9323

Ulyana A. Budanova, Cand. Sci. (Chem.), Associate Professor, N.A. Preobrazhensky Department of Chemistry and Technology of Biologically Active Compounds, Medical and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: c-221@yandex.ru. Scopus Author ID 14622352500, ResearcherID E-1659-2014, https://orcid.org/0000-0003-1702-9435

Yury L. Sebyakin, Dr. Sci. (Chem.), Professor, N.A. Preobrazhensky Department of Chemistry and Technology of Biologically Active Compounds, Medical and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: c-221@yandex.ru. Scopus Author ID 6701455145, ResearcherID T-2835-2019, https://orcid.org/0000-0002-7027-378X

Об авторах:

Короткин Максим Дмитриевич, магистрант кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: maks.korotkin.99@mail.ru. https://orcid.org/0000-0002-4730-1244

Филатова Светлана Михайловна, магистрант кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: svetochka9806@mail.ru. https://orcid.org/0000-0002-5066-9074

Дениева Зарет Гезимахмаевна, инженер 1 категории лаборатории «Биоэлектрохимия» Института физической химии и электрохимии им. А.Н. Фрумкина Российской академии наук (ИФХЭ РАН) (119071, Россия, Москва, Ленинский пр-т, д. 31/4). E-mail: zaret03@mail.ru. Scopus Author ID 57203550055, ResearcherID T-5756-2019, https://orcid.org/0000-0001-5388-9323

Буданова Ульяна Александровна, к.х.н., доцент кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: c-221@yandex.ru. Scopus Author ID 14622352500, ResearcherID E-1659-2014, https://orcid.org/0000-0003-1702-9435

Себякин Юрий Львович, д.х.н., профессор, профессор кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: c-221@yandex.ru. Scopus Author ID 6701455145, ResearcherID T-2835-2019, https://orcid.org/0000-0002-7027-378X

The article was submitted: November 22, 2021; approved after reviewing: January 21, 2022; accepted for publication: February 17, 2022.

Translated from Russian into English by H. Moshkov
Edited for English language and spelling by Enago, an editing brand of Crimson Interactive Inc.

Tonkie Khimicheskie Tekhnologii = Fine Chemical Technologies. 2022;17(1):65–75

SYNTHESIS AND PROCESSING OF POLYMERS AND POLYMERIC COMPOSITES

СИНТЕЗ И ПЕРЕРАБОТКА ПОЛИМЕРОВ И КОМПОЗИТОВ НА ИХ ОСНОВЕ

ISSN 2686-7575 (Online)
https://doi.org/10.32362/2410-6593-2022-17-1-65-75
UDC 678.5.046

RESEARCH ARTICLE

Study of the stress state of polycarbonate monolithic sheets using optical-polarization methods

Anatoly V. Markov✉**, Valery A. Lobanov**

MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia
✉*Corresponding author, e-mail: markovan@bk.ru*

Abstract

Objectives. *The study assessed the possibility of using optical-polarization methods to test quantitatively the stress state and residual stress in polycarbonate (PC) monolithic sheets. This stress is the leading cause of the cracking of PC sheets and the products made of them.*
Methods. *The objects were samples of monolithic PC sheets made by various manufacturers (Monogal and Novattro). The birefringence method was used to study the stress state of the samples, and the interference images obtained in polarized light in crossed polaroids were analyzed.*
Results. *The efficiency of optical-polarization research methods, such as the birefringence and the analysis of the interference images of stretched PC samples combined into an additive spectrum, was shown. The residual stress in the monolithic PC sheets made by various manufacturers was estimated.*
Conclusions. *The quantitative relationship between the stress acting on the PC samples, their birefringence, and the characteristics of their additive spectrum of interference images of stressed*

samples obtained in polarized light in crossed polaroids was established. The possibility of a quantitative assessment of the residual stress in monolithic PC sheets based on an analysis of their additive spectrum of interference images was shown. The measured residual stress did not exceed 1 MPa.

