ISSN 2518-718X

№ 3(87)/2017

ХИМИЯ сериясы
Серия ХИМИЯ
CHEMISTRY Series

ҚАРАҒАНДЫ УНИВЕРСИТЕТІНІҢ ХАБАРШЫСЫ

ВЕСТНИК КАРАГАНДИНСКОГО УНИВЕРСИТЕТА

BULLETIN OF THE KARAGANDA UNIVERSITY

ISSN 2518-718X
Индексі 74617
Индекс 74617

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Шілде–тамыз–қыркүйек
29 қыркүйек 2017 ж.
Июль–август–сентябрь
29 сентября 2017 г.
July–August–September
September, 29, 2017

1996 жылдан бастап шығады
Издается с 1996 года
Founded in 1996

Жылына 4 рет шығады
Выходит 4 раза в год
Published 4 times a year

Қарағанды, 2017
Караганда, 2017
Karaganda, 2017

Редакцияның мекенжайы: 100028, Қазақстан, Қарағанды қ., Университет к-сі, 28
Тел.: (7212) 77-03-69 (ішкі 1026); факс: (7212) 77-03-84.
E-mail: vestnick_kargu@ksu.kz. Сайты: vestnik.ksu.kz

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ISSN 2518-718X.

Меншік иесі: «Академик Е.А. Бөкетов атындағы Қарағанды мемлекеттік университеті» РММ.

Қазақстан Республикасының Мәдениет және ақпарат министрлігімен тіркелген. 23.10.2012 ж. № 13110–Ж тіркеу куәлігі.

Басуға 29.09.2017 ж. қол қойылды Пішімі 60×84 1/8. Қағазы офсеттік. Көлемі 17,5 б.т. Таралымы 300 дана. Бағасы келісім бойынша. Тапсырыс № 94.

Е.А. Бөкетов атындағы ҚарМУ баспасының баспаханасында басылып шықты.
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Компьютерная верстка
В.В. Бутяйкин

Вестник Карагандинского университета. Серия «Химия».
ISSN 2518-718X.
Собственник: РГП «Карагандинский государственный университет имени академика Е.А. Букетова».
Зарегистрирован Министерством культуры и информации Республики Казахстан. Регистрационное свидетельство № 13110–Ж от 23.10.2012 г.

Подписано в печать 29.09.2017 г. Формат 60×84 1/8. Бумага офсетная. Объем 17,5 п.л. Тираж 300 экз. Цена договорная. Заказ № 94.
Отпечатано в типографии издательства КарГУ им. Е.А. Букетова.
100012, Казахстан, г. Караганда, ул. Гоголя, 38, тел.: (7212) 51-38-20. E-mail: izd_kargu@mail.ru

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Editor
Zh.T. Nurmukhanova

Computer layout
V.V. Butyaikin

Bulletin of the Karaganda University. «Chemistry» series.
ISSN 2518-718X.
Proprietary: RSE «Academician Ye.A. Buketov Karaganda State University».
Registered by the Ministry of Culture and Information of the Republic of Kazakhstan. Registration certificate No. 13110–Zh from 23.10.2012.
Signed in print 29.09.2017. Format 60×84 1/8. Offset paper. Volume 17,5 p.sh. Circulation 300 copies. Price upon request. Order № 94.
Printed in the Ye.A. Buketov Karaganda State University Publishing house.
38, Gogol Str., Karaganda, 100012, Kazakhstan. Tel.: (7212) 51-38-20. E-mail: izd_kargu@mail.ru

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Synthesis and structure of condensed biheterocycles on the basis of 3-amino-1,2,4-triazole

The article is devoted to the development of preparatively convenient methods for the synthesis of new derivatives of 3-amino-1,2,4-triazole with the aim of constructing new condensed systems of industrially important substances. The synthesis of triazolopyrimidines, prepared by three-component condensation of 1,3-dicarbonyl compounds (anilide of acetoacetic acid and acetoacetic ether) with substituted aromatic aldehydes and 3-amino-1,2,4-triazole. It is shown that by melting at 120–140 ºC, in the absence of a solvent in equimolecular amounts of acetylacetyl anilide and acetoacetic ether with a mixture of 3-amino-1,2,4-triazole and substituted aromatic aldehydes (3-ethoxy-4-hydroxybenzaldehyde, salicylic aldehyde), leads to the 7-aryl-5-methyl-N-phenyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxamides and ethyl 7-aryl-5-methyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidin-6-carboxylate-titrate respectively. The structures of the synthesized compounds were studied by ^{1}H and ^{13}C NMR spectroscopy, as well as with the data of the two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C). The values of chemical shifts, multiplicity and integrated intensity of the ^{1}H and ^{13}C signals in one-dimensional NMR spectra are determined. Homo- and heteronuclear interactions were established using spectra in the formats COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), confirming the structure of the compounds under study.

Keywords: 3-amino-1,2,4-triazole, 7-aryl-5-methyl-N-phenyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxamides, aromatic aldehydes, ^{1}H- and ^{13}C NMR-spectra.

Introduction

The growing needs of mankind in new materials predetermine the vector orientation and tasks of organic synthesis, which involve the development of fundamentally new, convenient, economically and technologically sound, safe and competitive synthesis methods, as well as the production of previously unknown chemical products. One of the modern trends in organic synthesis is the using of the polycomponent condensations. Their attractiveness for synthetic chemists is connected with the combinatorial possibilities, the environmentally oriented idea of «green chemistry», one-pot and the rejection of the solvent as the preferred methods of practical implementation, allowing the synthesis of extensive libraries of substances in a short time. Multicomponent reactions involving 1,3-dicarbonyl compounds (1,3-DCC), aldehydes, mono- and bi-N-nucleophiles play an important role in fine organic synthesis and medical chemistry as universal methods for the synthesis of a large number of biologically active compounds, for example, derivatives of pyridines, pyrimidines [1, 2].

Pyrimidines are an important component of nucleic acids, and they have been used as building blocks in pharmaceutical preparations for the synthesis of antiviral [3], anticancer [4], antibacterial and antifungal agents [5].

Previously [6], we synthesized the condensed biheterocycles — tetrazolopyrimidines obtained by three-component condensation of anilide of acetoacetic acid with substituted aromatic aldehydes and the monohydrate of 5-aminotetrazole. The closest structural analogue of 5-aminotetrazole is 3-amino-1,2,4-triazole. It should be noted that derivatives of 1,2,4-triazole have wide range of physiological activity: hepatoprotective, wound healing, antiviral, germicidal, etc. [7, 8]. They are used as additives to high photographic materials, exhibit fungicidal, herbicidal and insecticidal properties [9, 10].

Continuing research into the synthesis of pyrimidine compounds [11, 12] with the aim of constructing new condensed systems, we carried out the reaction of substituted aromatic aldehydes with 3-amino-1,2,4-triazole and 1,3-dicarbonyl compounds (anilide of acetoacetic acid and acetoacetic acid ether), leading to the formation of triazolopyrimidines.

Experimental

The ^{1}H and ^{13}C NMR spectra of compounds (1, 2) were removed in DMSO-d6 using a JNN-ECA 400 spectrometer (400 and 100 MHz on ^{1}H and ^{13}C nuclei) from Jeol, Japan. The survey was carried out at room temperature using a DMSO solvent. Chemical shifts are measured relative to signals of residual protons or carbon atoms of a deuterated solvent.

General procedure for the preparation of triazolopyrimidines (1–4). A mixture of 1,3-dicarbonyl compound, aromatic aldehyde and 3-amino-1,2,4-triazole in equimolar amounts was held at 130–150 °C for 5–10 minutes until gas evolution ceased. The reaction mixture was cooled to room temperature, treated with ethyl alcohol, and the precipitate was filtered off. The precipitate was recrystallized from acetonitrile.

7-(3-Ethoxy-4-hydroxyphenyl)-5-methyl-N-phenyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (1). The yield of the product (1) was 2.16 g (56 %), m.p. 245–247 ºC.

7-(2-Hydroxyphenyl)-5-methyl-N-phenyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (2). Product yield (2) was 2.6 g (63 %) with m.p. 100–105 °C.

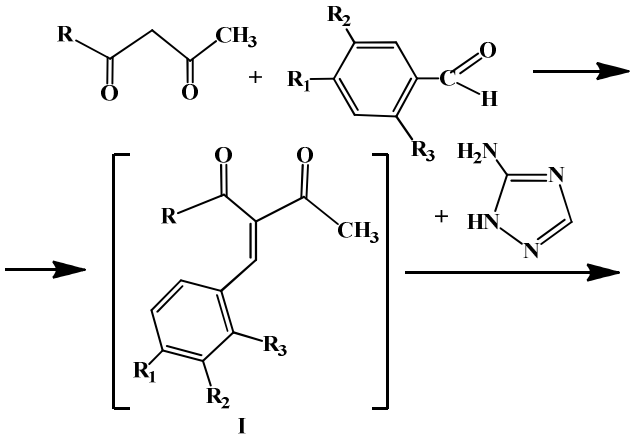
Ethyl 7-(3-ethoxy-4-hydroxyphenyl)-5-methyl-N-phenyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (3). The yield of product (3) was 3.55 g (43 %), m.p. 225–228 ºC.

Ethyl 7-(2-hydroxyphenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (4). The yield of the product (4) was 3 g (83 %), m.p. 145–148 ºC.

Results and discussion

In this paper we present the results of the research of the product of a three-component reaction of the anilide of acetoacetic acid and acetoacetic ether with substituted aromatic aldehydes and 3-amino-1,2,4-triazole in the absence of a solvent and a catalyst. The three-component Biginelli reaction, originally proposed for the synthesis of dihydropyrimidine-2(1*H*)-one by the reaction of aromatic aldehyde, urea and acetoacetic ether, is now used with great success in the synthesis of dihydropyrimidine-2(1*H*)-thione and various annelated pyrimidines [13–23].

We found that the fusion of equimolecular amounts of an acetoacetyl anilide with a mixture of 3-amino-1,2,4-triazole and substituted aromatic aldehydes at 130–150 ºC resulted in 7-aryl-5-methyl-N-phenyl-4,7-dihydro[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxamides (1, 2), and with acetoacetic ether — ethyl 7-aryl-5-methyl-4,7-dihydro-[1,2,4-triazolo[1,5-a]pyrimidine-6-carboxylate (3, 4). The resulting compounds (1–4) are pale yellow powders soluble in DMF, DMSO, heated in ethanol, acetonitrile, insoluble in water.



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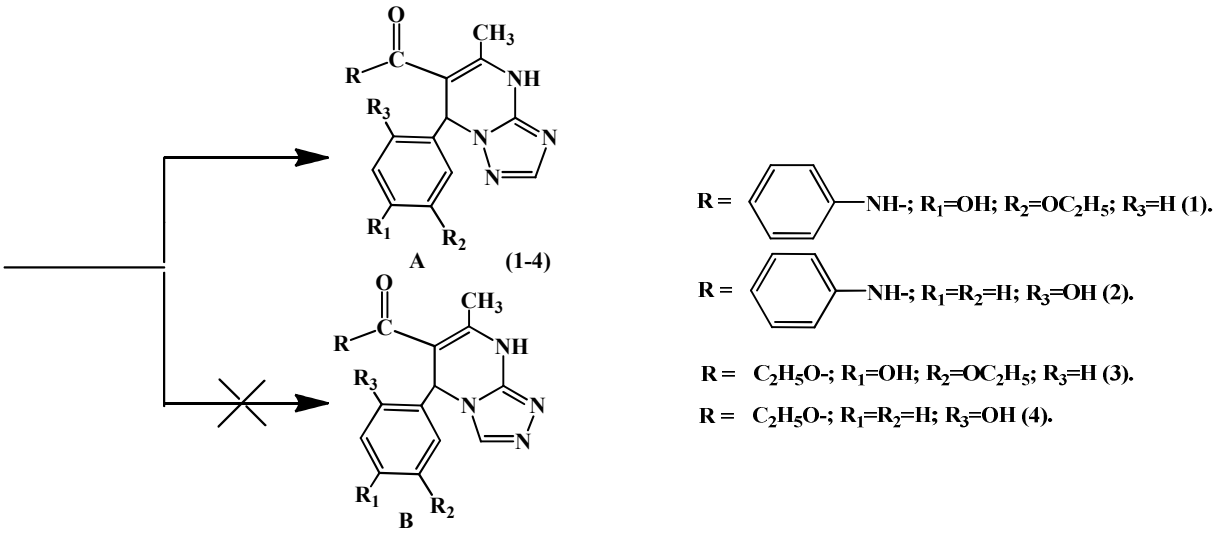
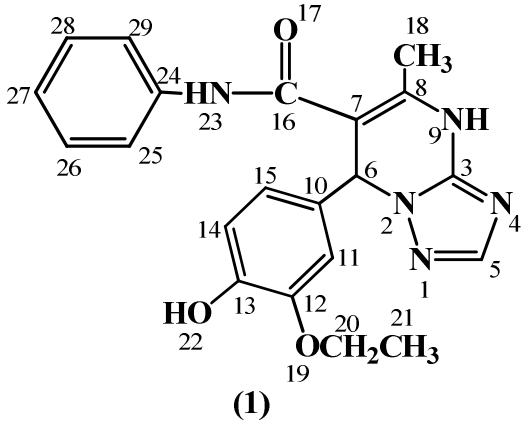


Based on the analysis of the published data [4–6, 11, 12], it is possible to assume that at the first stage of the reaction, as a result of the interaction of the 1,3-dicarbonyl compound with the aromatic aldehyde molecule, an unsaturated compound I is formed, the interaction of which with 3-amino-1,2,4-triazole, leads to the final reaction product. It is shown that in the 3-amino-1,2,4-triazole molecule there are two unequal nitrogen atoms in positions 2 and 4 of the heterocycle, which allows us to consider the two most probabilistic reaction products. However, the main and nucleophilic character of nitrogen in position 2 of the heterocycle, apparently, causes the reaction to proceed in the direction predominantly to form the structure of A.

The proposed mechanism is confirmed by analysis of the IR and NMR spectra of ^{1}H-, ^{13}C. The IR spectra of compounds (1, 2) exhibit bands due to stretching vibrations of amide groups (1672–1684 cm^{-1}) and NH groups (3085–3120 cm^{-1}).

The ^{1}H NMR spectrum of compound (1) is characterized by the presence in the strong-field region of the spectrum at 1.19 ppm triplet signal with an intensity of 3H with ^{3}J 6.9 Hz atoms of the methyl group CH_3^{21} ethyl radical. Another CH_3^{18} methyl radical bound to the C^{8} atom of a heterocyclic six-membered ring does not have spin-spin interactions with neighboring protons and is manifested at 2.12 ppm singlet signal with a content of 3H. In this part of the spectrum at 2.46 and 3.32 ppm the presence of solvent signals of DMSO-d6 and residual amounts of water was noted. The methylene protons of the hydroxyethyl radical were resonated with a multiplet signal in the range 3.76–3.89 ppm with an integrated intensity of 2H. The singlet signal with intensity IH at 6.39 ppm corresponds to proton H^{6}. The protons of the aromatic system H^{15} and H^{14}, which have hydrogen atoms adjacent to each other, which contribute to the splitting of the spectrum, were manifested by doublet signals at 6.56 (^{3}J 7.8 Hz) and 6.56 (^{3}J 8.2 Hz) ppm with intensities IH. The proton H^{11} of the aromatic cycle under consideration, which does not have hydrogen atoms adjacent to it, was indicated by a singlet at 6.71 ppm with an intensity of 1H. For an unsubstituted phenyl radical, all the protons appeared in the aromatic zone of the spectrum. The asymmetric proton H^{27} was manifested in the form of a triplet signal at 6.96 ppm, corresponding to the intensity IH, with ^{3}J 7.3 Hz. Equivalent $H^{26,28}$ protons were manifested by triplet signals at 7.20 ppm with ^{3}J 7.8 Hz with an integrated intensity of 2H, whereas equivalent protons of $H^{25,29}$ were detected by doublet signals at 7.48 ppm with ^{3}J 7.9 Hz with a 2H content. The multiplicity of the signals under consideration, their integrated intensity, and the values of the spin-spin interaction constants are in good agreement with the NMR indices for aromatic systems. The methyl proton H^{5} of the five-membered heterocyclic system adjacent to two nitrogen atoms was manifested by the expected singlet at 7.59 ppm with an integrated intensity of 1H. The protons of the hydroxyl group H^{22} and the protons bound to the nitrogen atoms of H^{23} and H^{9} were manifested in the form of singlets with an integrated intensity of 1H each at 8.90, 9.66 and 10.10 ppm respectively.



In the ^{13}C NMR spectrum of compound (1), the carbon atoms of the methyl groups resonated at 15.15 (C^{21}) and 17.81 (C^{18}) ppm in the strong-field part of the spectrum. Then they showed themselves at 60.47 ppm C^6 atoms and at 64.43 ppm C^{20} atoms, which have a small screening effect on the carbon nucleus. The other carbons of the bicyclic fragment were resonated at 104.35 (C^7), 136.75 (C^8), 148.24 (C^3), and 150.23 (C^5) ppm. Signals with chemical shifts at 113.35 (C^{11}), 115.96 (C^{14}), 120.02 ($C^{25,29}$), 120.25 (C^{15}), 123.77 (C^{27}), 129.08 ($C^{26,28}$), 132.17 (C^{10}), 139.58 (C^{24}), 146.86 (C^{12}) and 147.29 (C^{13}) ppm belong to the carbon nuclei of the two aromatic rings. In the most weakly-field region of the spectrum at 165.58 ppm the carbonyl carbon atom C^{16} resonated.

The structure of compound (1) was also confirmed by two-dimensional spectroscopy of COSY (^1H-^1H) NMR spectroscopy and HMQC (^1H-^{13}C), which makes it possible to establish spin-spin interactions of homo- and heteronuclear nature (Fig. 1–4). The observed correlations in the molecule are shown in the diagram. In the spectra of the ^1H-^1H COSY compound, spin-spin correlations are observed through three proton bonds of neighboring methylene groups $H^{25,29}$-$H^{26,28}$ (7.47, 7.20 and 7.17, 7.48), H^{26}-H^{27} (7.20, 6.96 and 6.96, 7.21) and H^{27}- H^{28} (6.96, 7.20 and 7.20, 6.96). The coordinates 3.84, 1.18 and 1.16, 3.80 correspond to homolytic interaction through three bonds of neighboring aliphatic protons H^{20} and H^{21}. Heteronuclear interactions of protons with carbon atoms through one bond were established using ^1H-^{13}C HMQC spectroscopy for all pairs present in the compound: H^5-C^5 (7.57, 150.23), $H^{25,29}$-$C^{25,29}$ (7.48, 119.93), $H^{26,28}$-$C^{26,28}$ (7.19, 129.15), H^{27}-C^{27} (6.94, 123.73), H^{11}-C^{11} (6.70, 113.34), H^{20}-C^{20} (3.82, 64.45), H^{14}-C^{14} (6.65, 120.32), H^6-C^6 (6.37, 60.47), H^{18}-C^{18} (2.11, 17.83) and H^{21}-C^{21} (1.17, 15.05).