Keywords: *monolithic polycarbonate sheets, stretching, residual stress, crack resistance, birefringence, interference image*

For citation: Markov A.V., Lobanov V.A. Study of the stress state of polycarbonate monolithic sheets using optical-polarization methods. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(1):65–75 (Russ., Eng.). https://doi.org/10.32362/2410-6593-2022-17-1-65-75

НАУЧНАЯ СТАТЬЯ

Оценка напряженного состояния поликарбонатных монолитных листов оптико-поляризационными методами

А.В. Марков✉**, В.Н. Лобанов**

МИРЭА – Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия
✉*Автор для переписки, e-mail: markovan@bk.ru*

Аннотация

Цели. *Работа посвящена изучению возможности использования оптико-поляризационных методов для количественной оценки напряженного состояния и остаточных напряжений в поликарбонатных монолитных листах. Эти напряжения являются основными причинами растрескивания листов поликарбоната и изделий из них.*
Методы. *Объектами исследования являлись образцы поликарбонатных монолитных листов различных производителей («Monogal» и «Novattro»). Для исследования напряженного состояния образцов использовали методы двойного лучепреломления и анализ интерференционных изображений образцов, полученных в поляризованном свете в скрещенных поляроидах.*
Результаты. *Показана эффективность использования оптико-поляризационных методов исследования: двойного лучепреломления и анализа характеристик объединенного спектра интерференционных изображений напряженных образцов поликарбоната. Проведена оценка остаточных напряжений в монолитных поликарбонатных листах различных производителей.*
Выводы. *Установлена количественная связь между натяжениями, действующими на образцы поликарбоната, их двойного лучепреломления и характеристиками объединенного спектра интерференционных изображений нагруженных образцов, полученных в поляризованном свете в скрещенных поляроидах. Показана возможность количественной оценки значений остаточных напряжений в монолитных листах поликарбоната на основе анализа их спектров интерференционных изображений. Измеренные остаточные напряжения не превысили 1 МПа.*

Ключевые слова: *листовой монолитный поликарбонат, остаточные напряжения, трещиностойкость, двойное лучепреломление, интерференционное изображение*

Для цитирования: Марков А.В., Лобанов В.Н. Оценка напряженного состояния поликарбонатных монолитных листов оптико-поляризационными методами. *Тонкие химические технологии*. 2022;17(1):65–75. https://doi.org/10.32362/2410-6593-2022-17-1-65-75

INTRODUCTION

Studying the stress state of organic glasses and their products is necessary for more accurate predictions of their service life [1, 2]. In addition to the external stress that accelerates the cracking of glass during operation, for example, mechanical (upon glazing) or thermal stresses (upon their nonuniform heating), internal residual stress is also "harmful," for example, when it arises in the plexiglass molding process [3]. The following technological conditions for the occurrence of increased residual stress in the manufacture of an extruded monolithic polycarbonate (PC) sheet can be distinguished:

- high viscosity of the PC polymer melts during workpiece molding;
- low temperatures during PC sheet calibration;
- high deformation of the workpiece during PC sheet calibration;
- the high rate of sheet PC calibration;
- the high rate of PC sheet cooling;
- nonuniformity of the PC sheet heating and cooling;
- low-quality of PC sheet cutting;
- incorrect PC sheet storage.

The physical and chemical nature of the influence of external and internal stress on the acceleration of cracking of organic glasses and products made from them is the same; this is a deformation effect on the molecular bonds of the polymer. The cracking process can be considered within the framework of Zhurkov's theory of durability [2, 4]:

$$\tau_p = \tau_0 exp(\frac{U - \nu\sigma}{RT}) \tag{1}$$

where τ_c is the time before the onset of PC cracking (s); U is the activation energy for the destruction of the polymer macromolecules determined by the strength of the PC chemical bonds, equal to 150–160 kJ/(mol·K) [5]; σ is the applied stress (Pa); T is the temperature (K); τ_0 is a constant related to the frequency of vibrations of atoms of molecules upon their thermal motion ($\tau_0 = 10^{-12}$–10^{-14} s); ν is the activation volume of destruction or structure-sensitive parameter (m^3); R (8.314 J/mol·K) is the universal gas constant.

There are methods for estimating the stress state in plexiglasses and their products[1]. These methods are based on the conclusions of Zhurkov's theory (Eq. 1) and are related to the acceleration of plexiglass cracking at elevated temperatures [6] and stresses [1, 2], as well as when their surface comes into contact with adsorption-active test liquids [7, 8]. Several attempts have been made to relate the times of accelerated cracking quantitatively with the residual stress in PC sheets [8]. However, these methods lead to the destruction of the products. Test liquids[2] can only be used for final control of the finished products, indicating the permissible stress level in PC sheets [8].