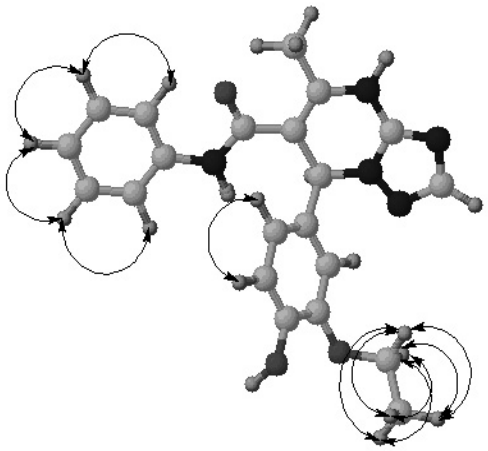


Figure 1. Correlations of COSY (^1H-^1H) compound (**1**)

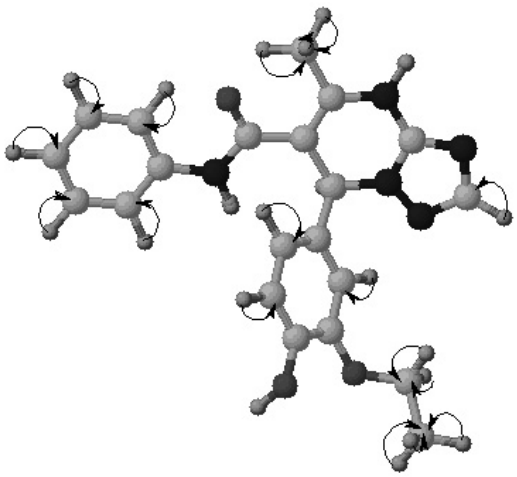


Figure 2. Correlations of HMQC (^1H-^{13}C) compound (**1**)

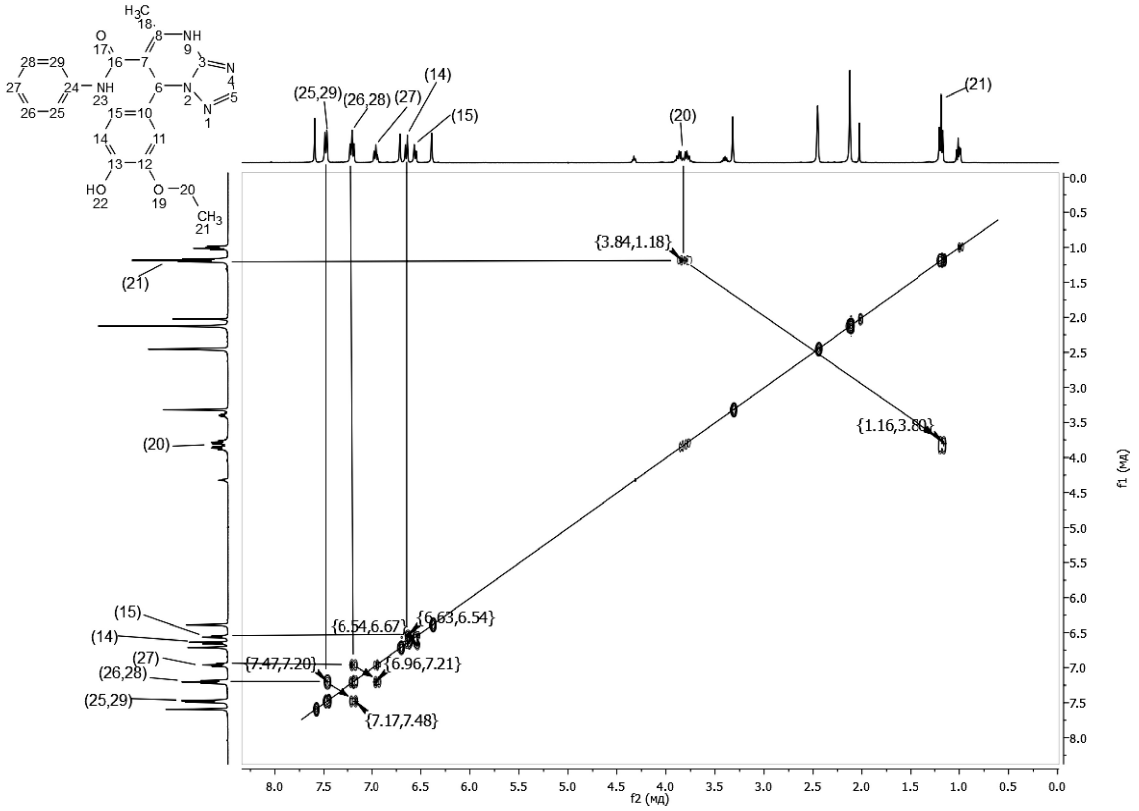


Figure 3. COSY (^{1}H-^{1}H) NMR spectrum of compound (**1**)

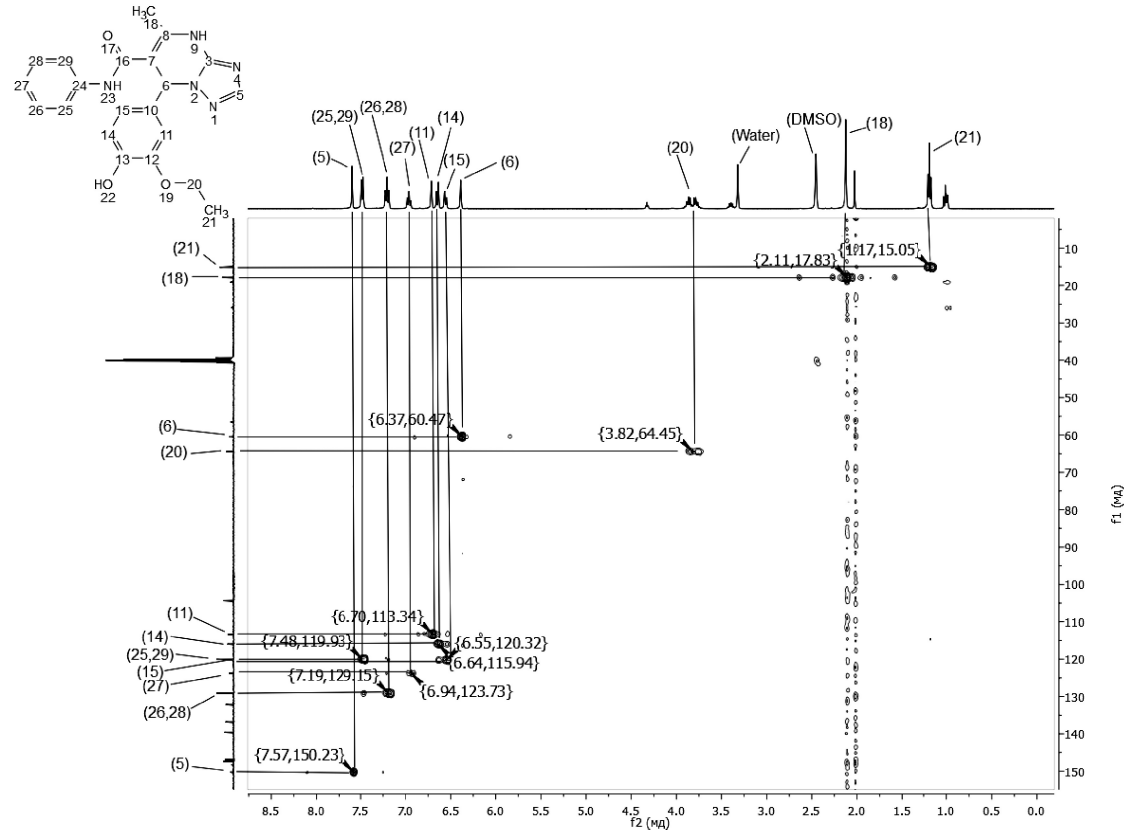


Figure 4. HMQC (^{1}H-^{13}C) NMR spectrum of compound (**1**)

The structures of other compounds (2), (3), and (4) are also confirmed by single-dimensional ^{1}H NMR and ^{13}C NMR spectroscopy (Table) and homo- and heteronuclear correlations of COSY and HMQC NMR.

Table

^{1}H and ^{13}C NMR spectroscopy data for compounds (1–4)

Compound No.	δ, ppm.	
	^{1}H	^{13}C
1	1.19 t (3H, CH_3^{14}, ^{3}J 6.9 Hz), 2.12 s (3H, CH_3^{18}), 3.76–3.89 m (2H, CH_2^{20}), 6.39 s (1H, H^{6}), 6.56 d (1H, H^{15}, ^{3}J 7.8 Hz), 6.65 d (1H, H^{14}, ^{3}J 8.2 Hz), 6.71 s (1H, H^{11}), 6.96 t (1H. H^{27}, ^{3}J 7.3 Hz), 7.20 t (2H, $H^{26,28}$, ^{3}J 7.8 Hz), 7.48 d (2H, $H^{25,29}$, ^{3}J 7.8 Hz), 8.90 s (1H, OH^{22}), 9.66 s (1H, NH^{23}). 10.10 s (1H, NH^{9})	15.15 (C^{21}), 17.81 (C^{18}), 60.47 (C^{6}), 64.43 (C^{20}), 104.35 (C^{7}), 113.35 (C^{11}), 115.96 (C^{14}), 120.02 ($C^{25,29}$), 120.25 (C^{15}), 123.77 (C^{27}), 129.08 ($C^{26,28}$), 132.17 (C^{10}), 136.75 (C^{8}), 139.58 (C^{24}), 146.86 (C^{12}), 147.29 (C^{13}), 148.24 (C^{3}), 150.23 (C^{5}), 165.58 (C^{16})
2	2.26 s (3H, CH_3^{18}), 5.78 s (1H, H^{3}), 6.70 t (1H, H^{13}), 6.95 d (1H, H^{12}), 7.15–7.26 m (3H, $H^{14,24,26}$), 7.36–7.59 m (3H, $H^{22,23,25}$), 7.87 d (1H, H^{15}), 9.64 s (1H, OH^{19}), 9.99 s (1H, NH^{6}). 10.37 s (1H, NH^{20})	19.20 (C^{18}), 60.29 (C^{3}), 118.86 ($C^{22,26}$), 119.18 (C^{12}), 119.71 (C^{13}), 120.19 (C^{24}), 128.06 (C^{10}), 128.81 (C^{15}), 129.02 (C^{14}), 129.09 ($C^{23,25}$), 129.32 (C^{21}), 150.18 (C^{5}), 151.22 (C^{9}), 152.38 (C^{7}), 156.43 (C^{21}), 170.88 (C^{16})
3	1.01 t (3H, CH_3^{25}, ^{3}J 7.0 Hz), 1.24 t (3H, CH_3^{21}, ^{3}J 7.0 Hz), 2.35 s (3H, CH_3^{18}), 3.87–3.98 m (4H, CH_2^{20}, CH_2^{22}), 6.11 s (1H, H^{6}), 6.50 dd (1H, H^{15}, ^{3}J 8.2, 1.8 Hz), 6.64 d (1H, H^{14}, ^{3}J 8.2 Hz), 6.72 s (1H, H^{11}), 6.96 t (1H. H^{27}, ^{3}J 7.3 Hz), 7.20 t (2H, $H^{26,28}$, ^{3}J 7.8 Hz), 7.48 d (2H, $H^{25,29}$, ^{3}J 7.8 Hz), 8.90 s (1H, OH^{22}), 9.66 s (1H, NH^{23}). 10.10 s (1H, NH^{9})	14.49 (C^{25}), 15.21 (C^{21}), 18.88 (C^{18}). 59.62 (C^{6}), 59.82 (C^{24}), 64.41 (C^{20}), 98.08 (C^{7}), 113.41 (C^{11}), 115.91 (C^{14}), 119.80 (C^{15}), 133.70 (C^{10}), 146.70 ($C^{3,8}$), 147.09 (C^{12}), 147.41 (C^{13}), 150.45 (C^{5}), 165.75 (C^{16})
4	1.16 t (3H, CH_3^{22}, ^{3}J 6.9 Hz), 2.26 s (3H, CH_3^{18}), 3.99 k (2H, CH_2^{21}, ^{3}J 7.0 Hz), 6.76 d (1H, H^{12}, ^{3}J 8.8 Hz), 6.80 s (1H, H^{3}), 6.93 t (1H, H^{13}, ^{3}J 6.3 Hz), 7.06 t (1H, H^{14}, ^{3}J 7.3 Hz), 7.68 d (1H, H^{15}, ^{3}J 8.2 Hz), 9.38 s (1H, OH^{19}), 9.65 s (1H, NH^{6})	14.32 (C^{22}), 19.18 (C^{18}), 44.87 (C^{3}), 61.06 (C^{21}), 98.67 (C^{4}), 120.01 (C^{12}), 122.79 (C^{13}), 125.44 (C^{10}), 127.07 (C^{15}), 128.87 (C^{14}), 147.60 (C^{9}), 150.20 (C^{5}), 151.19 (C^{7}), 156.42 (C^{11}), 165.39 (C^{16})

Conclusions

The studies carried out for the first time the synthesis of novel 7-aryl-5-methyl-N-phenyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxyethylamidesi and 7-aryl-5-methyl-4,7-dihydro-[1,2,4-triazolo][1,5-a]pyrimidine-6-carboxylates. On basis of analysis of spectral data of their structure and methods NMR ^{1}H- and ^{13}C-spectroscopy as well as two-dimensional spectra data COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) provided a mechanism of the reaction whereby the formation of the final product takes place through the intermediate step of reacting 1,3-dicarbonyl compounds with molecules of aromatic aldehyde.

The source of research funding. The work was carried out with the financial support of the Committee of Science and the Ministry of Education of the Republic of Kazakhstan on «Program-Targeted Financing», No. Registration 0115PK01782.

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3-Амино-1,2,4-триазол негізінде конденсирленген бигетероциклдердің синтезі мен құрылымы

Мақала 3-амино-1,2,4-триазолдың жаңа туындыларын синтездеуде препаратты тиімді әдістерін дамытып, өндіріске қажетті жаңа конденсирленген жүйелерді құру мақсатына арналған. 1,3-дикарбонилді қосылыстардың (ацетосірке қышқылының анилиді және ацетосірке қышқылы), орынауыстырылған ароматтық альдегидтер және 3-амино-1,2,4-триазолымен үшкомпонентті конденсациясы арқылы алынатын триазоло-пиримидиндерді синтездеу туралы мәліметтер келтірілді. Еріткішсіз эквимолекулярлық мөлшерде ацетосірке қышқылының анилиді мен ацетосірке қышқылын қоспасымен 3-амино-1,2,4-триазол және орынауыстырылған ароматтық альдегидтер (3-этокси-4-гидроксибензальдегид, салицил альдегид) қоспасымен 120–140 ºС-да балқыту арқылы сәйкесінше

7-арил-5-метил-N-фенил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксамидтер мен этил 7-арил-5-метил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксилаттар алынуы көрсетілді. Синтезделген қосылыстардың құрылымы ЯМР ^{1}H- мен ^{13}C-спектроскопия, екі кеңістікті COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) әдістерімен зерттеліді. Бір кеңістікті ЯМР спектрлерінде химиялық қозғалыстардың сандық мәндері, мултиплеттілігі және ^{1}H, ^{13}C сигналдарының интегралды қарқындылығы анықталды. Зерттелген қосылыстардың құрылымы COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) спектрлері көмегімен гомо- и гетероядролық арақатынасын анықтау арқылы дәлелденді.

Кілт сөздер: 3-амино-1,2,4-триазол, 7-арил-5-метил-N-фенил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксамидтер, ароматтық альдегидтер, ЯМР^{1}H- и ^{13}C-спектрлер.

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Синтез и строение конденсированных бигетероциклов на основе 3-амино-1,2,4-триазола

Статья посвящена разработке препаративно удобных способов синтеза новых производных 3-амино-1,2,4-триазола с целью построения новых конденсированных систем промышленно важных веществ. Приведены данные по синтезу триазолопиримидинов, полученных трехкомпонентной конденсацией 1,3-дикарбонильных соединений (анилид ацетоуксусной кислоты и ацетоуксусный эфир) с замещенными ароматическими альдегидами и 3-амино-1,2,4-триазолом. Показано, что сплавление при 120–140 ºС в отсутствие растворителя эквимолекулярных количеств анилида ацетоуксусной кислоты и ацетоуксусного эфира со смесью 3-амино-1,2,4-триазола и замещенных ароматических альдегидов (3-этокси-4-гидроксибензальдегид, салициловый альдегид) приводит к 7-арил-5-метил-N-фенил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксамидам и этил 7-арил-5-метил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*]пиримидин-6-карбоксилатам соответственно. Исследовано строение синтезированных соединений методами ЯМР ^{1}H- и ^{13}C-спектроскопии, а также данными двумерных спектров COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C). Определены значения химических сдвигов, мультиплетность и интегральная интенсивность сигналов ^{1}H и ^{13}C в одномерных спектрах ЯМР. С помощью спектров в форматах COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) установлены гомо- и гетероядерные взаимодействия, подтверждающие структуру исследуемых соединений.

Ключевые слова: 3-амино-1,2,4-триазол, 7-арил-5-метил-N-фенил-4,7-дигидро-[1,2,4-триазоло][1,5-*a*] пиримидин-6-карбоксамиды, ароматические альдегиды, ЯМР^{1}H- и ^{13}C-спектры.

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UDC 547.587.11

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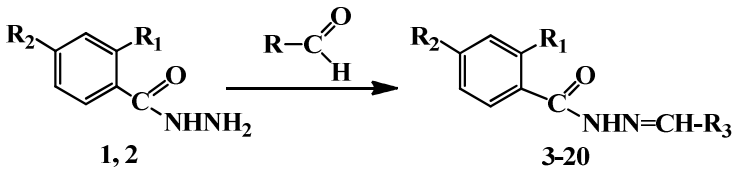
Synthesis, structure and computer bioprognosis new hydrazons based on hydrosides *o*- and *p*-hydroxybenzoic acids

Interaction of hydrazides of *o*- and *p*-hydroxybenzoic acids with substituted aromatic aldehydes yielded the corresponding hydrazone derivatives. Using the computer program PASS, a bioproject of N-arylidene hydrazones was carried out and it was shown that their expected activity combines both the physiological activity of the initial hydrazides of *o*- and *p*-hydroxybenzoic acids and the constituent components of the structural molecule. The structures of the synthesized compounds were studied by ^{1}H NMR and ^{13}C NMR spectroscopy, as well as with the data of the two-dimensional spectra COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C). The values of chemical shifts, multiplicity and integrated intensity of the ^{1}H and ^{13}C signals in one-dimensional NMR spectra are determined. Homogeneous and heteronuclear interactions are established using spectra in the formats COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), confirming the structure of the compounds under study. X-ray diffraction study of N-(5-bromo-2-hydroxybenzylidene)-4-hydroxybenzohydrazide, whose molecule is bound by a hydrogen bond to an ethanol solvate molecule.

Keywords: *o*- and *p*-hydroxybenzoic acid hydrazide, hydrazone, aromatic aldehydes, NMR spectroscopy.

Advances in the chemistry of hydrazides of carboxylic acids in recent decades are largely due to the widespread use of these compounds as antituberculous drugs in medicine. It should be noted that considerable progress has been made in the chemistry of hydrazides, which led to the creation of such antituberculosis drugs as phtivazide, saluside, and metazide [1, 2]. In recent years, interest in hydrazones has increased again [3, 4], which is associated with a wide range of their biological properties. Hydrazones are used in medical practice and agriculture [5]. It was interesting to obtain on the basis of hydrazides *o*- and *p*-hydroxybenzoic acids carbohydrazones containing pharmacophore groupings. The structure of hydrazides of *o*- and *p*-hydroxybenzoic acids has a great synthetic and biological potential, which makes it possible to develop methods for the synthesis of new biologically active substances [6, 7]. Earlier, we synthesized various derivatives [8] based on *o*- and *p*-hydroxybenzoic acid hydrazides, which showed pronounced antimicrobial activity against Gram-positive strains (*Staphylococcus aureus, Bacillus subtilis*).

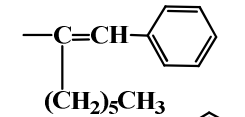
In the present work we synthesized hydrazones **3–20**, the condensation of hydrazides of *o*- and *p*-hydroxybenzoic acids **1, 2** with various aromatic aldehydes by heating equimolar amounts of aldehyde and hydrazides in an ethyl alcohol medium at 60–70 ºC and stirring for several hours.



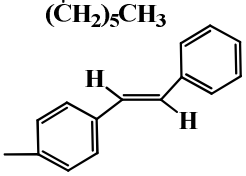
1, 2 **3-20**

R_1 = OH; R_2 = H (1; 3-11); **R_1 = H; R_2 = OH (2; 12-20)**

R_3 = ***4*-FC_6H_4 (1, 3; 2, 12);**
***2*-HO-*5*-BrC_6H_3 (1, 4; 2, 13);**
***4*-CH_3O-C_6H_4 (1, 5; 2, 14);**
***2*-HO-C_6H_4(1, 6; 2, 15);**
***4*-HO-C_6H_4 (1, 7; 2, 16);**
C_5H_5N (1, 8; 2, 17);
***4*-HO-*5*-C_2H_5O-C_6H_3 (1, 9; 2, 18);**



(1, 10; 2, 19);

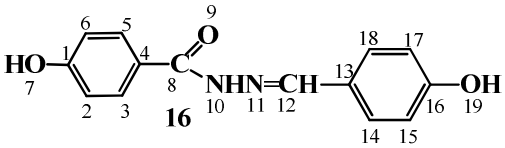


(1, 11; 2, 20);

The reaction products **3–20** are highly crystallizable white substances, soluble in many organic solvents; the yield of compounds is 70–90 %.

In the IR spectra of N-arylidenehydrazones of *o*- and *p*-hydroxybenzoic acids, **3–20** absorption bands of stretching vibrations of the N–H group appear in the region of 3285–3355 cm^{-1}, and C=O of the hydrazone group at 1675–1690 cm^{-1}. The group of characteristic bands 1600–1440 cm^{-1} refers to stretching vibrations of the aromatic ring.

In the strong-field NMR part of the ^{1}H-spectrum of compound **16**, signals of residual protons of solvent and water are observed. The protons of methine groups of aromatic systems resonate in a weaker field: δ(H-2, H-6, H-15, H-17) = 6.80 ppm, 4 H; δ(H-14,18) = 7.49 ppm, 2H; δ(H-3,5) = 7.75 ppm, 2H. Signal with a chemical shift of 8.28 ppm. And the integral intensity 1H belongs to the proton H-12. The highest-frequency signals (9.95 and 11.40 ppm) can be attributed to the protons of one amino and two hydroxo groups, respectively.



NMR ^{13}C spectrum of compound **16** carbon atoms of CH-groups of two benzene nuclei give signals in the weak-field region: δ(C-2,6) = 115.49 ppm; δ(C-15,17) = 116.21 ppm; δ(C-14,18) = 129.21 ppm; δ(C-3,5) = 130.07 ppm. Quaternary atoms of aromatic systems give signals at 124.63 (C-4), 126.03 (C-13), 159.75 (C-16) and 161.04 ppm. (C-1). The signal with a chemical shift of 147.74 ppm. Corresponds to the sp^2-hybridized C-12 atom. High-frequency signal at 163.07 ppm. Refers to the carbonyl atom C-8.

Spin-spin interactions of compound **16** between H-H and H-C atoms via one or more bonds were established by means of two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C).

Spin-spin interactions of compound **16** between H-H and H-C atoms via one or more bonds and compounds **20** between H-H atoms through three bonds were established by means of the two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H -^{13}C) (Fig. 1–4).

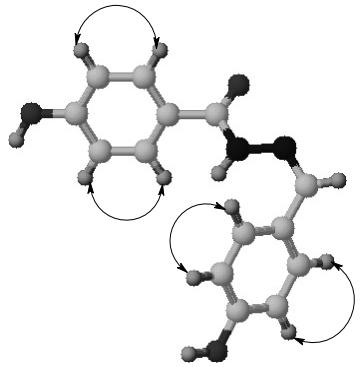


Figure 1. Correlations of COSY (^{1}H-^{1}H) of compound **16**

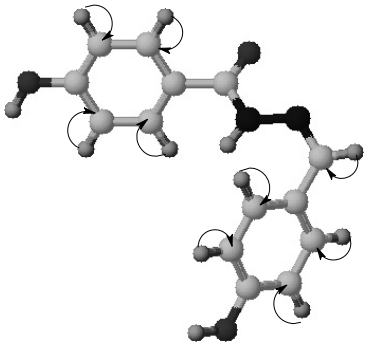


Figure 2. HMQC correlations (^{1}H-^{13}C) of compound **16**

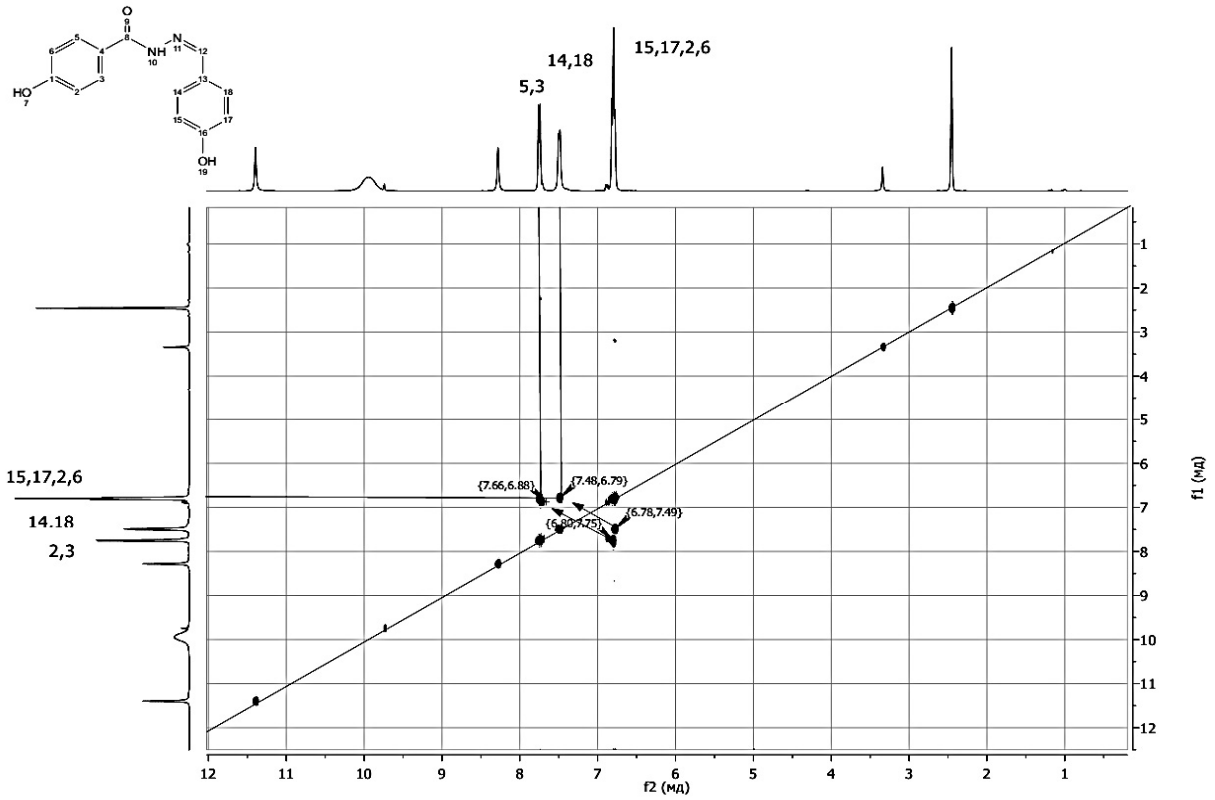


Figure 3. Shooting the COSY (^{1}H-^{1}H) spectrum of compound **16**

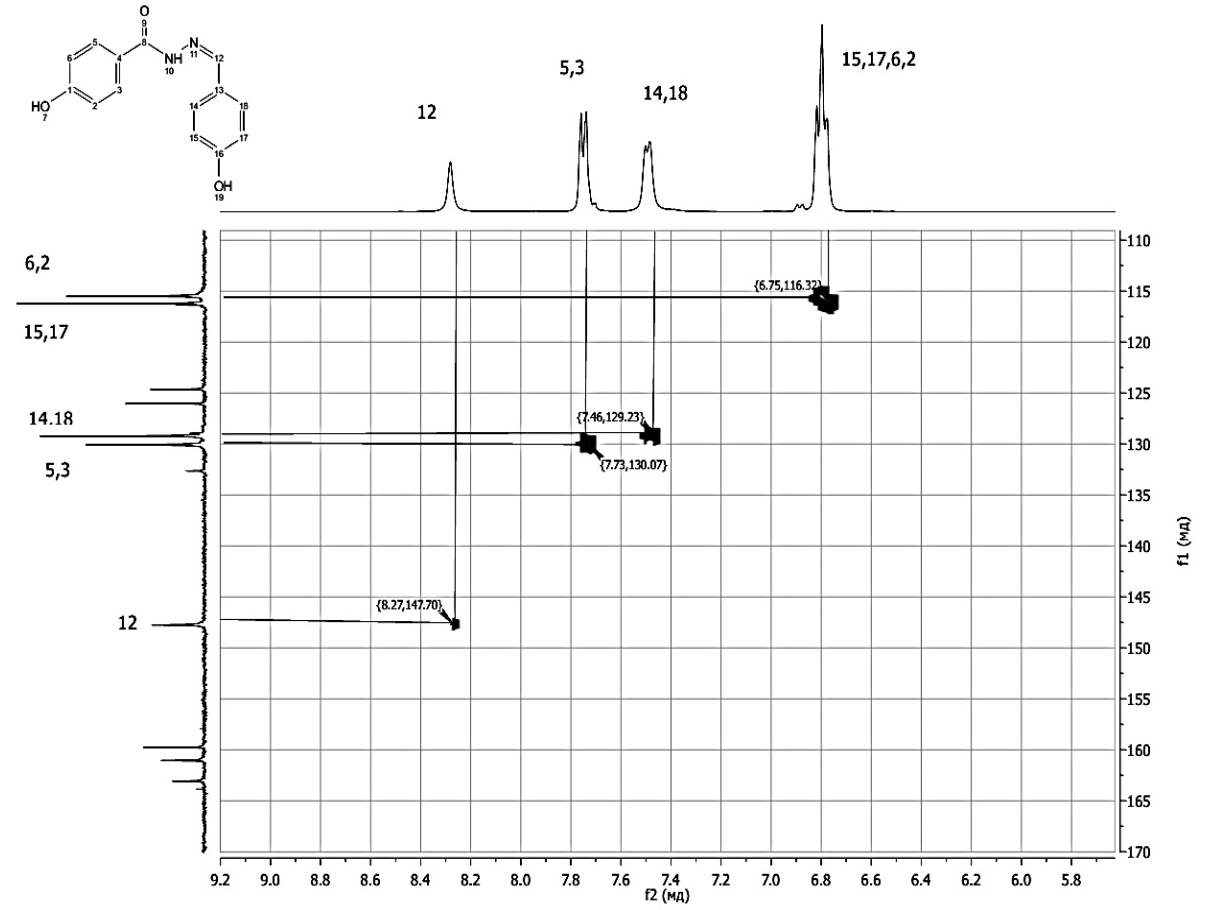


Figure 4. Shooting the HMQC (^{1}H-^{13}C) spectrum of compound **16**

To prove the spatial structure of the N-arylidene-hydrazone derivatives of *p*-hydroxybenzoic acid, an X-ray diffraction study of the ethanolic solvate of N-(5-bromo-2-hydroxybenzylidene)-4-hydroxybenzo-hydrazide **(13)** was performed (Fig. 5).

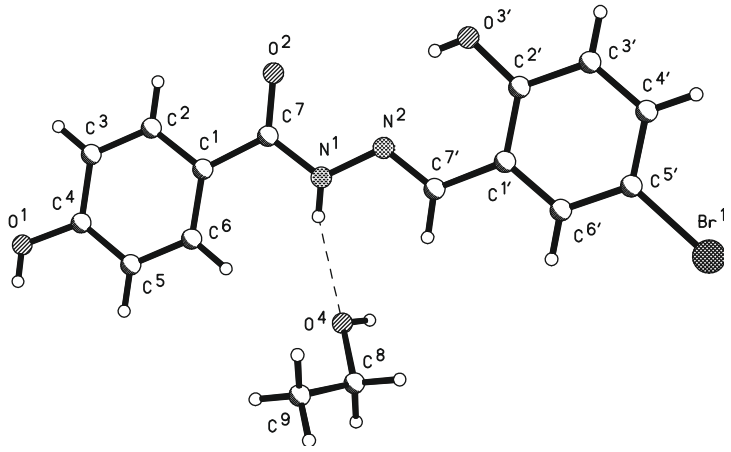


Figure 5. Spatial structure of the ethanol solvate molecule
N-(5-Bromo-2-hydroxybenzylidene)-4-hydroxybenzohydrazide **(13)**

It follows from the obtained data that the bond lengths and valence angles in compounds **13** are close to the usual ones (Tables 1–5) [9]. Molecule **13** is practically flat, but there is a slight reversal of the phenyl cycles relative to each other (the dihedral angle between them is 5.9°).

Table 1

Bond lengths (*d*, Å) in the structure of compound 13

Bond	*d*	Bond	*d*
Br(1)-C(5')	1.894(5)	C(6)-H(6)	0.9300
O(1)-C(4)	1.361(5)	C(1')-C(6')	1.388(6)
O(1)-H(01)	0.76(4)	C(1')-C(2')	1.409(6)
O(2)-C(7)	1.226(4)	C(1')-C(7')	1.451(5)
O(3')-C(2')	1.353(6)	C(2')-C(3')	1.385(6)
O(3')-H(03')	0.68(5)	C(3')-C(4')	1.380(6)
N(1)-C(7)	1.354(5)	C(3')-H(3')	0.9300
N(1)-N(2)	1.366(5)	C(4')-C(5')	1.384(6)
N(1)-H(1)	0.76(4)	C(4')-H(4')	0.9300
N(2)-C(7')	1.274(5)	C(5')-C(6')	1.372(6)
C(1)-C(2)	1.384(6)	C(6')-H(6')	0.9300
C(1)-C(6)	1.392(5)	C(7')-H(7')	0.9300
C(1)-C(7)	1.483(6)	O(4)-C(8)	1.407(6)
C(2)-C(3)	1.383(6)	O(4)-H(04)	0.82(6)
C(2)-H(2)	0.9300	C(8)-C(9)	1.440(8)
C(3)-C(4)	1.389(5)	C(8)-H(8A)	0.9700
C(3)-H(3)	0.9300	C(8)-H(8B)	0.9700
C(4)-C(5)	1.370(6)	C(9)-H(9A)	0.9600
C(5)-C(6)	1.378(6)	C(9)-H(9B)	0.9600
C(5)-H(5)	0.9300	C(9)-H(9C)	0.9600

Table 2

Valent angles (ω, deg.) in the structure of compound 13

Angle	ω	Angle	ω
C(4)-O(1)-H(01)	109(4)	O(3')-C(2')-C(1')	122.9(4)
C(2')-O(3')-H(03')	115(5)	C(3')-C(2')-C(1')	119.7(4)
C(7)-N(1)-N(2)	119.0(4)	C(4')-C(3')-C(2')	120.2(4)
C(7)-N(1)-H(1)	120(3)	C(4')-C(3')-H(3')	119.9
N(2)-N(1)-H(1)	121(3)	C(2')-C(3')-H(3')	119.9
C(7')-N(2)-N(1)	117.7(4)	C(3')-C(4')-C(5')	120.0(4)
C(2)-C(1)-C(6)	118.0(4)	C(3')-C(4')-H(4')	120.0
C(2)-C(1)-C(7)	117.6(4)	C(5')-C(4')-H(4')	120.0
C(6)-C(1)-C(7)	124.4(4)	C(6')-C(5')-C(4')	120.6(4)
C(3)-C(2)-C(1)	121.3(4)	C(6')-C(5')-Br(1)	118.5(4)
C(3)-C(2)-H(2)	119.4	C(4')-C(5')-Br(1)	120.9(4)
C(1)-C(2)-H(2)	119.4	C(5')-C(6')-C(1')	120.3(4)
C(2)-C(3)-C(4)	119.8(4)	C(5')-C(6')-H(6')	119.9
C(2)-C(3)-H(3)	120.1	C(1')-C(6')-H(6')	119.9
C(4)-C(3)-H(3)	120.1	N(2)-C(7')-C(1')	121.3(4)
O(1)-C(4)-C(5)	123.3(4)	N(2)-C(7')-H(7')	119.3
O(1)-C(4)-C(3)	117.2(4)	C(1')-C(7')-H(7')	119.3
C(5)-C(4)-C(3)	119.5(4)	C(8)-O(4)-H(04)	111(4)
C(4)-C(5)-C(6)	120.6(4)	O(4)-C(8)-C(9)	111.6(5)
C(4)-C(5)-H(5)	119.7	O(4)-C(8)-H(8A)	109.3
C(6)-C(5)-H(5)	119.7	C(9)-C(8)-H(8A)	109.3
C(5)-C(6)-C(1)	120.9(4)	O(4)-C(8)-H(8B)	109.3
C(5)-C(6)-H(6)	119.5	C(9)-C(8)-H(8B)	109.3
C(1)-C(6)-H(6)	119.5	H(8A)-C(8)-H(8B)	108.0
O(2)-C(7)-N(1)	121.3(4)	C(8)-C(9)-H(9A)	109.5
O(2)-C(7)-C(1)	121.1(4)	C(8)-C(9)-H(9B)	109.5
N(1)-C(7)-C(1)	117.6(4)	H(9A)-C(9)-H(9B)	109.5
C(6')-C(1')-C(2')	119.3(4)	C(8)-C(9)-H(9C)	109.5
C(6')-C(1')-C(7')	118.7(4)	H(9A)-C(9)-H(9C)	109.5
C(2')-C(1')-C(7')	122.0(4)	H(9B)-C(9)-H(9C)	109.5
O(3')-C(2')-C(3')	117.4(4)		

Table 3

The coordinates of the atoms in the fractions of the cell in the structure of compound 13

Atom	*x*	*y*	*z*	*U*(eq)
1	2	3	4	5
Br(1)	5593(1)	8504(1)	1603(1)	80(1)
O(1)	7718(2)	1056(2)	3868(4)	67(1)
O(2)	4490(2)	3531(2)	914(3)	56(1)
O(3')	3466(3)	5582(2)	39(4)	69(1)
N(1)	5754(3)	4310(2)	1903(4)	51(1)
N(2)	5162(2)	4921(2)	1392(4)	49(1)
C(1)	6028(3)	2970(2)	2255(4)	44(1)
C(2)	5628(3)	2261(2)	1928(4)	53(1)
C(3)	6198(3)	1627(2)	2472(4)	56(1)

Table 3 continuation

1	2	3	4	5
C(4)	7193(3)	1698(2)	3364(4)	50(1)
C(5)	7598(3)	2398(3)	3692(4)	57(1)
C(6)	7027(3)	3028(2)	3147(4)	57(1)
C(7)	5362(3)	3618(2)	1629(4)	47(1)
C(1')	4979(3)	6244(2)	1203(4)	47(1)
C(2')	3970(3)	6227(3)	409(4)	52(1)
C(3')	3459(3)	6891(3)	-19(5)	62(1)
C(4')	3933(3)	7568(3)	333(5)	62(1)
C(5')	4924(4)	7584(2)	1116(5)	55(1)
C(6')	5443(3)	6931(3)	1550(4)	54(1)
C(7')	5551(3)	5565(2)	1680(4)	53(1)
O(4)	7693(3)	4784(2)	2979(4)	75(1)
C(8)	8410(4)	5181(3)	4147(6)	105(2)
C(9)	8659(5)	4818(4)	5308(6)	119(3)