Nondestructive methods for estimating the stress state in plexiglas can be optical-polarization methods, i.e., the method of measuring birefringence (BR), as well as an analysis of interference images of samples in crossed polaroids (IICP) obtained in polarized light [9, 10]. The essence of the latter method is as follows. BR results in cyclic changes in the intensity of polarized white light transmitted in the material upon loading. This leads to the appearance of an interference image with alternating color bands called isochromes [9–17]. The points on these isochromes correspond to specific values of BR and stress. For uniaxial loading, this stress can be calculated as follows [11]:

$$N = C\sigma\frac{\delta}{\lambda} \tag{2}$$

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[1] GOST P 51372-99. State standard of the Russian Federation. *Accelerated life and storable life test methods in special aggresive and other special media for technical products, materials and systems of materials*. M.: Gosstandart; 2000 (in Russ.).

[2] *Bonding and general data on adhesives*. Practice Guide of the compeny EVONIK-RÖHM GmbH; 2011. URL: https://orgsteklo-shop.ru/articles/

where σ is the effective stress (Pa); N is the order (number) of the isochrome bands on the IICP; δ is the thickness (m), λ is the wavelength of light (m); C is the optical sensitivity of the material in terms of stress (1/Pa).

Currently, these techniques are commercially used to assess the quality of PC blanks for laser disks [13]. On the other hand, they can be used more widely, e.g., estimating the residual stress in PC sheets and products made from them [14–20]. This study examined the possibility of using optical-polarization methods to assess the stress state and residual stress quantitatively in monolithic PC sheets.

EXPERIMENTAL

The objects of the study were samples of monolithic colorless light-stabilized 3 mm thick PC sheets, Novattro (*SafPlast*, Kazan, Russia, TU 2246-03-81057157-2008), as well as monolithic colorless light-stabilized 3 mm thick PC sheets, Monogal (*Polygal Vostok*, Kurovskoye, Russia, TU 2246-02-93726592-2008). The test specimens were plates, 100 ± 1 mm long, 3.0 ± 0.1 mm thick, and 30 ± 1 mm wide.

Experiments on the PC sample loading were carried out on an AI-7000-LA5 universal testing machine (Instron) (*GOTECH Testing Machines Inc.*, Taiwan). The samples were fastened in the testing machine clamps using a torque wrench [2]. This ensured the constancy and uniformity of pressure on the pulling clamps on the ends of the tested samples. The sample loading was accompanied by continuous fixation of the current elongation (L_τ, m) and load (P_τ, N). The test section length before loading (L_0) was 60 mm. Relative deformation (ε) and stress (σ, MPa) were calculated automatically. The stress σ was calculated considering the decrease in the initial cross-section (s_0, m^2) of the sample upon deformation:

$$\sigma_\tau = P_\tau(1-\varepsilon_\tau)/s_0 , \tag{3}$$

$$\varepsilon_\tau = (L_\tau - L_0)/L_0 . \tag{4}$$

A polarizing microscopeMIN-10(*Geologorazvedka*, Russia) with a rotary compensator was used to assess the stress state of the samples by the BR method according to GOST 3519-69[3] [3]. After measuring the compensating rotation angles of this compensator (α and β), the parameter F, which is proportional to the sample BR value (Δn), was then calculated using the following equation:

$$F = d(\frac{\alpha-\beta}{2})^e \tag{5}$$

where F is the sample BR parameter (nm); α and β are the angles of the compensator rotation relative to the neutral position (deg); d and e are the device constants (d = 3.085 nm, e = 1.985) [2, 3]. The value of Δn was calculated considering the test sample thickness (δ) using the following formula [3]:

$$\Delta n = F/\delta . \tag{6}$$

The test samples were loaded at 20°C until the specified stress was reached [1, 2], and the sample was kept loaded for 600 s until the values of α and β were measured. Measurements were then taken using a polarizing microscope MIN-10.

A digital camera with a microlens adjusted to capture an image at specified time intervals (5 s) was used to fix the IICP of the loaded samples in transmitted polarized light.

RESULTS AND DISCUSSION

The BR of the original unloaded monolithic PC sheets was evaluated first. Previously, transverse strips were cut across the entire width of the sheets (2000 mm) perpendicular to the extrusion direction. The Δn values were measured across the width of the sheets (H) of the strips central part every 20 mm to avoid the influence of edge effects associated with cutting.

Figure 1 presents the results of these tests. The initial samples had an optical anisotropy associated with extrusion and calendar effects, with the value Δn_0. Meanwhile, these data on the nonuniformity of the BR of different monolithic PC sheets do not indicate the “poor” quality of the studied materials because the values of this nonuniformity are small compared to the maximum possible value for PC, which is 0.106 [3].