Table 4

The coordinates of the atoms in the fractions of the cell ($\times 10^4$) in the structure of compound 13

Atom	*x*	*y*	*z*	U(eq)
H(2)	4962	2210	1330	64
H(3)	5917	1155	2241	67
H(5)	8264	2447	4287	68
H(6)	7312	3499	3380	69
H(3')	2793	6882	–544	74
H(4')	3587	8014	45	75
H(6')	6108	6948	2078	64
H(7')	6215	5601	2206	63
H(01)	8240(30)	1150(30)	4440(50)	66(17)
H(03')	3740(40)	5270(30)	330(50)	70(20)
H(1)	6290(30)	4350(20)	2280(40)	40(13)
H(8A)	8184	5684	4085	126
H(8B)	8979	5219	4234	126
H(9A)	9152	5100	6086	179
H(9B)	8890	4322	5377	179
H(9C)	8100	4790	5235	179
H(04)	7590(40)	4970(30)	2330(60)	100(20)

Table 5

Torsion angles (τ, deg.) for compound 13

Angle	τ	Angle	τ
1	2	3	4
C(7)-N(1)-N(2)-C(7')	179.2(4)	C(6')-C(1')-C(2')-O(3')	-179.3(4)
C(6)-C(1)-C(2)-C(3)	-179.7(4)	C(7')-C(1')-C(2')-O(3')	0.3(7)
C(7)-C(1)-C(2)-C(3)	0.3(7)	C(6')-C(1')-C(2')-C(3')	0.3(7)
C(1)-C(2)-C(3)-C(4)	-0.1(7)	C(7')-C(1')-C(2')-C(3')	179.9(4)
C(2)-C(3)-C(4)-O(1)	179.9(4)	O(3')-C(2')-C(3')-C(4')	179.6(5)

Table 5 continuation

1	2	3	4
C(2)-C(3)-C(4)-C(5)	-0.1(7)	C(1')-C(2')-C(3')-C(4')	-0.1(7)
O(1)-C(4)-C(5)-C(6)	-179.9(5)	C(2')-C(3')-C(4')-C(5')	0.0(8)
C(3)-C(4)-C(5)-C(6)	0.2(8)	C(3')-C(4')-C(5')-C(6')	-0.1(8)
C(4)-C(5)-C(6)-C(1)	0.1(8)	C(3')-C(4')-C(5')-Br(1)	179.5(4)
C(2)-C(1)-C(6)-C(5)	-0.3(7)	C(4')-C(5')-C(6')-C(1')	0.3(7)
C(7)-C(1)-C(6)-C(5)	179.8(5)	Br(1)-C(5')-C(6')-C(1')	-179.3(3)
N(2)-N(1)-C(7)-O(2)	1.4(7)	C(2')-C(1')-C(6')-C(5')	-0.4(7)
N(2)-N(1)-C(7)-C(1)	-177.0(4)	C(7')-C(1')-C(6')-C(5')	180.0(4)
C(2)-C(1)-C(7)-O(2)	4.5(6)	N(1)-N(2)-C(7')-C(1')	-178.6(4)
C(6)-C(1)-C(7)-O(2)	-175.5(4)	C(6')-C(1')-C(7')-N(2)	180.0(4)
C(2)-C(1)-C(7)-N(1)	-177.1(4)	C(2')-C(1')-C(7')-N(2)	0.3(7)
C(6)-C(1)-C(7)-N(1)	2.8(7)		

In a crystal, the molecule **13** forms the hydrogen bond N^1 H... O^4 (x, y, z) (distance N... O 2.956(5) Å, H... O 2.22(4) Å, angle N H... O 164(2)°) c Solvate molecule of ethanol. The intermolecular hydrogen bond O^1-H... O^2 (distance O... O 2.243(4) Å, H... O 1.89 5) Å, the angle O H... O 174(5)°) is also observed, owing to which the molecules **13** form Chains along the diagonal [*a, o, c*] parallel to the plane of this diagonal with the *b* axis.

In order to establish the expected type of biological activity of the synthesized derivatives of **3–20** hydrides of *o*- and *p*-hydroxybenzoic acids, we conducted a bioprojection using one of the most effective PASS (Prediction of Activity Spectra for Substances) computer program to date Chemical structure and a universal mathematical algorithm for establishing «structure-activity» dependencies [10]. Types of biological activity of compounds are presented in Table 6.

From the analysis of the bioprognosis data of N-arylidene hydrazones it follows that their expected activity combines both the physiological activity of the initial hydrazides of *o*- and *p*-hydroxybenzoic acids and the constituent components of the structural molecule. With a fairly high degree of probability, the compounds can exhibit antibacterial, antitubercular, antiseptic, inhibitory activities and are of interest for the synthesis and study of their biological properties.

Table 6

The results of a computer bioprojection of the expected type of biological activity of compounds 3–9, 12–18

Comp. No.	Probability	Ranging	Activity type names
1	2	3	4
3	0.807	0.005	HMGCS2 expression enhancer
	0.807	0.012	Beta-adrenergic receptor kinase inhibitor
	0.784	0.003	Antituberculosic
	0.785	0.004	Antimycobacterial
	0.751	0.003	PfA-M1 aminopeptidase inhibitor
4	0.921	0.002	HMGCS2 expression enhancer
	0.898	0.002	Antituberculosic
	0.875	0.003	Antimycobacterial
	0.811	0.002	PfA-M1 aminopeptidase inhibitor
	0.799	0.004	Antiseptic
5	0.826	0.003	Antimycobacterial
	0.823	0.003	Antituberculosic
	0.814	0.004	HMGCS2 expression enhancer
	0.810	0.012	Beta-adrenergic receptor kinase inhibitor
	0.810	0.012	G-protein-coupled receptor kinase inhibitor
	0.731	0.003	PfA-M1 aminopeptidase inhibitor

Table 6 continuation

1	2	3	4
6	0.902	0.002	HMGCS2 expression enhancer
	0.837	0.003	Antituberculosic
	0.830	0.004	Threonine aldolase inhibitor
	0.819	0.004	Antimycobacterial
	0.813	0.002	PfA-M1 aminopeptidase inhibitor
	0.813	0.011	Taurine dehydrogenase inhibitor
7	0.851	0.008	Beta-adrenergic receptor kinase inhibitor
	0.851	0.008	G-protein-coupled receptor kinase inhibitor
	0.846	0.004	HMGCS2 expression enhancer
	0.836	0.003	Antituberculosic
	0.818	0.004	Antimycobacterial
	0.782	0.003	PfA-M1 aminopeptidase inhibitor
8	0.907	0.002	Antituberculosic
	0.875	0.003	Threonine aldolase inhibitor
	0.873	0.003	Antimycobacterial
	0.869	0.005	Taurine dehydrogenase inhibitor
	0.861	0.003	Amine dehydrogenase inhibitor
	0.813	0.004	HMGCS2 expression enhancer
	0.738	0.004	Antiviral (Picornavirus)
9	0.876	0.002	Antituberculosic
	0.863	0.007	Beta-adrenergic receptor kinase inhibitor
	0.863	0.007	G-protein-coupled receptor kinase inhibitor
	0.850	0.004	Antiseptic
	0.843	0.003	Antimycobacterial
	0.743	0.007	HMGCS2 expression enhancer
12	0.822	0.011	Beta-adrenergic receptor kinase inhibitor
	0.811	0.005	HMGCS2 expression enhancer
	0.758	0.004	Antituberculosic
	0.760	0.004	Antimycobacterial
	0.732	0.003	PfA-M1 aminopeptidase inhibitor
13	0.919	0.002	HMGCS2 expression enhancer
	0.893	0.002	Antituberculosic
	0.872	0.003	Antimycobacterial
	0.803	0.002	PfA-M1 aminopeptidase inhibitor
	0.759	0.005	Antiseptic
14	0.824	0.011	Beta-adrenergic receptor kinase inhibitor
	0.824	0.011	G-protein-coupled receptor kinase inhibitor
	0.818	0.004	HMGCS2 expression enhancer
	0.804	0.004	Antimycobacterial
	0.802	0.003	Antituberculosic
	0.710	0.003	PfA-M1 aminopeptidase inhibitor
15	0.895	0.003	HMGCS2 expression enhancer
	0.876	0.003	Threonine aldolase inhibitor
	0.831	0.003	Antituberculosic
	0.831	0.009	Taurine dehydrogenase inhibitor
	0.814	0.004	Antimycobacterial
	0.798	0.002	PfA-M1 aminopeptidase inhibitor
16	0.862	0.003	HMGCS2 expression enhancer
	0.862	0.007	Beta-adrenergic receptor kinase inhibitor
	0.862	0.007	G-protein-coupled receptor kinase inhibitor
	0.815	0.003	Antituberculosic
	0.801	0.004	Antimycobacterial
	0.776	0.003	PfA-M1 aminopeptidase inhibitor

Table 6 continuation

1	2	3	4
17	0.922	0.002	Threonine aldolase inhibitor
	0.898	0.004	Taurine dehydrogenase inhibitor
	0.898	0.004	Amine dehydrogenase inhibitor
	0.883	0.002	Antituberculosic
	0.855	0.003	Antimycobacterial
	0.818	0.004	HMGCS2 expression enhancer
	0.758	0.004	Antiviral (Picornavirus)
18	0.872	0.006	Beta-adrenergic receptor kinase inhibitor
	0.872	0.006	G-protein-coupled receptor kinase inhibitor
	0.845	0.003	Antituberculosic
	0.819	0.004	Antimycobacterial
	0.772	0.004	Antiseptic
	0.747	0.007	HMGCS2 expression enhancer

Experimental part

^{1}H and ^{13}C NMR spectra of compounds **3–20** were recorded on a JNN-ECA Jeol 400 spectrometer (frequency 399.78 and 100.53 MHz, respectively) using a DMSO-d_6 solvent. Chemical shifts are measured relative to signals of residual protons or carbon atoms of deuterated dimethylsulfoxide.

X-ray analysis of compound (**13**). The cell parameters and the intensity of 6311 reflections (3293 independent, R_{int}=0.0516) were measured on a diffractometer «Xcalibur Ruby (Oxford Diffraction)» (CuK_α, graphite monochromator, φ, θ scan, 4.03≤76.13) at 293 K. The crystals are monoclinic, a=18.233(4), b=17.857(4), c=13.191(3) Å, β=130.3 (3)^o, V=3275(1) Å3, Z=8 ($C_{14}H_{11}N_2O_3Br \cdot C_2H_5OH$), The space group *C2/c*, d_{calc}=1.546 g/cm^3, μ=3.618 mm^{-1}. The processing of the initial array of measured intensities and accounting for the absorption was carried out according to the SAINT and SADABS programs.

The structure of compound **13** is deciphered by a direct method. The positions of non-hydrogen atoms are refined in the anisotropic approximation by the full-matrix least squares. Hydrogen atoms at N^1, O^1, $O^{3'}$ and O^4 are revealed from the difference synthesis and their positions are refined in the isotropic approximation. The remaining hydrogen atoms were placed in geometrically calculated positions and positions were refined in an isotropic approximation with fixed positional and thermal parameters (the «rider» model). The structure is deciphered and refined by the complex of programs «SHELXS-97» and «SHELXL-97» [11, 12]. The calculations used 1750 independent reflections with $I \geq 2\sigma(I)$, the number of parameters to be refined 225. The final divergence factors R_1=0.0501, $_wR_2$=0.0938 (in reflections with $I \geq 2\sigma(I)$), R_1=0.1085, $_wR_2$=0.1190 (For all reflections), *GooF*=0.969. Peaks of residual density: Δρ=0.258 and -0.430 e/Å^3. The CIF file containing the complete information on the structure examined is deposited in CCDC under number 1546889, from which it can be freely obtained on request at the following Internet site: www.ccdc.cam.ac.uk/data_request/cif.

N-(4-Fluoro-benzylidene)-2-hydroxybenzohydrazide (**3**). Yield 1.08 g (83.8 %), mp. 250–251 °C (1.4-dioxane-hexane (1:2)). ^{1}H-NMR (DMSO-d_6), δ, ppm.: 6.23 d (1H, $CH^1_{arom,}$ $^2J_{HH}$ 7.5 Hz), 6.62 t (1H, $CH^2_{arom,}$ J_{HH} 8.4Hz), 6.45 t (1H, $CH^3_{arom,}$ $^2J_{HH}$ 8.5 Hz), 6.77 t (1H, $CH^4_{arom,}$ $^2J_{HH}$7.3 Hz), **7**.74 d (2H, $CH^{15,17}_{arom,}$ $^2J_{HH}$ 8.55 Hz), 7.89 d (2H, $CH^{14,18}_{arom,}$ $^2J_{HH}$ 8.54 Hz), 8.57 s (1H, N=CH), 10.45 s (1H, OH), 11.85 s (1H, N<u>H</u>-N).

N-(5-Bromo-2-hydroxybenzylidene)-2-hydroxybenzohydrazide **(4).** Yield 1.35 g (80 %), mp. 295 ^{o}C. ^{1}H-NMR (DMSO-d_6), δ, ppm.: 6.90 d (1H, $CH^{15}_{arom,}$ $^2J_{HH}$ 8.76 Hz), 6.95 t (1H, $CH^2_{arom,}$ J_{HH} 7.42 Hz), 7.02 d (1H, $CH^1_{arom,}$ J_{HH} 8.03 Hz), 7.32 d (1H, $CH^4_{arom,}$ J_{HH} 7.58 Hz), 7.42 t (1H, $CH^3_{arom,}$ J_{HH} 8.35 Hz), 7.42 d (1H, $CH^{16}_{arom,}$ J_{HH} 8.73 Hz), 7.76 s (1H, CH_{arom}), 8.57 s (1H, N=CH), 10.32 s (1H, OH^7), 11.42 s (1H, OH), 11.98 s (1H, N<u>H</u>-N).

2-Hydroxy-N-(4-methoxybenzylidene)benzohydrazide (**5**)**.** Yield 1.12 g (83 %), mp. 215–218 ^{o}C (2-propanol). ^{1}H NMR (DMSO-d_6), δ, ppm.: 3.76 s (3H, -O-CH_3), 6.26 d (1H, CH^1_{arom}, J_{HH} 7.5 Hz), 6.48 t (1H, CH^3_{arom}, J_{HH} 8.5 Hz), 6.65 t (1H, CH^2_{arom}, J_{HH} 8.4 Hz), 6.80 d (1H, CH^4_{arom}, J_{HH} 7.1 Hz), 6.84 d (2H, $CH^{15,17}_{arom}$, $^3J_{HH}$ 8.7 Hz), 7.60 d (2H, $CH^{14,18}_{arom}$, $^3J_{HH}$ 8.7 Hz), 8.35 s (1H, N=CH), 10.01 s (1H, OH), 11.49 s (1H, NH). ^{13}C NMR DMSO-d_6), δ, ppm.: 55.81 (-O-CH_3), 114.84 ($CH^{2,6}_{arom}$), 115.51 ($CH^{15,17}_{arom}$), 119.81 (C^4_{arom}), 129.06 ($CH^{14,18}_{arom}$), 130.11 ($CH^{3,5}_{arom}$), 147.36 (N=CH), 161.21 (C^1_{arom}, C^{16}_{arom}), 163.21 (-C=O).

2-Hydroxy-N-(2-hydroxybenzylidene)benzohydrazide (**6**). Yield 1.15 g (90 %), mp. 273–275 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.84–6.90 m (4H, $CH^{4,6,15,17}_{arom}$), 7.26 t (1H, CH^5_{arom}, $^3J_{HH}$ 7.3 Hz), 7.47 d (1H, CH^3_{arom}, $^3J_{HH}$ 8.7 Hz), 7.67 d (1H, CH^{18}_{arom}, $^3J_{HH}$ 7.8 Hz), 7.79 t (1H, CH^{16}_{arom}, $^3J_{HH}$ 8.2 Hz), 8.56 s (1H, N=CH), 10.14 s (1H, OH^{19}), 11.40 s (1H, OH^7), 11.89 c (1H, NH). ^{13}C NMR DMSO-d_6), δ, ppm.: 115.12 (C^2_{arom}), 115.67 (CH^{15}_{arom}), 116.93 (CH^6_{arom}), 119.22 (C^{17}_{arom}), 119.81 (CH^4_{arom}), 123.72 (C^{13}_{arom}), 128.12 (CH^{18}_{arom}), 130.27 (CH^{16}_{arom}, CH^3_{arom}), 131.66 (CH^5_{arom}), 148.18 (N=CH), 157.98 (C^{14}_{arom}), (C^1_{arom}), 166.48 (-C=O).

2-Hydroxy-N-(4-hydroxybenzylidene)benzohydrazide (**7**). Yield 1.06 g (83 %), mp. 277–278 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.83 d (2H, $CH^{15,17}_{arom}$, $^2J_{HH}$ 8.2 Hz), 6.92 dd (2H, $CH^{4,6}_{arom}$, $^2J_{HH}$ 16.0, $^3J_{HH}$ 7.6 Hz), 7.38 t (1H, CH^5_{arom}, $^2J_{HH}$ 7.8 Hz), 7.54 d (2H, $CH^{14,18}_{arom}$, $^2J_{HH}$ 8.2 Hz), 7.86 d (1H, CH^3_{arom}, $^2J_{HH}$ 7.8 Hz), 8.33 s (N=CH), 9.92 br.s (1H, OH^{19}), 11.66 s (1H, NH), 11.96 br.s (1H, OH^7). ^{13}C NMR DMSO-d_6), δ, ppm.: 116.20 (C^2_{arom}), 116.29 ($CH^{15,17}_{arom}$), 117.85 (CH^6_{arom}), 119.38 (CH^4_{arom}), 125.60 (C^{13}_{arom}), 128.81 (CH^3_{arom}), 129.62 ($CH^{14,18}_{arom}$), 134.25 (CH^5_{arom}), 149.78 (N=CH), 159.85 (C^{16}_{arom}), 160.21 (C^1_{arom}), 165.25 (C=O).

2-Hydroxy-N-(pyridin-4-yl-methylene)benzohydrazide (**8**). Yield 1.09 g (91 %), mp. 238–239 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.95 m (2H, $CH^{4,6}_{arom}$), 7.41 t (1H, CH^5_{arom}), 7.63 d (2H, $CH^{14,18}_{arom}$), 7.84 d (1H, CH^3_{arom}), 8.42 s (1H, N=CH), 8.62 d (2H, $CH^{15,17}_{arom}$), 11.96 br.s (2H, NH, OH). ^{13}C NMR DMSO-d_6), δ, ppm.: 116.83 (C^2_{arom}), 117.77 (CH^6_{arom}), 119.61 (C^4_{arom}), 121.59 ($CH^{14,18}_{arom}$), 129.46 (CH^3_{arom}), 134.47 (CH^5_{arom}), 141.89 (C^{13}_{arom}), 146.63 (N=CH), 150.81 ($CH^{15,17}_{arom}$), 159.17 (C^1_{arom}), 165.34 (C=O).