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[3] GOST 3519-69. USSR State Standard. Optical glass. Method for determination of stress birefringence on polarimeter. Moscow: Izd. Standartov, 1969 (in Russ.).

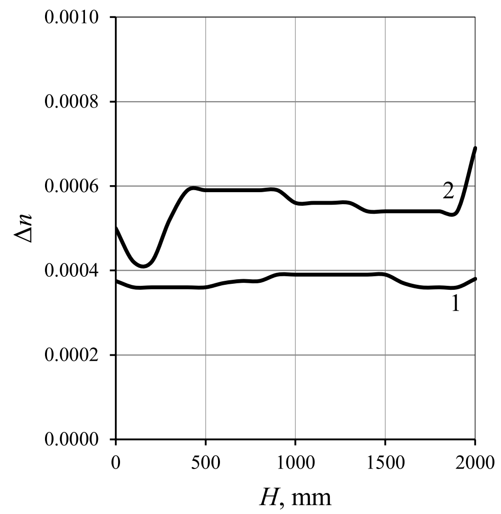

Fig. 1. Change in the value of Δn along the width of monolithic polycarbonate sheets for two industrial samples without specifying their manufacturer.

The recorded changes in BR are not related directly to the nonuniform thickness of the samples because the value of thickness (δ) was considered when calculating the value of Δn (Eq. 6). On the other hand, the thickness nonuniformity itself can cause thermal and deformation stress indirectly. Explicit edge effects are due to the special conditions of forming the sheet edges and their mechanical processing, including cutting.

Next, this study examined the stress state of PC samples of monolithic sheets subjected to external uniaxial loading using optical-polarization methods. At the initial stage, the dependence $\sigma = f(\varepsilon)$ of the PC samples was studied over a wide range of stress and strain. Figure 2 presents a diagram of uniaxial loading (curve 1), which describes the dependence $\sigma = f(\varepsilon)$ of the PC samples. The nature of stress growth is typical for loading diagrams of rigid amorphous PC: elastic deformation at σ up to 20–30 MPa is accompanied by noticeable plastic deformation at $\sigma > 30$ MPa, which ends with specimen destruction at stress $\sigma_d = 61.5$ MPa.

When analyzing the stressed state of the loaded samples, the relaxational decrease in the stress attained upon deformation should be considered when the sample is kept for some time at a constant deformation. This decrease is characteristic of polymers. In this regard, equilibrium stress was used in further calculations (curve 2 in Fig. 2), which was established after keeping the loaded samples at constant deformation (creep) for 600 s (Fig. 3). At stresses below 30 MPa, which is of interest in this study, this relaxation decreased when σ is small: curves 1 and 2 in Fig. 2 at this stress are the same. At stresses exceeding 30 MPa, the relaxation character of the dependences $\sigma = f(\tau)$ becomes more pronounced (Fig. 3). At stresses above 50 MPa, the samples were destroyed in less than 600 s (in Fig. 2, these stress values corresponded to the dashed section on curve 2).

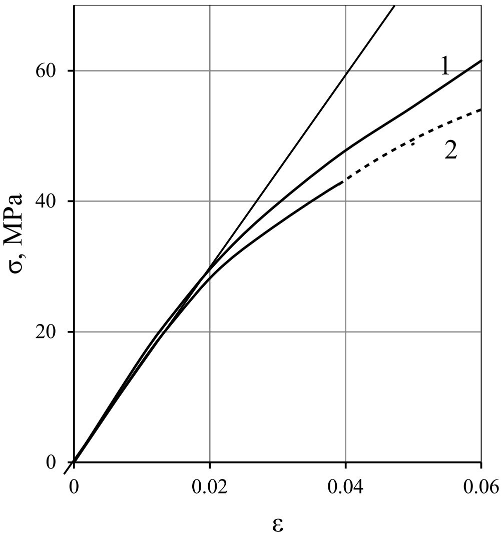

Fig. 2. Stress–strain diagrams for polycarbonate (strain rate 50 mm/min): (1) measurement during deformation and (2) measurement after relaxation for 600 s.

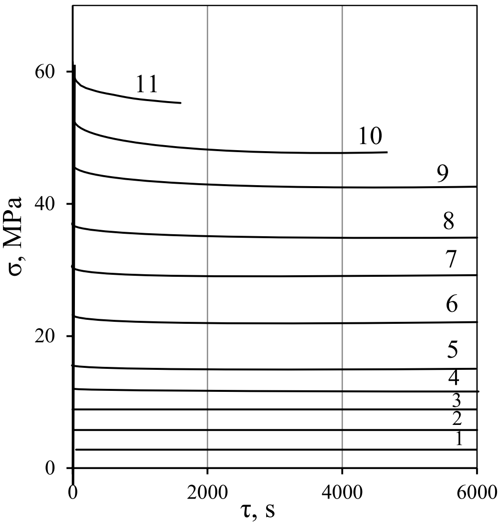

Fig. 3. Stress (σ)–relaxation time (τ) dependences at constant deformation of samples ε: (1) 0.0015, (2) 0.003, (3) 0.005, (4) 0.007, (5) 0.010, (6) 0.015, (7) 0.020, (8) 0.028, (9) 0.039, (10) 0.050, and (11) 0.063.

During further optical-polarization tests of the samples, the stress did not exceed 30 MPa. During these experiments, the strain rate was reduced to 1 mm/min to eliminate the uncertainty caused by relaxation processes. The stress values recorded in this case (curve 2 in Fig. 2) coincided with curve 1. The strain ε did not exceed 0.5%, which minimized the effects of creep. Under these conditions, the loading rate had little effect on the stress.

The BR method is the most developed and frequently used optical technique for studying the photoelasticity of polymeric materials. Figure 4 shows the results of measuring the standard Δn value of the samples (GOST 3519-69) under the action of various specified external stress. The original sample (with residual BR $\Delta n_{\mathrm{res}} = 0.00039$) was loaded stepwise to achieve a specified external stress during these tests. The loading was stopped at a given σ_i, and Δn_i was measured. The loading continued up to σ_{i+1}, and the value of Δn_{i+1} was determined up to 30 MPa.

The analysis of photoelasticity dependence suggests a linear relationship between the Δn value of the sample and the stress applied to it in the studied stress range. The dashed straight line in Fig. 4 describes the relationship between the external stress and Δn at $\Delta n_{\mathrm{res}} = 0$.

$$\sigma' = a_1 \Delta n \tag{7}$$

where σ' is the stress in the sample at $\Delta n_{\mathrm{res}} = 0$ in MPa, and a_1 is a constant ($a_1 = 11000$ MPa). Equation (7) can be used as a calibration formula when estimating the stress state in the studied monolithic PC sheets. Considering the additional residual stress of the original sample (σ_{res}), which is added to the applied external stress,

$$\sigma - \sigma_{\mathrm{res}} = a_1(\Delta n - \Delta n_{\mathrm{res}}) \tag{8}$$

where σ is the stress applied to the sample; σ_{res} and Δn_{res} are the residual stress (MPa) and initial BR of the original unloaded sample ($\Delta n_{\mathrm{res}} = 0.00039$).

In accordance with Eq. 8 in Fig. 4, the point corresponding to the BR of an unloaded sample is situated on the trend line describing the linear function $\Delta n = f(\sigma)$ and extrapolated to the region of negative stress. This is because the residual stress in the sample is compressive compared to the pulling stress applied to the sample. Equation 8 shows that σ_{res} for the studied sample at the point of the BR measurement is approximately 0.9 MPa (the deformation of the sample was less than 0.05%).

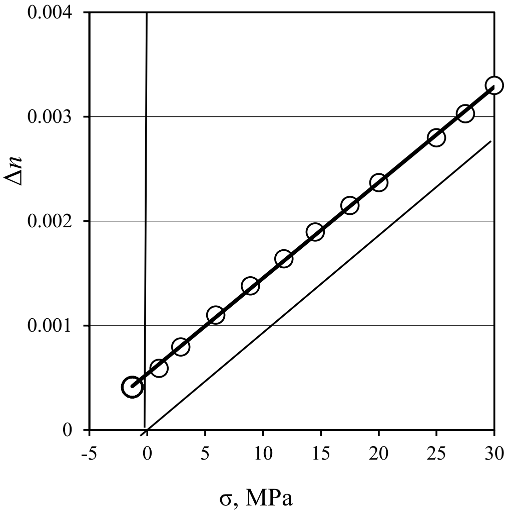

Fig. 4. Diagram describing the relationship between the birefringence value in the loaded polycarbonate specimens (conditions as in Fig. 2) and the stress applied to them (σ, MPa). The dashed line indicates the Δn values reduced to $\Delta n_{\mathrm{res}} = 0$.