N-(3-Ethoxy-4-hydroxybenzylidene)-2-hydroxybenzohydrazide (**9**). Yield 0.9 g (60.6 %), mp. 196–198 °C (C_6H_6). ^{1}H NMR (DMSO-d_6), δ, ppm.: 1.33 t (3H, CH_3, $^3J_{HH}$ 6.9 Hz), 4.01–4.06 m (2H, O-CH_2), 6.84 d (1H, CH^3_{arom}, $^3J_{HH}$ 8.2 Hz), 6.94 dd (2H, $CH^{18,20}_{arom}$, $^3J_{HH}$ 7.6, 13.5 Hz), 7.07 d (1H, CH^4_{arom}, $^3J_{HH}$ 8.2 Hz), 7.28 c (1H, CH^6_{arom}), 7.34–7.41 m (1H, CH^{19}_{arom}), 7.88 dd (1H, CH^{21}_{arom}, $^3J_{HH}$ 7.8, 13.7 Hz), 8.30 s (1H, N=CH).

N-(2-Benzylidenoctylidene)-2-hydroxybenzohydrazide (**10**). Yield 1.20 g (69 %), mp. 157–158 °C (1.4-dioxane). ^{1}H NMR (DMSO-d_6), δ, ppm.: 0.80 t (3H, $C\underline{H}_3$-$(CH_2)_3$-CH_2-CH_2–, $^2J_{HH}$ 6.4 Hz), 1.21–1.32 m (6H, CH_3-$(C\underline{H}_2)_3$-CH_2-CH_2–), 1.48–1.55 m (2H, CH_3-$(CH_2)_3$-$C\underline{H}_2$-CH_2–), 2.56 t (2H, CH_3-$(CH_2)_3$-CH_2-$C\underline{H}_2$–), 6.80 s (1H, C=CH-), 6.89–6.93 m (2H, CH^4_{arom}, CH^6_{arom}), 7.26–7.32 m (2H, CH^3_{arom}, CH^5_{arom}), 7.38 d (2H, $CH^{17,19}_{arom}$, $^3J_{HH}$ 4.3 Hz), 7.40 d (2H, $CH^{16,20}_{arom}$, $^3J_{HH}$ 4.3 Hz), 7.41 s (1H, N=CH), 7.83 d (1H, CH^{18}_{arom}, $^3J_{HH}$ 7.3 Hz). ^{13}C NMR DMSO-d_6), δ, ppm.: 14.47 ($\underline{C}H_3$-$(CH_2)_3$-CH_2-CH_2–), 22.61 (CH_3-$\underline{C}H_2$- CH_2-CH_2-CH_2-CH_2–), 26.24 (CH_3-CH_2-CH_2- CH_2-$\underline{C}H_2$-CH_2–), 28.52 (CH_3-CH_2-CH_2- $\underline{C}H_2$-CH_2-CH_2–), 29.46 (CH_3-CH_2-$\underline{C}H_2$-CH_2-CH_2-CH_2–), 31.46 (CH_3-CH_2-CH_2-CH_2-CH_2-$\underline{C}H_2$–), 116.39 (C^2_{arom}), 117.79 (CH^4_{arom}), 119.41 (CH^6_{arom}), 128.41 (CH^{18}_{arom}), 128.96 (CH^3_{arom}), 129.15 ($CH^{17,19}_{arom}$), 129.43 ($CH^{16,20}_{arom}$), 134.28 (CH^5_{arom}, C^{15}_{arom}), 136.61 ($\underline{C}$=CH-), 137.87 (C=$\underline{C}$H-), 139.62 (N=CH), 159.65 (C^1_{arom}), 165.15 (C=O).

2-Hydroxy-N-(4-((E-)-styryl)benzylidene)benzohydrazide (**11**). Yield 1.55 g (91 %), mp. 278–279 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.94 br.t (1H, CH^4_{arom}), 6.95 br.d (1H, CH=C$\underline{H}$-Ph, $^2J_{HH}$ 7.3 Hz), 7.27 d (2H, $CH^{23,25}_{arom}$, $^2J_{HH}$ 11.0 Hz), 7.36 d (2H, $CH^{15,17}_{arom}$), 7.37 d (1H, CH^6_{arom}), 7.40 d (1H, C$\underline{H}$=CH-Ph), 7.58 d (2H, $CH^{22,26}_{arom}$, $^2J_{HH}$ 6.9 Hz), 7.67 t (1H, CH^5_{arom}), 7.69 d (2H, $CH^{14,18}_{arom}$), 7.88 d (1H, CH^3_{arom}, $^2J_{HH}$ 6.4 Hz), 8.42 s (N=C$\underline{H}$-Ph), 11,81 s (NH). ^{13}C NMR DMSO-d_6), δ, ppm.: 116.48 (C^2_{arom}), 117.83 (CH^6_{arom}), 119.48 (CH^4_{arom}), 127.19 ($CH^{15,17}_{arom}$), 127.44 ($CH^{22,26}_{arom}$), 128.18 ($CH^{14,18}_{arom}$), 128.29 ($\underline{C}$H=CH-Ph), 129.09 (CH^3_{arom}), 129.28 ($CH^{23,25}_{arom}$), 130.25 (CH=$\underline{C}$H-Ph), 133.81 (C^{13}_{arom}), 134.34 (CH^5_{arom}), 137.39 (C^{21}_{arom}), 139.52 (C^{16}_{arom}), 148.87 (N=$\underline{C}$H-Ph), 159.60 (C^1_{arom}), 165.28 (C=O).

N-(4-Fluoro-benzylidene)-4-hydroxybenzohydrazide (**12**). Yield 0.87 g (67.5 %), mp. 183–185 °C (2-propanol). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.81 d (2H, $CH^{2,6}_{arom}$, $^2J_{HH}$ 8.7 Hz), 7.78 t (2H, $CH^{3,5}_{arom}$, J_{HH} 8.7 Hz), 7.74 d (2H, $CH^{15,17}_{arom}$, $^2J_{HH}$ 8.55 Hz), 7.89 d (2H, $CH^{14,18}_{arom}$, $^2J_{HH}$ 8.54 Hz), 8.58 s (1H, N=CH), 10.50 s (1H, OH), 11.83 s (1H, N$\underline{H}$-N).

N-(5-Bromo-2-hydroxybenzylidene)-4-hydroxybenzohydrazide (**13**). Yield 0.85 g (51.1 %), mp. 293–295 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.88 d (2H, $CH^{2,6}_{arom}$, $^2J_{HH}$ 8.69 Hz), 6.90 d (1H, CH^{15}_{arom}, J_{HH} 8.76 Hz), 7.42 d (1H, CH^{16}_{arom}, J_{HH} 8.73 Hz), 7.76 s (1H, CH^{18}_{arom}), 7.83 d (2H, $CH^{3,5}_{arom}$, $^2J_{HH}$ 8.54 Hz), 8.57 s (1H, N=CH), 10.15 s (1H, OH^7), 11.42 s (1H, OH), 11.98 s (1H, N$\underline{H}$-N).

4-Hydroxy-N-(4-methoxybenzylidene)benzohydrazide (**14**). Yield 1.21 g (90 %), mp. 220 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 3.76 s (3H, -O-CH_3), 6.83 d (2H, $CH^{15,17}_{arom}$, $^3J_{HH}$ 8.7 Hz), 6.97 d (2H, $CH^{2,6}_{arom}$, $^3J_{HH}$ 8.7 Hz), 7.61 d (2H, $CH^{14,18}_{arom}$, $^3J_{HH}$ 8.7 Hz), 7.77 d (2H, $CH^{3,5}_{arom}$, $^3J_{HH}$ 7.8 Hz), 8.34 s (1H, N=CH), 10.03 s (1H, OH), 11.46 s (1H, NH). ^{13}C NMR (DMSO-d_6), δ, ppm.: 55.80 (-O-CH_3), 114.85

($CH^{2,6}_{arom}$), 115.51 ($CH^{15,17}_{arom}$), 124.61 (C^{4}_{arom}), 127.64 (C^{13}_{arom}), 129.05 ($CH^{14,18}_{arom}$), 130.11 ($CH^{3,5}_{arom}$), 147.34 (N=CH), 161.21 (C^{1}_{arom}, C^{16}_{arom}), 163.19 (-C=O).

4-Hydroxy-N-(2-hydroxybenzylidene)benzohydrazide (**15**). Yield 0.85 g (67 %), mp. 260 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.85 d (2H, $CH^{2,6}_{arom}$, J_{HH} 8.7 Hz), 6.90 d (2H, $CH^{15,17}_{arom}$, J_{HH} 8.76 Hz), 7.74 d (2H, $CH^{3,5}_{arom}$, J_{HH} 7.8 Hz), 7.54 д (2H, $CH^{14,18}_{arom}$, $^2J_{HH}$ 8.2 Hz), 8.28 s (1H, N=CH), 9.98 br.s (2H, $OH^{7,19}$), 11.40 s (1H, NH).

4-Hydroxy-N-(4-hydroxybenzylidene)benzohydrazide (**16**). Yield 0.94 g (73,8 %), mp. 265 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.80 m (4H, $CH^{2,6,15,17}_{arom}$), 7.50 d (2H, $CH^{14,18}_{arom}$), 7.74 d (2H, $CH^{5,3}_{arom}$), 8.28 s (1H, N=CH), 9.95 br.s (2H, $OH^{7,19}$), 11.40 s (1H, NH). ^{13}H NMR (DMSO-d_6), δ, ppm.: 115.49 ($CH^{2,6}_{arom}$), 116.21 ($CH^{15,17}_{arom}$), 124.63 (C^{4}_{arom}), 126.03 (C^{13}_{arom}), 129.21 ($CH^{14,18}_{arom}$), 130.07 ($CH^{5,3}_{arom}$), 147.74 (N=CH), 159.75 (C^{16}_{arom}), 161.04 (C^{1}_{arom}), 163.07 (C=O).

4-Hydroxy-N-(pyridin-4-ylmethylene)benzohydrazide (**17**). Yield 1.07 g (89 %), mp. 261–263 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.84 d (2H, $CH^{2,6}_{arom}$), 7.60 d (2H, $CH^{14,18}_{arom}$), 7.79 d (2H, $CH^{3,5}_{arom}$), 8.37 s (N=CH), 8.60 d (2H, $CH^{15,17}_{arom}$), 10.12 br.s (1H, NH), 11.83 s (1H, OH). ^{13}H NMR (DMSO-d_6), δ, ppm.: 115.62 ($CH^{2,6}_{arom}$), 121.41 ($CH^{14,18}_{arom}$), 124.07 (C^{4}_{arom}), 130.48 ($CH^{3,5}_{arom}$), 142.26 (C^{13}_{arom}), 144.83 (N=CH), 150.75 ($CH^{15,17}_{arom}$), 161.45 (C^{1}_{arom}).

N-(3-Ethoxy-4-hydroxybenzylidene)-4-hydroxybenzohydrazide (**18**). Yield 1.37 g (91.9 %), mp. 240–242 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 1.02 t (3H, -CH-C$\underline{H}_3$, $^3J_{HH}$ 6.9 Hz), 1.31 t (3H, -O-CH_2-C$\underline{H}_3$, $^3J_{HH}$ 6.9 Hz), 3.33–3.43 m (1H, -C$\underline{H}$-CH_3), 3.93–4.04 m (2H, -O-C$\underline{H}_2$-CH_3), 6.80 d (2H, $CH^{18,20}_{arom}$, $^3J_{HH}$ 8.2 Hz), 6.82 d (1H, CH^{3}_{arom}, $^3J_{HH}$ 3.7 Hz), 7.03 d (1H, CH^{4}_{arom}, $^3J_{HH}$ 7.8 Hz), 7.24 s (1H, CH^{6}_{arom}), 7.77 d (2H, $CH^{17,21}_{arom}$, $^3J_{HH}$ 8.7 Hz), 8.27 c (1H, N=CH). ^{13}H NMR (DMSO-d_6), δ, ppm.: 15.24 (-O-CH_2-$\underline{C}H_3$), 19.06 (-CH-$\underline{C}H_3$), 56.58 (-$\underline{C}$H-CH_3), 64.43 (-O-$\underline{C}H_2$-CH_3), 110.87 (CH^{6}_{arom}), 115.49 ($CH^{18,20}_{arom}$, 116.07 (CH^{4}_{arom}), 122.42 (CH^{3}_{arom}), 124.64 (C^{5}_{arom}), 126.47 (C^{16}_{arom}), 130.07 ($CH^{17,21}_{arom}$), 147.70 (N=CH), 149.60 (C^{2}_{arom}), 161.06 (C^{1}_{arom}), 163.15 (C^{19}_{arom}).

N-(2-Benzylidenoctylidene)-4-hydroxybenzohydrazide (**19**). Yield 0.52 g (30 %), mp. 255–257 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 0.80 t (3H, -CH_2-$(CH_2)_4$-C$\underline{H}_3$), 1.21–1.54 m (8H, -CH_2-(C$\underline{H}_2$)$_4$-CH_3), 2.57 t (2H, -C$\underline{H}_2$-$(CH_2)_4$-CH_3), 6.80 t (2H, $CH^{17,19}_{arom}$), 6.89 s (1H, C=CH), 7.31 d (2H, $CH^{3,5}_{arom}$), 7.39 d (2H, $CH^{2,6}_{arom}$), 7.40 d (2H, $CH^{16,20}_{arom}$), 7.84 t (1H, CH^{18}_{arom}), 8.12 s (1H, N=CH), 11.64 s (1H, NH), 11,87 s (1H, OH). ^{13}H NMR (DMSO-d_6), δ, ppm.: 14.45 (-CH_2-$(CH_2)_4$-$\underline{C}H_3$), 22.60 (-CH_2-CH_2-CH_2-CH_2-$\underline{C}H_2$-CH_3), 26.25 (-CH_2-$\underline{C}H_2$-CH_2-CH_2-CH_2-CH_3), 28.52 (-CH_2-CH_2-$\underline{C}H_2$-CH_2-CH_2-CH_3), 29.44 (-CH_2-CH_2-CH_2-$\underline{C}H_2$-CH_2-CH_3), 31.46 (-$\underline{C}H_2$-CH_2-CH_2-CH_2-CH_2-CH_3), 116.37 ($CH^{2,6}_{arom}$), 117.81(C^{4}_{arom}), 119.40 (C=$\underline{C}$H), 128.39 (CH^{18}_{arom}), 128.95 ($CH^{17,19}_{arom}$), 129.13 ($CH^{16,20}_{arom}$), 134.27 ($CH^{5,3}_{arom}$), 137.85 (C^{15}_{arom}), 139.64 ($\underline{C}$=CH), 153.97 (N=CH), 159.70 (OH-C^{1}_{arom}), 165.19 (C=O).

4-Hydroxy-N-(4-((E-)-styryl)benzylidene)benzohydrazide (**20**). Yield 1.36 g (80 %), mp. 274–275 °C (C_2H_5OH). ^{1}H NMR (DMSO-d_6), δ, ppm.: 6.83 d (2H, $CH^{2,6}_{arom}$, $^3J_{HH}$ 9.2 Hz), 7.22–7.29 m (4H, CH^{19}, CH^{24}_{arom}, $CH^{15,17}_{arom}$), 7.34 t (2H, $CH^{23,25}_{arom}$, $^3J_{HH}$ 7.6 Hz), 7.58 d (2H, $CH^{22,26}_{arom}$, $^3J_{HH}$ 7.9 Hz), 7.63–7.68 m (3H, $CH^{14,18}_{arom}$, CH^{20}), 7.78 d (2H, $CH^{3,5}_{arom}$, $^3J_{HH}$ 8.5 Hz), 8.38 s (1H, N=CH), 10.11 s (1H, NH), 11.64 s (1H, OH). ^{13}H NMR (DMSO-d_6), δ, ppm.: 115.56 ($CH^{2,6}_{arom}$), 124.39 (C^{4}_{arom}), 127.41 ($CH^{15,17}_{arom}$), 127.87 ($CH^{22,26}_{arom}$), 128.31 (CH^{24}_{arom}), 128.42 (CH^{19}), 129.28 ($CH^{14,18}_{arom}$), 129.96 (CH^{20}), 130.22 ($CH^{23,25}_{arom}$), 134.22 ($CH^{3,5}_{arom}$, C^{13}_{arom}), 137.39 (C^{21}_{arom}), 139.06 (C^{16}_{arom}), 146.94 (N=CH), 161.23 (C^{1}_{arom}), 163.24 (C=O).

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о- және *п*-гидроксибензой қышқылдары негізіндегі жаңа гидразондардың синтезі, құрылымы мен компьютерлік биоболжам

о- және *п*-гидроксибензой қышқыл гидразидтерінің орынбасылған ароматикалық альдегидтермен әрекеттесуі нәтижесінде тиісті гидразон туындылары алынды. PASS компьютерлік бағдарламаны қолдана отырып, N-арилиденгидразондарға биоболжам жүргізіліп, олардың болжамды белсенділігінің бастапқы *о*- және *п*-гидроксибензой қышқыл гидразидтерінің физиологиялық белсенділікпен және құрылымдық молекуланың құрамындағы компоненттерімен біріктірілгені анықталды. Синтезделген қосылыстар ЯМР ^{1}H- және ^{13}C-спектроскопия әдістермен, сондай-ақ екі өлшемді спектрлермен COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) зерттелінді. ^{1}H пен ^{13}C ЯМР кешенді спектрлеріндегі сигналдардың өлшем құндылықтары мен қарқындылығы, химиялық ауысымның еселілігі белгіленді. COSY (^{1}H-^{1}H) мен HMQC (^{1}H-^{13}C) пішінді спектрлердің көмегімен зерттелінген қосылыстардың құрылымын дәлелдейтін гомо- және гетероядролық өзара байланыстары бекітілді. N-(5-бром-2-гидроксибензилиден)-4-гидроксибензогидразидінің рентгенқұрылымдық зерттеуі жүргізіліп, оның сутектік байланыс молекуласының этанолды сольваттың молекуласымен байланысты екендігі белгілі болды.

Кілт сөздер: о- және *п*-гидроксибензой қышқыл гидразиді, гидразон, ароматикалық альдегидтер, ЯМР спектроскопия.

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Синтез, строение и компьютерный биопрогноз новых гидразонов на основе гидразидов *о*- и *п*-гидроксибензойных кислот

Взаимодействием гидразидов *о*- и *п*-гидроксибензойных кислот с замещенными ароматическими альдегидами получены соответствующие производные гидразонов. С использованием компьютерной программы PASS проведен биопрогноз N-арилиденгидразонов и показано, что их предполагаемая активность комбинирует как физиологическую активность исходного гидразидов *о*- и *п*-гидроксибензойных кислот, так и составляющих компонентов структурной молекулы. Исследованы строения синтезированных соединений методами ЯМР ^{1}H- и ^{13}C-спектроскопии, а также данными двумерных спектров COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C). Определены значения химических сдвигов, мультиплетность и интегральная интенсивность сигналов ^{1}H и ^{13}C в одномерных спектрах ЯМР. С помощью спектров в форматах COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) установлены гомо- и гетероядерные взаимодействия, подтверждающие структуру исследуемых соединений. Проведено рентгеноструктурное исследование N-(5-бром-2-гидроксибензилиден)-4-гидроксибензогидразида, молекула которого связана водородной связью с молекулой этанольного сольвата.

Ключевые слова: гидразид *о*- и *п*-гидроксибензойных кислот, гидразон, ароматические альдегиды, ЯМР-спектроскопия.