This technique for assessing the stress state makes it possible to characterize the product quality quantitatively. However, this method has the following disadvantages:

- the discreteness of BR measurements and the complexity of assessing the inhomogeneity on very small and large areas of the product (diameter of a light beam passing through the sample is from 1 to 3 mm);
- tests on large areas are laborious and lengthy, and it is difficult to assess the changes in product tension during its loading by this method;
- the need to cut samples from the product;
- the sensitivity of this method in the region of low stress is low.

The phenomenon of photoelasticity caused by BR in polymeric products under stress can be used to measure Δn. The nondestructive method of samples IICP analysis is based on the same physical principles. However, the area of the sample analyzed by this method is limited only by the size of the polarizer. As mentioned above, the source of polarized light was a computer monitor tuned to white light. This allows continuous real-time recording of the changes in the stress state over large areas, including changes in the process of external mechanical or thermal action on the product. The product does not need to be cut into samples for such tests.

Figure 5 shows the IICP of an unloaded sample of a monolithic PC sheet. The presence of color on the IICP of the original sample at σ = 0 was attributed

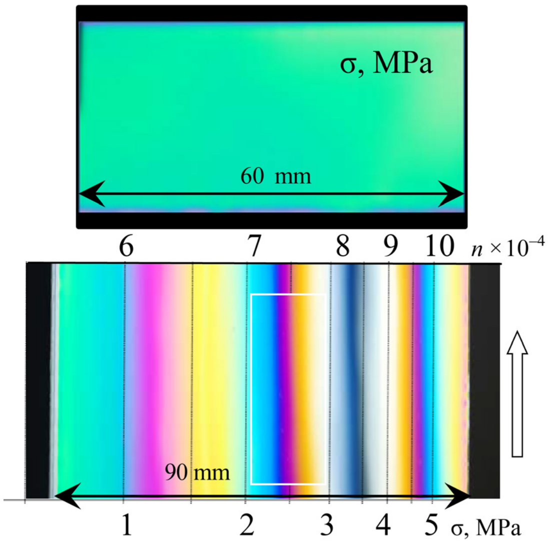

Fig. 5. Interference image in crossed polaroids of the initial sample (σ = 0 MPa) and the interference spectrum of its loading (the arrow indicates the direction of loading).

to the presence of BR, and consequently, the residual stress σ_{res}. Note that this color depends on the value of σ_{res} and the PC sheet thickness. In the full absence of BR in the sample, polarized light should not pass through the analyzer located perpendicularly to the polarizer. Therefore, the samples and background around the IICP of the original sample in Fig. 5 should be black.

The inhomogeneity of the original sample color at σ = 0 MPa (the appearance of a yellow tint in the right part of the IICP of the original unloaded sample) indicates the inhomogeneity of its Δn_{res} and σ_{res}. In addition to this "centimeter" inhomogeneity in the IICP color, the "millimeter" inhomogeneity, i.e., the change in color (from green to blue and then to pink) at the lateral edges of the sample. This reveals the residual stress that has arisen when cutting the sheet into strips, which cannot be fixed when measuring the BR. This should be considered when studying the IICP.

The step loading of the samples was carried out with the simultaneous fixing of stress values (σ_i) and interference images of the sample (similar to the step loading described above when determining Δn_i). As a basis for evaluating the change in photoelasticity in the course of loading, it is customary to measure the number of isochromatic bands (N) that appear on the sample IICP. Stress σ in the working part of the sample is calculated using the following formula [13]:

$$\frac{\sigma}{\sigma_0} = \frac{N}{\delta} \tag{9}$$

where δ is the sheet thickness; σ_0 is the division value of the strip on the IICP, which was determined in the calibration experiments by comparing the calculated stress with the observed optical effect. Mathematical programs have been developed to interpret the IICP samples [13].

This study used the superimposing identical isochromic lines of many photographs of a loaded sample IICP taken at different applied stresses in the region of most interest from 0.3 to 5 MPa. All the points on the IICP isochromes had the same Δn value. This allowed it to combine all the IICPs obtained at different stresses affecting the studied sample into its single isochrome spectrum. Figure 5 shows a generalized picture of the colored bands (IICP spectrum). For example, the superimposed part of the sample IICP at a stress of 4.5 MPa is marked with a white contour in the IICP spectrum. However, this process can be automated. A similar IICP spectrum at different stress values can be obtained in a sample of sufficient thickness under transverse bending.

Under a load, pronounced colored isochromic bands appear at external stress above 1 MPa (not pronounced in the original samples). Figure 5 shows the actual dimensions of the sample and the resulting IICP spectrum. The stripes are oriented along the direction of the loaded sample tension. As stress increases, the isochromes "move" perpendicular to this direction, and new isochrome lines appear. Figure 5 shows the applied external stress σ_i (in MPa) and the corresponding values of Δn_i.

The distances (periods) between the isochromic lines of different orders Δi (where i indicates stresses of 1, 2, 3, 4, and 5 MPa) on the IICP spectrum (Fig. 5) become narrow with increasing acting stress according to Eq. 9. Figure 6 shows the dependence of these distances on the stress placed on the sample. The dependence is regular and adequately described by the hyperbolic function $\sigma_i = f(1/\Delta i)$.

This made it possible to use dependencies similar to Eq. 8 for BR and extrapolate their values to negative residual stress. In this case, the function $\sigma = f(1/\Delta)$ can be described as follows:

$$\sigma - \sigma_{res} = a_2 (1/\Delta - 1/\Delta_{res}) \tag{10}$$

where σ is the stress applied to the sample; σ_{res} and Δ_{res} are the residual stress (MPa) and Δ is the residual period in an original unloaded sample; k_2 is a coefficient depending on the image scale (in the present case, a_2 = 0.014 MPa). In the case under consideration, $\sigma_{res} \neq 0$ and $1/\Delta_{res} \neq 0$ in Fig. 6.

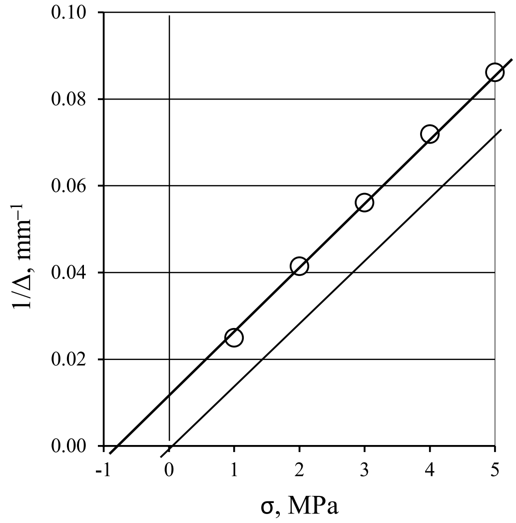

Fig. 6. Relationship between the Δ values in mm on spectrum of interference images of samples in crossed polaroids of the loaded polycarbonate samples and the stress applied to them (σ, MPa). The dashed line indicates the hypothetical 1/Δ values reduced to $1/\Delta_{res}$.

This dependence can be universalized using relative units, e.g., Δ_1/Δ:

$$\sigma - \sigma_{res} = a_3(\Delta_1/\Delta - \Delta_1/\Delta_{res}) \qquad (11)$$

where Δ_1 is the calculated value Δ = 78 mm from 0 to σ_1 = 1 MPa in Fig. 6; $a_3 = a_2\Delta_1 \approx 1$ (a_3 = 1.1 MPa). In this case, $\Delta_1/\Delta = 1$ at σ_1 = 1 MPa in Eq. 1. However, the analysis result will not change in this case.

The linearity of this dependence makes it possible to estimate the magnitude of residual stress in the sample, as shown in the analysis of the dependence, $\Delta n = f(\sigma)$, by extrapolation to the region of negative values of σ (compressive stress). In this case, the value of σ_{res} was 0.7 MPa, which is close to the value of σ_{res} obtained from the analysis of the stress state using the BR value of Δn_{res} (0.9 MPa). The average stress, 0.8 ± 0.1 MPa, is small, corresponding to <0.05% elastic deformation of the PC sheet. This does not exceed the usual thermal deformation of PC sheets upon their operation, which can be considered safe. Previous studies [1, 2] showed that less than 10 MPa is the safe stress that ensures the long-term operation of PC sheets and products made from them.