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УДК 547.597:542.933'78:543.552

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Исследование антиоксидантной активности представителей тритерпеноидов лупанового и олеанового ряда методом вольтамперометрии

В связи с пристальным вниманием исследователей к изучению биологической активности природных соединений и их синтетических производных разработка простых и экспрессных методов для решения этих задач становится особо актуальной. Вследствие значительной стоимости и трудоемкости проведения экспериментов *in vivo* в последнее время более широкое применение находят физико-химические методы анализа, адаптированные под измерение определенного вида биологической активности. К подобным методам относятся электрохимические методы, область применения которых распространяется на электрохимические процессы, протекающие с участием электроактивных частиц. Несмотря на многообразие известных методов, литературные сведения о способах и результатах измерения антиоксидантной активности пентациклических тритерпеноидов ограничены несколькими сообщениями. С целью расширения возможностей применения электрохимических методов для исследования биологической активности указанного ряда соединений, нами было проведено определение их антиоксидантной активности вольтамперометрическим методом. В работе сравнивались показатели антиоксидантной активности следующих представителей лупанового и олеанового рядов: бетулина, диацетата бетулина и аллобетулина. Показано, что диацетат бетулина проявляет более выраженную антиоксидантную активность. Сделано предположение о том, что двойная связь в изопропенильном фрагменте выступает как наиболее активный центр, взаимодействующий с радикалами кислорода. Бетулин показывает среднюю антиоксидантную активность, поскольку в его структуре присутствуют три конкурентных и менее активных при окислении реакционных центра: кратная связь и ОН-группы в 3- и 28- положениях. Наименьшую антиоксидантную активность проявляет аллобетулин с менее активной гидроксильной группой в 3-м положении.

Ключевые слова: пентациклические тритерпеноиды, бетулин, диацетат бетулина, аллобетулин, антиоксидантная активность, катодная вольтамперометрия.

В настоящее время существенное внимание исследователей уделяется изучению биологической активности природных соединений, в том числе тритерпеноидов и их синтетических производных [1–4].

Известно, что тритерпеноиды лупанового ряда обладают широким спектром фармакологической активности: антивирусной, противоязвенной, противоопухолевой, капилляроукрепляющей [5–9]. Следует отметить, что ценность тритерпеноидов лупанового ряда заключается в их доступности в природе, что выгодно для внедрения в фармацевтическую промышленность. К числу наиболее доступных тритерпеноидов относится бетулин — 3β,28-дигидрокси-20(29)-лупен, содержащийся в значительных количествах (до 40 %) во внешней коре березы [10].

Наряду с повышенным интересом к бетулину, неуклонно растет внимание специалистов к его производным, обладающим ценными свойствами. Так, диацетат бетулина — 3β,28-диацетокси-луп-20(29)-ен — проявляет желчегонную и гиполипидемическую активность [5, 11], аллобетулин — 3β-гидрокси-19β,28-эпокси-18α-олеан и его производные обладают противовирусным и антифидантным действиями [12, 13].

Ранее в работе [14] была определена антиоксидантная активность (АОА) некоторых производных бетулина и аллобетулина с использованием амперометрического метода. Максимальное значение АОА было установлено для 3,28-ди-О-циннамата бетулина. Авторы работы [15] проводили изучение АОА диацетата бетулина в экспериментах *in vitro* и *in vivo*; на основании полученных данных было сделано предположение, что диацетат бетулина выступает в роли ловушки для активных форм кислорода, а также способен либо стимулировать синтез антиоксидантных ферментов — супероксиддисмутазы и каталазы, либо непосредственно влиять на их активность.

Недостатками экспериментов *in vivo* являются высокая стоимость расходных материалов и трудоемкость анализа. Поэтому в последнее время более широкое применение находят физико-химические методы анализа (ФХМА), которые позволяют не только быстро и качественно провести идентификацию сложных органических веществ, но и определить параметры некоторых биологически значимых свойств органических соединений. Среди таких методов анализа особое место занимают электрохимические методы, область применения которых распространяется на процессы, связанные с участием электроактивных частиц. Однако, несмотря на многообразие модификаций известных методов, литературные сведения о способах и результатах измерения АОА пентациклических тритерпеноидов ограничены несколькими сообщениями. Следовательно, разработка чувствительных, экспрессных и селективных методов анализа для этого ряда соединений до сих пор остается актуальной задачей.

Целью исследования является сравнение антиоксидантной активности ряда пентациклических тритерпеноидов — бетулина, диацетата бетулина и аллобетулина на основе применения вольтамперометрического метода.

Оборудование и реагенты

Бетулин выделяли из предварительно измельченной бересты *Betula pendula* по методу [16]. Диацетат бетулина и аллобетулин получали по методам, описанным в работах [15] и [17] соответственно. Согласно литературным данным, пентациклические тритерпеноиды практически не растворимы в воде, поэтому в качестве растворителя для приготовления стандартных растворов бетулина, диацетата бетулина и аллобетулина нами был выбран этанол. Использование данного растворителя позволяет получать водно-органические смеси со значительным содержанием тритерпеноидов без расслоения. Основной стандартный раствор получали растворением навески субстанции массой 0,02 г в этаноле объемом 10 мл.

Исследования проводили на универсальном вольтамперометрическом анализаторе «ТА–2» (ООО «Томьаналит», г. Томск, Россия). Условия проведения эксперимента: развертка потенциала от 0,0 до –0,8 В с линейной скоростью 30 мВ/с, время перемешивания и успокоения раствора 10 с и 20 с соответственно, трехэлектродная ячейка с индикаторным ртутно-пленочным электродом и хлорид-серебряными электродами как электрод сравнения и вспомогательный электрод, фоновый электролит 0,1 М спиртовый раствор перхлората натрия.

Методика проведения эксперимента

Антиоксидантные свойства бетулина, диацетата бетулина и аллобетулина определялись методом катодной вольтамперометрии по известной методике, основанной на использовании процесса восстановления кислорода [18].

Методика определения активности исследуемых веществ заключается в регистрации через определенный промежуток времени вольтамперограмм тока электровосстановления кислорода в отсутствие и в присутствии анализируемого вещества в электрохимической ячейке.

Показателем антиоксидантной активности исследуемого образца является уменьшение предельного тока электровосстановления кислорода по своему абсолютному значению. Предполагается, что это связано с взаимодействием исследуемых веществ с кислородом и его активными радикалами на поверхности индикаторного электрода.

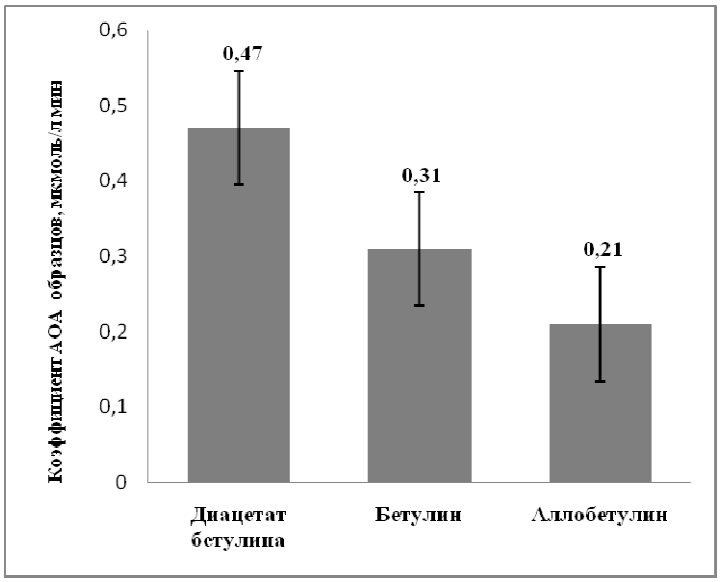
Коэффициент антиоксидантной активности образцов, K, мкмоль/(л·мин), рассчитывался по формуле

$$K = \frac{C_{\mathrm{o}_2}}{t}\left(1 - \frac{I_i}{I_{\mathrm{o}}}\right),$$

где Co_2 — концентрация кислорода в исходном растворе без вещества, мкмоль/л; I_i — текущее значение предельного тока ЭВ O_2, мкА; I_o — значение предельного тока ЭВ O_2 в отсутствии вещества в растворе, мкА; t — время протекания процесса, мин.

Статистическая обработка результатов проводилась по стандартному алгоритму [19].

На диаграмме представлены результаты измерения антиоксидантной активности бетулина, диацетата бетулина и аллобетулина.



$C_{раб}$ = 5·10^{-4} моль/л; относительное стандартное отклонение *S*r = 0,07 (диацетат бетулина), 0,05 (бетулин), 0,06 (аллобетулин)

Диаграмма. Коэффициенты антиоксидантной активности ряда пентациклических тритерпеноидов по отношению к ЭВ O_2

Для диацетата бетулина и аллобетулина были предложены маршруты их взаимодействия с активными формами кислорода (АФК) на поверхности индикаторного электрода (рис. 1, 2).

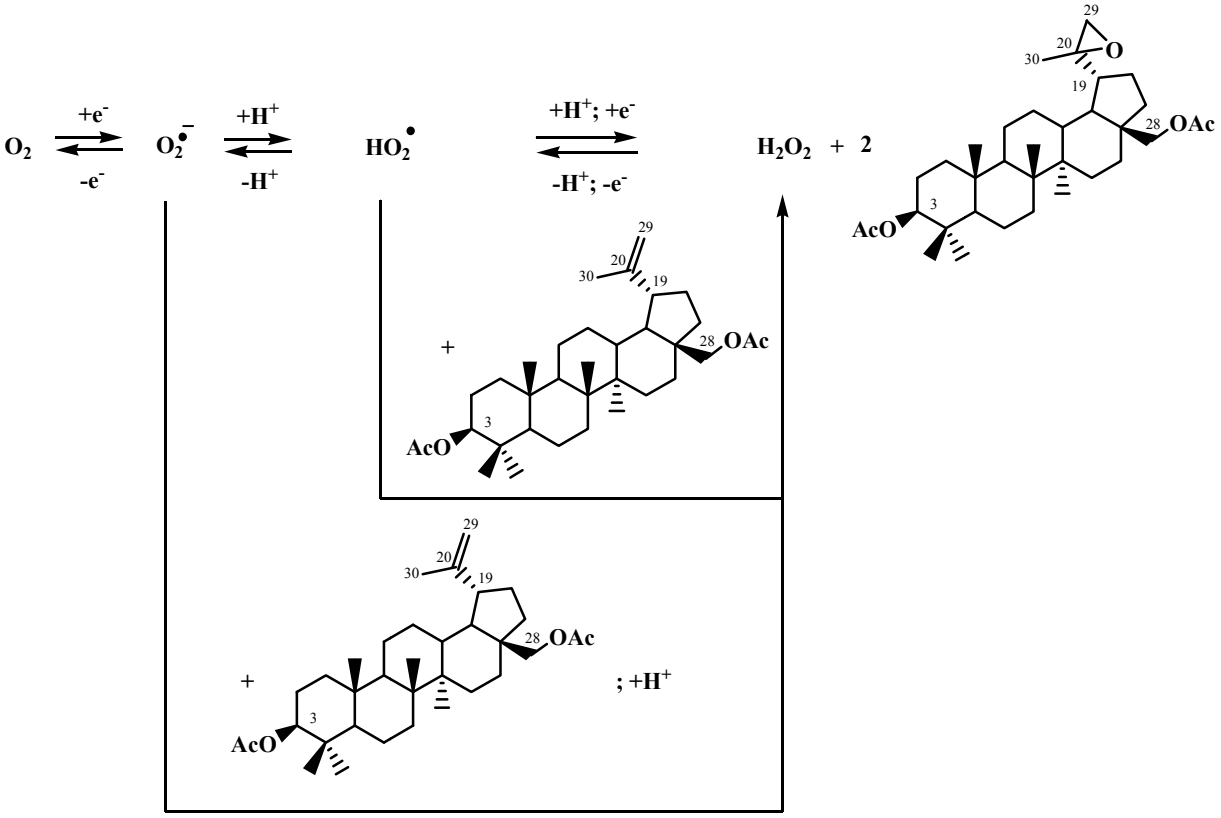


Рисунок 1. Предполагаемый маршрут взаимодействия АФК и диацетата бетулина на поверхности индикаторного электрода

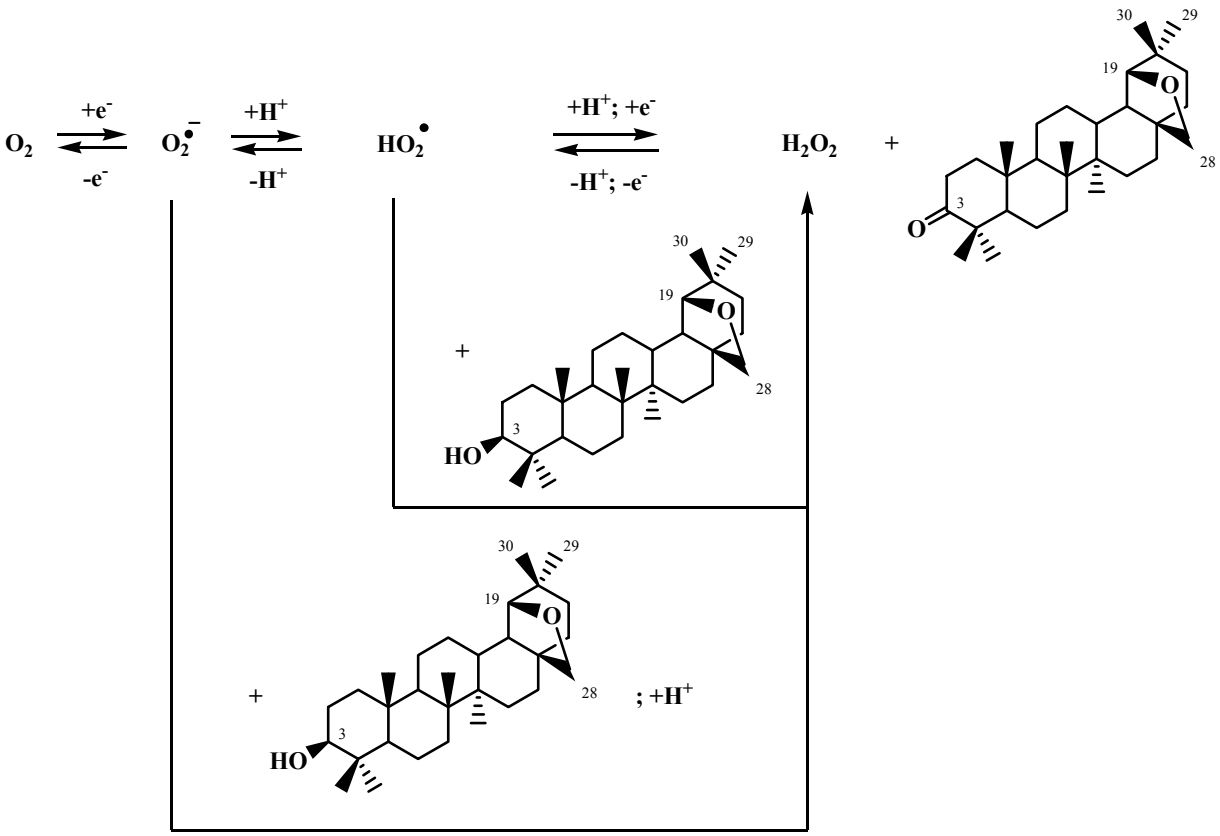


Рисунок 2. Предполагаемый маршрут взаимодействия АФК и аллобетулина на поверхности индикаторного электрода

Результаты экспериментов показали, что диацетат бетулина имеет наибольшую антиоксидантную активность по сравнению с другими исследуемыми веществами (бетулином и аллобетулином). Мы полагаем, что такой выраженный эффект ингибирования окисления связан с наличием в структуре диацетата бетулина наиболее активной двойной связи, которая подвергается более легкому окислению, чем в самом бетулине. Аргументом в пользу нашего предположения является то, что в 3-м и 28-м положении у диацетата бетулина гидроксильные группы защищены ацильными заместителями, что делает существенно затруднительным окисление по данным позициям. Бетулин показывает среднюю антиоксидантную активность, поскольку в его структуре присутствуют три конкурентных реакционных центра, но менее активные при окислении: кратная связь и гидроксильные группы в 3-м и 28-м положении. У аллобетулина наблюдается наименьшая антиоксидантная активность, предположительно за счет наличия в структуре слабо активного центра взаимодействия с радикалами кислорода, а именно — ОН-группы в 3-м положении.

Выводы

Методом катодной вольамперометрии проведено сравнение антиоксидантной активности ряда пентациклических терпеноидов: бетулина, диацетата бетулина и аллобетулина. Все исследуемые вещества снижали ток электровосстановления кислорода (ЭВ O_2), при этом потенциал сдвигался в положительную область, выявляя механизм EC (electrochemical-chemical) с дальнейшими химическими реакциями антиоксидантов с активными кислородными радикалами.

Показано, что в ряду исследуемых соединений наибольшую активность в отношении ингибирования процессов окисления проявляет диацетат бетулина, а наименьшую — аллобетулин. Несмотря на наличие в структуре бетулина трех конкурентных центров окисления, степень уменьшения тока ЭВ O_2 (как показателя антиоксидантной активности) была средней.

Предложены вероятные маршруты окисления диацетата бетулина и аллобетулина на поверхности индикаторного электрода при определении антиоксидантной активности методом вольтамперометрии.

К преимуществам данного метода можно отнести использование образцов в небольших количествах, экспрессность метода, простоту и дешевизну оборудования, отсутствие необходимости в дорогостоящих реактивах для проведения анализа.

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Е.А. Мамаева, А.К. Ташенов, А.А. Бакибаев

Вольтамперметрлік әдіспен лупан мен олеан қатарындағы тритерпеноидтар өкілдерінің тотығуға қарсы белсенділігін зерттеу

Табиғи қосылыстар мен олардың синтезделген туындыларының биологиялық белсенділігін анықтау зерттеушілердің ерекше назарында болуы себебінен, қарапайым және жылдам жүретін әдістерді табу өзекті мәселелердің бірі болып отыр. *In vivo* тәжірибелерін жасау жұмыстарының ауқымдылығы мен

маңыздылығының салдарынан, соңғы уақытта белгілі бір бейімделген түрдің биологиялық белсенділігін анықтауда физика-химиялық әдістердің қолдану аясы кеңеюде. Осындай әдістерге электрбелсенді бөлшектердің қатысында жүретін электрохимиялық процестердің қолдану аймағында кең таралған электрхимиялық әдістер жатады. Көптеген белгілі әдістерге қарамастан, пентациклді тритерпеноидтардың тотығуға қарсы белсенділігін анықтау нәтижелері мен әдістері туралы әдеби деректерде бірнеше ақпараттармен шектелген. Сондықтан, аталған қосылыс қатарының биологиялық белсенділігін зерттеу үшін электрхимиялық әдістердің қолдану мүмкіндігін кеңейту мақсатында біз вольтамперметрлік әдіспен пентациклді тритерпеноидтардың тотығуға қарсы белсенділігін анықтау жұмыстарын жасадық. Мақалада лупанды мен олеанды қатардағы мына қосылыстарға: бетулин, бетулиннің диацетаты, аллобетулиннің антиоксиданттық белсенділігінің көрсеткіштеріне салыстырмалы талдау жүргізілді. Яғни, бетулиннің диацетаты, аталған екі қосылысқа қарағанда, тотығуға қарсы белсенділігі айтарлықтай жоғары екендігі анықталды. Изопропенилдің көрінісіндегі қос байланыс оттектің радикалымен өзара әрекеттескенде белсенді орталық ретінде қатысатындығына болжам жасалды. Бетулиннің тотығуға қарсы белсенділігі орташа мәнді көрсетуінің себебі оның құрылысында бәсекелес және белсенді үш реакциялық орталықтың: 3- пен 28- жағдайындағы ОН-топтары мен еселенген байланыс тотығуға қатысады. Аллобетулин төменгі көрсеткіштегі тотығуға қарсы белсенділікті, яғни, 3-жағдайындағы әлсіз активті гидроксиль топтарымен көрсетеді.