The resulting IICP spectrum can be used to determine the stress in the studied PC samples based on their interference images. To accomplish this, it is sufficient to combine the same isochromic lines of the sample IICP and IICP spectrum and determine the coordinate of the test sample center from the IICP spectrum length. The latter is equal to the sum,

$$x_k = \sum \Delta_i = \sum_{n=1}^{k} \left(\frac{1}{n^a}\right) \qquad (12)$$

where *x* is the test sample coordinate on the IICP spectrum; *n* = 1, 2, 3 …, which corresponds to σ in MPa in Fig. 6; *a* is the exponent approximately equal to 1 (*a* = 1.1). The difference between exponent *a* and 1 is due to the residual stress in the sample. Figure 7 presents a diagram that graphically describes Eq. 12. The diagram can be used to determine the stress when analyzing the IICP spectrum shown in Fig. 5. Equation 12 makes it possible to extrapolate this diagram to higher stress in the elastic region. In Fig. 7, the dependence is extrapolated to 10 MPa. Previous studies [1, 2] reported that stresses less than this value are acceptable during the warranty period of PC sheets.

However, the picture of the IICP isochromes depends on the stress and other factors, e.g., on the sheet thickness and its thickness variation, the slope of the product sections. This may reduce the reliability of the quantitative assessment of its stress state. On the other hand, this problem for initial sheets or specific identical products made of them can be solved by developing a database of reference IICP

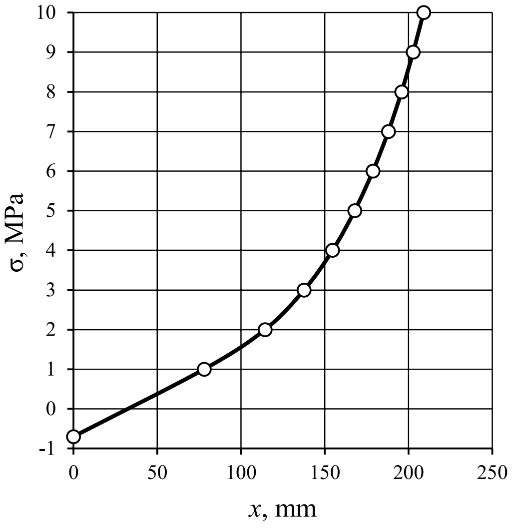

Fig. 7. Graphic depiction of Eq. (12). The dots are the experimental values.

spectra of quality products, as done for the automated assessment of the stress state of molded PC blanks of compact discs [15].

CONCLUSIONS

These studies showed that optical-polarization methods effectively assess the stress state of PC monolithic sheets made by various manufacturers in the Russian Federation. A quantitative relationship was established between the stress affecting PC samples, their BR values, and the characteristics of the combined spectrum of interference images of loaded samples obtained in polarized light in crossed polaroids. Overall, the residual stress values in monolithic PC sheets can be quantified by analyzing the spectra of their interference images. The measured residual stresses do not exceed 1 MPa.

Acknowledgments

This work was supported by the research initiative theme 150-ITHT.

Authors' contribution

A.V. Markov – design of the research concept, development of the experiment, discussion and analysis of the results, writing the text of the article;

V.N. Lobanov – studying the properties of samples, processing and analysis of the data obtained, discussion of the results.

The authors declare no conflicts of interest.

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About the authors:

Anatoly V. Markov, Dr. Sci. (Eng.), Professor, Department of Chemistry and Technology of Plastic Processing and Polymer Composites, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: markovan@bk.ru. https://orcid.org/0000-0001-7952-7419

Valery N. Lobanov, Assistant, Department of Physics and Technical Mechanics, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: lwnk@yandex.ru. https://orcid.org/0000-0002-9822-973X

Об авторах:

Марков Анатолий Викторович, д.т.н., профессор кафедры химии и технологии переработки пластмасс и полимерных композитов Института тонких химических технологий им. М.В. Ломоносова, ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: markovan@bk.ru. https://orcid.org/0000-0001-7952-7419

Лобанов Валерий Николаевич, ассистент кафедры физики и технической механики Института тонких химических технологий им. М.В. Ломоносова, ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: lwnk@yandex.ru. https://orcid.org/0000-0002-9822-973X

The article was submitted: October 29, 2021; approved after reviewing: December 27, 2021; accepted for publication: February 08, 2022.

Translated from Russian into English by M. Povorin
Edited for English language and spelling by Enago, an editing brand of Crimson Interactive Inc.

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Acknowledgments: words of gratitude to organizations or institutions, supervisors and other persons who assisted in the preparation of the article. Information about projects, research works, the results of which the article was published, can also be provided: information about grants or other sources of funding.

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78, Vernadskogo pr., Moscow, 119454, Russian Federation.
Signed to print on *February 28, 2022.*
Not for sale

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