Кілт сөздер: пентациклді тритерпеноидтар, бетулин, бетулиннің диацетаты, аллобетулин, тотығуға қарсы белсенділік, катодты вольтамперометрия.

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Investigation of antioxidant activity representatives of triterpenoids series of lupane and oleane by using voltammetry

In connection with the focus of researchers to study the biological activity of natural compounds and their synthetic derivatives, development of simple and rapid methods for the solution of these problems becomes particularly relevant. As a result of significant cost and labor intensity of conducting *in vivo* experiments in recent years more widely used are physical and chemical methods of analysis, adapted to the measurement of a particular type of biological activity. Similar methods include electrochemical methods, field of application which extends to the electrochemical processes occurring with the participation of electroactive species. Despite the variety of known methods, literature data about the methods and results of measuring the antioxidant activity of pentacyclic triterpenoids are limited by several messages. In order to extend application possibilities of electrochemical methods for the study of biological activity a specified series of compounds, we carried out the determination of their antioxidant activity by using voltammetric method. In the work compared the performance of the antioxidant activity for these representatives of lupane and olean series: betulin, betulin diacetate and allobetulin. It is shown that betulin diacetate has a more expressed antioxidant activity. It is suggested that the double bond in isopropenyl fragment appears as the most active center that interacts with oxygen radicals. Betulin shows average antioxidant activity, because of its structure is present three competitive and less active centers' by reaction of oxidation: multiple bonds and an OH — group at the 3- and 28-position. The lowest antioxidant activity shows allobetulin with less active hydroxyl group at the 3-position.

Keywords: pentacyclic triterpenoids, betulin, betulin diacetate, allobetulin, antioxidant activity, cathodic voltammetry.

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UDC 541.64+678

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Preparation, characterization and investigation of *in vitro* release of anti-tuberculosis drug p-amino salicylic acid based on human serum albumin

Nowadays the task of pharmaceutical chemistry is not only the search of the new drug preparations, but also the increase of the effectiveness of the latter by chemical modification or creation of new forms. With the aim of prolongation of the effect and decrease of single dose the possibility of immobilization of anti-tuberculosis drug p-amino salicylic acid (PASA) on human serum albumin (HSA) nanoparticles (NPs) by adsorption and incorporation methods was considered in this article. It is shown that independently of the immobilization method of the drug into polymer matrix the meanings of binding degree are very high. The study of the dependence of binding degree on drug concentration resulted in more than 95 % at maximum concentrations of the added drug. As it has been expected the drug release degrees have high meanings when incorporating as well as adsorption the drug on the surface of empty nanoparticles. They are 70 % and 80 % respectively. Therefore the results obtained allow us to hope on prolongation of the effect of p-amino salicylic acid and decrease of single dose of the drug in tuberculosis therapy.

Keywords: Human serum albumin; p-aminosalicylic acid, anti-tuberculosis drug, nanoparticles, adsorption, immobilization, incorporation, polymer matrix.

Introduction

Nowadays short period of action, low selectivity and rather high toxicity are considered as the main drawbacks of drug preparations used in medicine. The results of numerous investigations have shown the possibility of disposition of these shortcomings by binding the drugs with polymers [1–3]. Promising results have been obtained when nanoencapsulating the drugs [4, 5] which are used for the treatment of such diseases as tuberculosis and tumor with natural and synthetic polymers [6–11]. PASA is one of the first antibiotics used in the treatment of tuberculosis and it is currently the drug required for the use in the Republic of Kazakhstan. During the time of use of the drug the resistance to tuberculosis strain has been developed and a single dose now reached ten grams. In this regard, the task of researchers is to prolong the effect of anti-tuberculosis drug by binding it to polymer thus reducing the single dose of the drug.

One of the most widely used polymeric carriers of drugs is human serum albumin (HSA). Due to its ability to transport low molecular compounds, including different kinds of drugs into a great variety of cells, especially after conversion to NPs, it represents a unique transporting material which allows to carry drugs into certain target-organs, thus prolonging their efficiency [12–15].

In the present study the possibility of immobilization of antituberculosis drug PASA with albumin NPs by adsorption of the drug onto preliminary synthesized empty nanoparticles and incorporation of the PASA during the process of particle crosslinking will be investigated.

Materials and methods

Human serum albumin (HSA, fraction V, purity 96–99 %, 65.000 Da) and glutaraldehyde 8 % solution were purchased from Sigma (Steinheim, Germany). PASA were purchased from LLP «Romat» (Pavlodar Pharmaceutical Factory, Pavlodar, Kazakhstan). Solvents and all other reagents were purchased from Merck (Darmstadt, Germany). Deionized (DI) water was used throughout the study.

Empty albumin NPs have been synthesized by desolvation method according to the procedure given in [3, 12, 13, 15]. 200 mg of HSA were dissolved in 2 ml of purified water and the pH was adjusted to 8.2–8.5 with 0.01 M NaOH. Then under constant stirring (600 rpm) at room temperature 8 ml of ethanol (96 %) was added (1 ml/min) using a tubing pump. After the desolvation process the particles were stabilized by the addition of an aqueous 8 % glutaraldehyde solution (1.175 µl per ml HSA). In order for the process to be finished, the suspension was stirred for 24 h. The obtained nanoparticles were separated from low molecular

components by repeated centrifugation with the Centrifuge MiniSpin Plus 14500 (Eppendorf, Hamburg, Germany) at 14500 rpm and by washing them with water.

Adsorption of PASA onto empty nanoparticles of HSA carried out in two steps: obtaining empty nanoparticles and the subsequent binding of the drug with the polymer. Prepared solutions of the drug with concentrations of 0.16 %, 0.32 %, 1.0 %, 2.0 % and 4.0 % were added to the solutions of empty albumin NPs obtained by above said technique and were stirred for 2 hours at room temperature. The required particle by size is separated by repeated centrifugation within 15 minutes at 14,500 rpm/min and was purified by washing with water.

The yield of NPs was determined by a microgravimetric method.

Incorporation of PASA into serum albumin was carried out at one stage by the procedure described below:

Calculated amount of PASA was added to the 2 % solution of serum albumin with pH 8.0–8.5 and was stirred for 2 hours. For the formation of NPs calculated amount of 8 % solution of glutaric aldehyde was added to the drug solutions. The particles of needed sizes have been separated from low- and high molecular compounds by multiple centrifugation and washing with water.

The average particle size was measured by photon correlation spectroscopy (PCS) using a Malvern Zetasizer 3000HSA (Malvern Instruments Ltd., Malvern, UK) at a temperature of 25 ºC at a scattering angle of 90º. The samples were diluted 1:400 with water.

Drug content was determined by conductometric method. The measurements of electrical conductivity of solutions were performed on a Conductivity meter Type OK-102 (Hungary) № 1182 OOO «Econics-Expert» and INN/KPP 7728209000/772801001 (Moscow) using platinum electrodes and a thermostat UTU-2/77 (Polanol) with thermostatic electrical cell with a volume of 25 ml.

0.1, 0.08, 0.06, 0.04, 0.02, 0.01, 0.005 mg/ml drug solutions in water were prepared for a calibration curve. The quantity of unbound drug was calculated using a calibration curve.

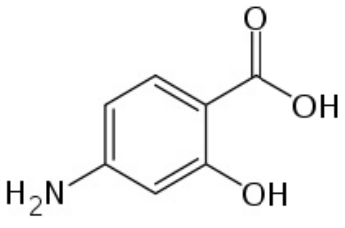
Results and discussion

Empty HSA nanoparticles were obtained according to the technique given above [3, 12, 13, 15]. Nanoparticles with average diameter of 310 nm (PDI = 0.142) were formed.

There are two main ways of binding of drugs to HSA nanoparticles [3, 12, 13, 15]: 1) physical adsorption of drugs on the surface of preliminary prepared NPs, and 2) incorporation of drugs into the polymer matrix during particle preparation. Therefore at first PASA was bound to the polymer by adsorption of the drug on the surface of preliminary synthesized empty HSA nanoparticles. The adsorption of the drug on HSA nanoparticles has been performed with concentrations of PASA in initial solution ranging from 0.16 to 4.0 %. The immobilization of PASA with empty NPs has been carried out by direct mixing of corresponding solutions. Adsorption of the drug on the surface of preliminary prepared NPs led to a minor increase of the particle size (d = 316 nm, PDI = 0.140).

It is necessary to note that molecules of both serum albumin (1) and PASA (2) contain carboxylic and amino groups which should lead to some effects when creating chemical bonds.

$$H_2N - [R^1 - NH - CO - R^2] - COOH \quad (1)$$



(2)

The binding degree of the drug with HSA nanoparticles was determined using conductivity measurements. Conductometry enables estimation of the binding of drug with polymer directly in the reaction medium without preliminary separation of nanoparticles from the solution. The quantity of unbound drug was calculated using a calibration curve. The results of the binding experiments of PASA on HSA nanoparticles are shown in Figure 1.

Increasing the concentration of PASA in solution leads to increase of binding degree with limiting meaning of 95 % (Fig. 1).

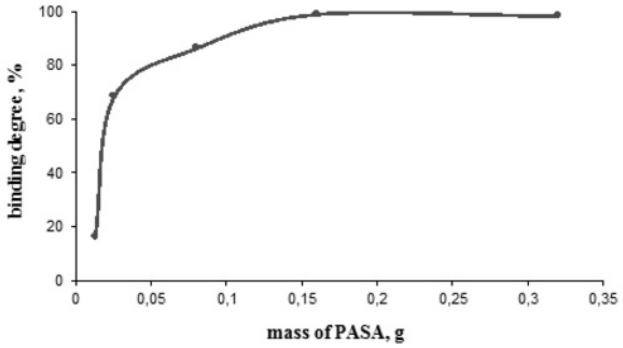


Figure 1. Dependence of binding degree on mass of PASA

This regularity correlates well with the assumption that the bond between drug and polymer was formed by ionic mechanism. The binding of the drug with HSA was investigated using photocolorimetry and viscosimetry. The results are shown in Figure 2.

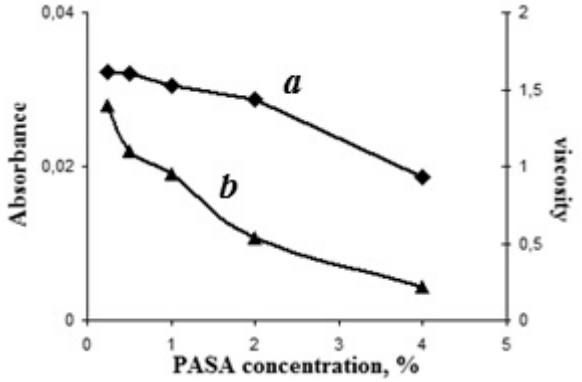


Figure 2. Dependence of viscosity (*a*) and absorbance (*b*) of albumin solution on concentration of PASA (using viscosimetry)

The above given assumptions are in good accordance with conducted viscosimetric measurements (Fig. 2). Decrease of viscosity of serum albumin solution is caused by suppression of polyelectrolytic effect on two directions: 1) the screening effect of amino- and carboxylic groups; 2) their chemical binding which is an advantage for the creation of novel drug preparations. The same dependence is observed from the graph of dependence of absorbance on concentration of drug added which points on compaction of polymeric particles (Fig. 2).

As a continuation of our study the kinetics of release of anti-tuberculosis drug PASA from the polymer matrix of serum albumin was investigated. Release of PASA from HSA nanoparticles produced by adsorption method was studied during the day. The results are shown in Figure 3.

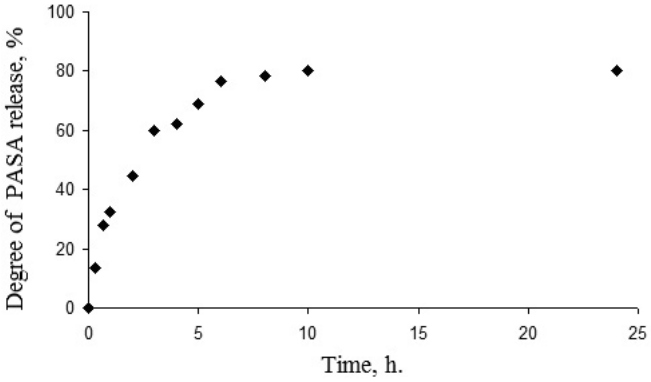


Figure 3. Drug release profile of PASA-loaded NPs (for the NPs obtained by adsorption method)

As seen from the graph, a significant portion of the drug released into the medium during first 3 hours (about 30 % per hour, about 60 % in 3 hours). This is apparently because of the desorption of the drug, located on the surface of NPs. Further, there is a gradual release of PASA from nanoparticles of HSA of up to 80 % of the drug. The remaining part of PASA did not release, which could be related to the structure of the crosslinked polymeric nanoparticles.

When adsorbing the drug onto the surface of NPs there is a risk of loss of some part of the drug by desorption, in this regard at the next stage we have studied the binding of the drug during particles' crosslinking.

In this case PASA was preliminarily dissolved in water solution of serum albumin and then desolvation was carried out. Average particle diameter obtained by incorporation method was 435 nm (PDI = 0,147). The concentration of the drug in initial solution was sustained as in case of adsorption. Binding degree of PASA was also determined by conductometry method (Fig. 1).

As it is seen from the graph in this case almost 100 % binding was possible (Fig. 1).

As in this case the drug is incorporated inside of NPs the curves of dependence of viscosity and absorbance are opposite to the ones obtained by adsorption method (Fig. 4).

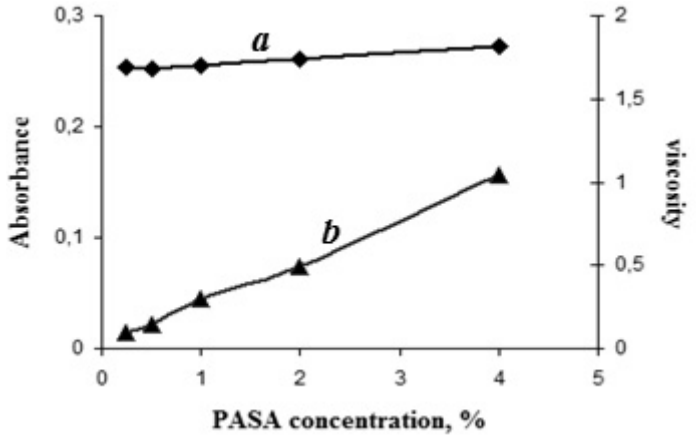


Figure 4. Dependence of viscosity (*a*) and absorbance (*b*) of albumin solution on concentration of PASA (using photocolorimetry)

Because of the presence of ionogenic groups on the surface of NPs this dependence tends to increase due to no suppression of polyelectrolytic effect.

Then the degree of drug release from the matrix HSA nanoparticles obtained by incorporation method has been studied, of which the results are shown in Figure 5.

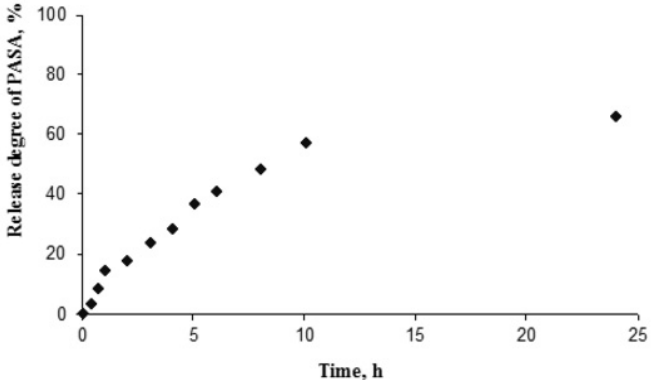


Figure 5. Drug release profile of PASA-loaded NPs (for the NPs obtained by incorporation method)

The graph shows that, as compared with the adsorption method in the case of incorporation a sustained release of PASA is observed. It is explained by release of the drug located inside the NPs. Thus, about 15 % of the drug released per hour, and only 24 % of PASA for 3 h. While the observation of the kinetics of drug release from NPs obtained by adsorption method, 2 times more of PASA released during the same period of time. Also the yield of NPs loaded with drug was determined (Table).

Table

Yield of HSA nanoparticles loaded with PASA

Drug content in initial solution, g	The yield of nanoparticles determined by microgravimetry, %	
	Obtained by adsorption	Obtained by incorporation
0.0125	92	92
0.025	43	89
0.08	41	55
0.16	13	10
0.32	67	35

In both cases the particle yields were high. The tendency of decreasing of the yield of NPs reaching a minimum with increasing of drug concentration was observed (Table 1). With the last sample high yield of NPs has been achieved.

Conclusion

Thus, in this work the possibility of obtaining polymer carriers of nanometric sizes based on HSA for the transport of anti-tuberculosis drug PASA has been shown. The results obtained have demonstrated that the loading of HSA with PASA by both adsorption and incorporation methods enables synthesizing NPs with satisfactory characteristics, high values of the binding degree and high nanoparticle yield. According to the results of the study on drug release it can be concluded that slower drug release is observed when immobilization of PASA by incorporation method in NPs. However, despite the relatively rapid release of PASA from HSA nanoparticles obtained by the adsorption method, these polymeric NPs can also be effectively used as drug delivery systems for anti-tuberculosis drug PASA.

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Адам сарысулы альбумин негізіндегі туберкулезге қарсы *n*-аминосалицил қышқылы препаратының алынуы, сипаттамасы және босап шығуын *in vitro* зерттеу

Қазіргі таңдағы фармацевтикалық химияның басты міндеттерінің бірі жаңа дәрілік препараттарды іздеу ғана емес, сонымен қатар жаңа үлгіні жасап шығару немесе химиялық түрлендіру арқылы оның тиімділігін арттыру болып табылады. Бір реттік қабылдау мөлшерін азайту және әсерін ұзарту мақсатында бұл мақалада туберкулезге қарсы препарат пара-аминосалицил қышқылын адам сарысу альбуминнің нанобөлшектеріне енгізу және адсорбция әдісімен иммобилизациялау мүмкіндігі қарастырылған. Дәрілік затты полимер матрицасына иммобилизациялау әдісінен тәуелсіз байланысу дәрежесінің мәндері жоғары болатыны көрсетілген. Байланысу дәрежесінің дәрілік зат концентрациясынан тәуелділігін зерттеу барысында дәрілік заттың максималды концентрациясында 95 % жоғары мәнді көрсететіндігі анықталды. Ал препаратты бос нанобөлшектердің бетіне енгізу және адсорбция әдісі арқылы иммобилизациялау дәрілік заттың босап шығу дәрежесінің жоғары мәндеріне ие болды. Олар сәйкесінше 70 және 80 % құрады. Сол себепті алынған нәтижелер пара-аминосалицил қышқылының туберкулезді емдеу барысында пролонгациялық әсер беретінін және бір реттік қабылдау мөлшерін азайтатынын дәлелдеді.

Кілт сөздер: адам сарысу альбумині, пара-аминосалицил қышқылы, туберкулезге қарсы препарат, нанобөлшектер, адсорбция, иммобилизация, енгізу, полимер матрицасы.

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Получение, характеристика и исследование высвобождения *in vitro* противотуберкулезного препарата *n*-аминосалициловой кислоты на основе человеческого сывороточного альбумина

В настоящее время задачей фармацевтической химии является не только поиск новых лекарственных препаратов, но и повышение эффективности действия препарата путем химической модификации или создания новых форм. С целью продления эффекта и уменьшения разовой дозы в этой статье была рассмотрена возможность иммобилизации лекарственного средства против туберкулеза — *n*-аминосалициловой кислоты (ПАСК) — на наночастицу человеческого сывороточного альбумина методом адсорбции и включения. Показано, что, независимо от способа иммобилизации лекарственного средства в полимерную матрицу, значения степени связывания очень велики. Изучение зависимости степени связывания от концентрации лекарственного средства приводило к более чем 95 % при максимальных концентрациях добавленного лекарственного средства. Как и ожидалось, степени высвобождения лекарственного средства имеют высокие значения при включении и адсорбции препарата на поверхности пустых наночастиц. Они составляют 70 и 80 % соответственно. По этой причине полученные результаты позволяют надеяться на пролонгированное действие *n*-аминосалициловой кислоты и снижение разовой дозы препарата при лечении туберкулеза.

Ключевые слова: сывороточный альбумин человека, *n*-аминосалициловая кислота, противотуберкулезный препарат, наночастицы, адсорбция, иммобилизация, включение, полимерная матрица.

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UDC 615.4–620.3

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Polyelectrolytic multilayers as drug delivery system

This article is devoted to preparation of polyelectrolytic microcapsules of two antitubercular drugs (ATDs) as the new drug delivery system (DDS). Co-encapsulation of oral antitubercular drugs pyrazinamide and moxifloxcin by polyelectrolytic multilayers is carried out for the first time. At first by ionotropic gelation method co-encapsulation of drugs to a polymeric matrix carried out. As a matrix biopolymers gellan and sodium alginate were used. The co-encapsulation efficiency was determined using UV-spectroscopy method as it is specified in the State pharmacopeia of the Republic of Kazakhstan. Then by the method of fiber adsorption (LbL-technique — Layer by layer deposition) on microcapsules sequentially coated a cationic polyelectrolyte chitosan and an anionic polyelectrolyte eudragit S100. The charge of each layer was determined by zeta-potential measurement. Microcapsules about 3, 5 and 10 bilayers of polyelectrolytes are prepared. The structure of microcapsules was studied by method of the scanning submicroscopy. In vitro drug release studies carried out at values pH, modeling various sites of digestive tract. As a result of a research it is shown that microcapsules possess the prolonged action. With increase in number of bilayers extent of prolongation of drugs increases. It is enough 5 bilayers of polyelectrolytes to achieve the 24th hour prolongation of drugs.

Keywords: antitubercular drugs, microcapsule, biopolymers, polyelectrolytic multilayers, controlled release.

Introduction

For the treatment of drug-resistant forms of tuberculosis, patients are forced to take 20 tablets of six types of drugs per day. It is interfaced by heavy side effects. Accordingly, any attempts to enhance drug-resistant tuberculosis treatment in order to it's endure by patients are actual and socially-implicated. Therefore, scientists conduct various researches on the dosage optimization, prolonged action and enhanced bioavailability of antitubercular drugs [1]. For this purpose various drug delivery systems (DDS) have been developed: microparticles, nanoparticles, liposomes, polymeric composites, the hollow and filled capsules. In the literature there is a lot of works devoted to the use of biopolymers as DDS [2, 3]. However, there are very few literary data on encapsulation of antitubercular drugs by polyelectrolytic multilayers. For example, rifampicin encapsulated into chitosan-dextran sulfate hollow microcapsules. Rifampicin released from these microcapsules within over 72 hours at pH=1.2 and pH=7.4 [4]. One of the urgent solutions of the problem of the dosage optimization is the development of new DDS for the preparation of combined and prolonged forms of ATDs.

The goals of this work are co-encapsulation of two antitubercular drugs — pyrazinamide and moxifloxacin in the biopolymer coated with polyelectrolytic multilayers, and evaluation of drug release at values pH, modeling various sites of a gastrointestinal tract (GIT).

Materials and methods

The biopolymers low-acetylated gellan (China producted) and sodium alginate (Sigma-Aldrich) were used as the containers for capsules. For preparation of multilayers the cationic polyelectrolyte chitosan (Chit) water-soluble, ≥ 8000 Da (Bioprogress, Moscow) and anionic polyelectrolyte Eudragit S100 (Eud) (Sigma-Aldrich) were chosen.

Substances of antitubercular drugs pyrazinamide (Pz), (Shanghai International Pharmaceutical Co), a moxifloxacin hydrochloride (Mfx) (Pavlodar Pharmaceutical Plant, Kazakhstan) were used.

Drug containing microcapsules were prepared by ionotropic gelation method [5, 6]. The co-encapsulation efficiency was determined using the methods given in Pharmacopoeia: the quantity of pyrazinamide and moxifloxacin were determined on the spectrophotometer (Specord 210, Germany) at 268 nm and 295 nm accordingly [7].

The coating of microcapsules by polyelectrolytic multilayers was carried out by LbL-technique (Layer by layer deposition), consistently immersing them in water solution of a chitosan and in Eudragit S100 solution in sodium chloride. After immersion in each polyelectrolyte the microcapsules were twice washed with distilled water. This procedure was repeated 3, 5 or 10 times. Thus, 3, 5 or 10 bilayers of oppositely charged polyelectrolytes have been formed.

Dzeta-potential of each polyelectrolytic layer was measured by dynamic light scattering method on Malvern Zetasizer Nano ZS90 (Great Britain).

The surface morphology of the microcapsules was studied by scanning electronic microscopy on a low-vacuum raster electronic microscope of «JEOL» of JSM-6390 LV (Japan).

In vitro drug release studies carried out according to Pharmacopoeia requirements [7], using the dissolution apparatus (Erweka, Germany) at a temperature (37 ± 0.5) ºC and the rotation speed 100 rpm. The tests were performed at gastric pH (0.1N HCl, pH=1.2) and intestinal pH (phosphate buffer, pH=7.4). Concentrations of the drugs were determined using UV-Visible spectrophotometric method at 268 and 295 nm. All quantitative analyses were repeated 3 times.

Results and discussion

Drug containing spherical microcapsules of size around of 1,5–2,0 mm were prepared. Microcapsules were kept within 10 min in calcium salt solution, then passed through a sieve and washed twice in distilled water and dried on air at room temperature. The solution was used for the determination of co-encapsulation efficiency.

SEM microphotographs of microcapsules same as gellan-isoniazide microcapsule with 5 bilayers Chit/DS [6], and also the border between the microcapsule and polyelectrolytic layers is visible (see Fig.).

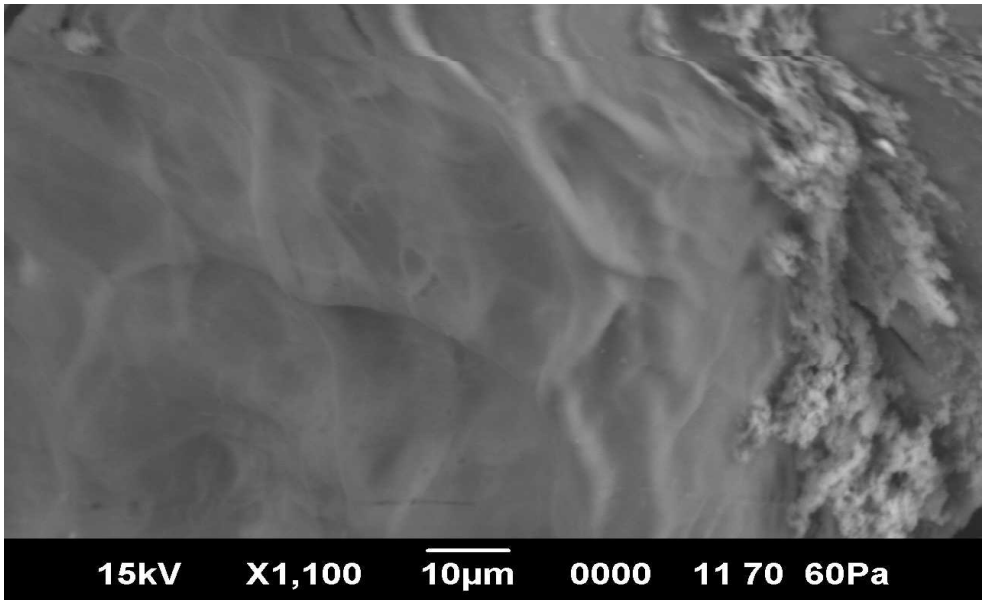

Figure. SEM microphotograph of microcapsule 3 % gellan/Pz/Mfx + 3 bilayers Chit/Eud

Results of co-encapsulation efficiency determination are given in Table 1.

Table 1

Co-encapsulation efficiency, %

Microcapsule matrix	Pyrazinamide	Moxifloxacin
1 % gellan	27,5 ± 1,3	27,6 ± 10,6
3 % gellan	39,9 ± 4,2	41,8 ± 2,2
2 % alginate	26,5 ± 3,1	32,1 ± 2,6
3 % alginate	28,0 ± 2,1	51,1 ± 3,4

Apparently from table 1, generally co-encapsulation efficiency increases with the increase of biopolymer concentration. It is interesting that co-encapsulation efficiency of drugs is a bit higher, comparing to the efficiency of their separate encapsulation [6].

After covering by polyelectrolytes dzeta potential of microcapsules were measured. Microcapsules possess a positive or negative charge after adsorption of chitosan and eudragit respectively (Table 2).

Table 2

Results of dzeta-potential measurements

Composition of microcapsule	3 % gellan/Pz/Mfx + Chit	3 % gellan/Pz/Mfx + Chit/Eud
Dzeta-potential, mV	19±2	–16±2

In vitro drug release studies have shown, that in acidic media at pH =1.2 (corresponds to the gastric) capsules did not dissolve within a day.

At pH =7.4 (corresponds to intestines) microcapsules gradually dissolved (Tables 3 and 4).

Table 3

Drug release from gellan capsules at pH = 7.4, %

Composition of microcapsule	Release time, hour	Extent of release, %	
		Pyrazinamide	Moxifloxacin
3 % gellan/Pz/Mfx (without multilayers)	4	34,6 ± 4,8	34,7 ± 4,5
	8	54,8 ± 4,5	49,4 ± 1,1
	12	81,2 ± 2,3	84,2 ± 1,2
3 % gellan/Pz/Mfx + 3 bilayers Chit/Eud	6	25,9 ± 0,9	27,0 ± 1,2
	12	48,6 ± 1,9	49,5 ± 0,6
	18	80,5 ± 1,3	78,3 ± 3,9
3 % gellan/Pz/Mfx + 5 bilayers Chit/Eud	12	26,3 ± 1,9	26,4 ± 7,5
	18	45,8 ± 0,7	46,5 ± 1,3
	24	75,6 ± 0,5	75,2 ± 1,9
3 % gellan/Pz/Mfx + 10 bilayers Chit/Eud	12	–	–
	18	–	–
	24	13,3 ± 3,3	10,4 ± 1,8

Table 4

Drug release from alginate capsules at pH=7.4, %

Composition of microcapsule	Release time, hour	Extent of release, %	
		Pyrazinamide	Moxifloxacin
3 % alginate/Pz/Mfx (without multilayers)	4	31,8 ± 3,8	32,9 ± 3,5
	8	52,1 ± 3,9	48,9 ± 1,8
	12	79,8 ± 3,6	81,2 ± 2,5
3 % alginate/Pz/Mfx + 3 bilayers Chit/Eud	6	28,9 ± 1,8	28,5 ± 2,5
	12	47,9 ± 2,4	48,9 ± 1,0
	18	80,0 ± 2,3	79,6 ± 4,1
3 % alginate/Pz/Mfx + 5 bilayers Chit/Eud	12	28,3 ± 3,8	27,5 ± 4,3
	18	46,5 ± 0,9	47,8 ± 2,2
	24	76,6 ± 1,4	75,9 ± 2,6
3 % alginate/Pz/Mfx + 10 bilayers Chit/Eud	12	–	–
	18	–	–
	24	10,9 ± 2,7	11,9 ± 2,8

Apparently from the table 3 and 4 the release (%) of pyrazinamide and moxifloxacin from combined microcapsules without polyelectrolytic multilayers in 4 hours is about 30 % of the active substance, in 8 hours — about 50 %, for 12 hours — about 80 %. Thus, the prolongation made 12 hours.

In case of the microcapsules covered with 3 polyelectrolytic bilayers more prolonged release was observed: in 6 hours 30 % of the active substance, in 12 hours — 50 %, in 18 hours — 80 % are released. In this case prolongation made 18 hours, i.e. is 1,5 times longer, than without multilayers.

In case the covering made 5 bilayers the prolongation is higher: in 12 clocks released 30 % of the active substance, in 18 hours — 50 %, in 24 hours — 80 % are released. In this case prolongation made 24 hours. Capsules with 10 bilayers of polyelectrolytes began to dissolve after 20 hours, in 24 hours only about 10 % of the active substance are released.

Conclusions

Thus, co-encapsulation of ATDs pyrazinamide and moxifloxacin by biopolymer and polyelectrolytic multilayers was carried out for the first time. Safe biodegradable and biocompatible polymers were used for co-encapsulation.

Co-encapsulation was performed in aqueous solutions at room temperature without using costly or special equipment, polyelectrolyte multilayers were coated using LbL-technique.

It is shown that polyelectrolytic co-encapsulation allows to prepare the prolonged form of the combined ATDs for oral use. It is enough to coat microcapsules with only 5 bilayers of polyelectrolytes for the achievement of 24 hour prolongation of drugs.

Acknowledgements

This study was performed with the financial support of the Ministry of Education and Science of the Republic of Kazakhstan, grant № 0794/ GF4.

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Полиэлектролитті мультқабаттар дәрілерді жеткізу жүйесі ретінде

Мақала жаңа дәрі-дәрмек жеткізу жүйесі ретінде екі туберкулезге қарсы препараттың полиэлектролитті микрокапсулаларын алуға арналды. Пероральді туберкулезге қарсы препараттар пиразинамид және моксифлоксацинді полиэлектролитті мультиқабаттармен біріктіре капсулдеу алғаш рет жүргізілді. Алдымен ионотропты гель түзу әдісімен препараттар полимерлік матрицаға капсулденді. Матрица ретінде геллан және натрий альгинаты биополимерлері пайдаланды. Препараттардың микрокапсулаға ену тиімділігі Қазақстан Республикасының Мемлекеттік фармакопеясында көрсетілгендей, УК-спектроскопия әдісімен анықталды. Содан кейін микрокапсулалар беті кезек қабаттармен адсорбциялау әдісімен (LbL техникасы — Layer by layer deposition) катиондық полиэлектролит хитозан және аниондық полиэлектролит эудрагитпен S100 қапталды. Әрбір қабаттың заряды дзета-потенциалын өлшеу арқылы анықталды. Полиэлектролиттердің 3, 5 және 10 қос қабатымен қапталған микрокапсулалар алынды. Микрокапсулалар құрылымы сканирлеуші электрондық микроскопия әдісімен зерттелді. Асқазан-ішек жолдарының әр түрлі бөліктерін модельдейтін pH мағыналарында препараттардың босап шығуы *in vitro* жағдайында зерттелді. Зерттеу нәтижесінде микрокапсулалардың ұзартылған әсері бар екені көрсетілді. Қос қабат сандары ұлғайған

сайын препараттардың әсерін ұзарту дәрежесі де артады. 5 полиэлектролитті қос қабатпен қаптағанда 24 сағаттық ұзартуға қолжеткізуге болады.

Кілт сөздер: туберкулезге қарсы препараттар, микрокапсула, биополимерлер, полиэлектролитті мультиқабаттар, бақыланатын босап шығу.

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Полиэлектролитные мультислои как система доставки лекарств

Статья посвящена получению полиэлектролитных микрокапсул двух противотуберкулезных препаратов в качестве новой системы доставки лекарств. Впервые проведено совместное капсулирование пероральных противотуберкулезных препаратов пиразинамида и моксифлоксацина полиэлектролитными мультислоями. Сначала методом ионотропного гелеобразования проводилось капсулирование препаратов в полимерную матрицу. В качестве матрицы использованы биополимеры геллан и альгинат натрия. Эффективность включения препаратов в микрокапсулы определяли методом УФ-спектроскопии, как указано в Государственной фармокопее Республики Казахстан. После этого методом послойной адсорбции (техника LbL — Layer by layer deposition) на микрокапсулы последовательно наносились катионный полиэлектролит хитозан и анионный полиэлектролит эудрагит S100. Заряд каждого слоя определяли измерением дзета-потенциала. Получены микрокапсулы с 3, 5 и 10 бислоями полиэлектролитов. Структуру микрокапсул изучали методом сканирующей электронной микроскопии. Изучено высвобождение препаратов *in vitro* при значениях pH, моделирующих различные участки желудочно-кишечного тракта. В результате исследования показано, что микрокапсулы обладают пролонгированным действием. С увеличением числа бислоев повышается степень пролонгации препаратов. Показано, что при нанесении 5 полиэлектролитных бислоев можно добиться 24-часовой пролонгации.

Ключевые слова: противотуберкулезные препараты, микрокапсула, биополимеры, полиэлектролитные мультислои, контролируемое высвобождение.

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ӘОЖ 541.64:678

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Органикалық қосылыстардың синтезіндегі үрдіс жағдайларын модельдеу және мұндағы полимерлі комплекстердің әрекеті

Мақалада қоршаған қанықпаған полиэфирлі шайырлар мен қанықпаған карбон қышқылдары негізіндегі гидрогельдердің құрамдық мәліметтері және құрылымы электронды-расторлық микроскоп арқылы зерттеліп, оның торлы құрылымды және металл бөлшектерін орнықтыруда «нанореактор» болатыны дәлелденген. Орта факторларының, атап айтқанда, температура мен ортаның pH мәні және еріткіштердің полиэтилен-(пропилен)гликольмалеинат негізіндегі жаңа металл-полимерлі комплекстерге әсері жан-жақты қарастырылды. Жүргізілген тәжірибелер металл-полимерлі комплекстердің ісіну дәрежесіне температураның әсері мардымсыз екенін көрсетті. Аталған комплекстердің сілтілік ортада ісіну дәрежесінің жоғары мәнге ие болып, еріткіштердің полярлығы жоғарлаған сайын ісіну дәрежесі де артатындығы байқалды. Сілтілік ортада металл-полимерлі комплекстердің ісіну дәрежесінің өскені электркаталитикалық гидрлеу үрдісінде оңтайлы әсер етеді, себебі комплекстің ісіну қабілетінің жоғарлауымен субстраттың катализаторға қолжетімділігі де өседі. Диэлектрлік өтімділік пен полимерлердің ісіну дәрежелері арасында, нақтырақ айтқанда, орта полярлы ерітінділерден пиридинге қарай корреляция байқалады. Алайда ісіну дәрежесінің төмендеуінің байқалмайтындығы көрінді.

Кілт сөздер: полиэтиленгликольмалеинат, полипропиленгликольмалеинат, қанықпаған полиэфирлі шайырлар, катализ, нанобөлшектер, нанореактор, катализатор, металл-полимерлі комплекстер, полимерлі матрица, электркаталитикалық гидрлеу.

Кіріспе

Каталитикалық гидрлеу өндірісте де, зерттеу тәжірибелерінде де қолданыс тауып жүрген маңызды реакциялардың бірі. Соңғы жылдары ғалымдардың қызығушылығын органикалық заттардың электрхимиялық айналымдары, оның ішінде катодтағы тотықсыздану үрдістері тудырып отыр. Сонымен қатар органикалық синтезде электр тоғын қолдану экономикалық тұрғыдан тиімді екені анықталған. Аталған электрокаталитикалық үрдістер атомдық-абсорбцияланған сутегі көмегімен жүргізіледі [1].

Гетероциклді қосылыстардың гидрленуіне аса маңызды көңіл бөлінеді. Атап айтқанда, пиридиннің тотықсызданууының қызығушылық тудыруы пипиридиндік цикл туындыларының алколоидтар, жансыздандыру және тағы басқа заттарының синтезінде қолданылуынан болып отыр.

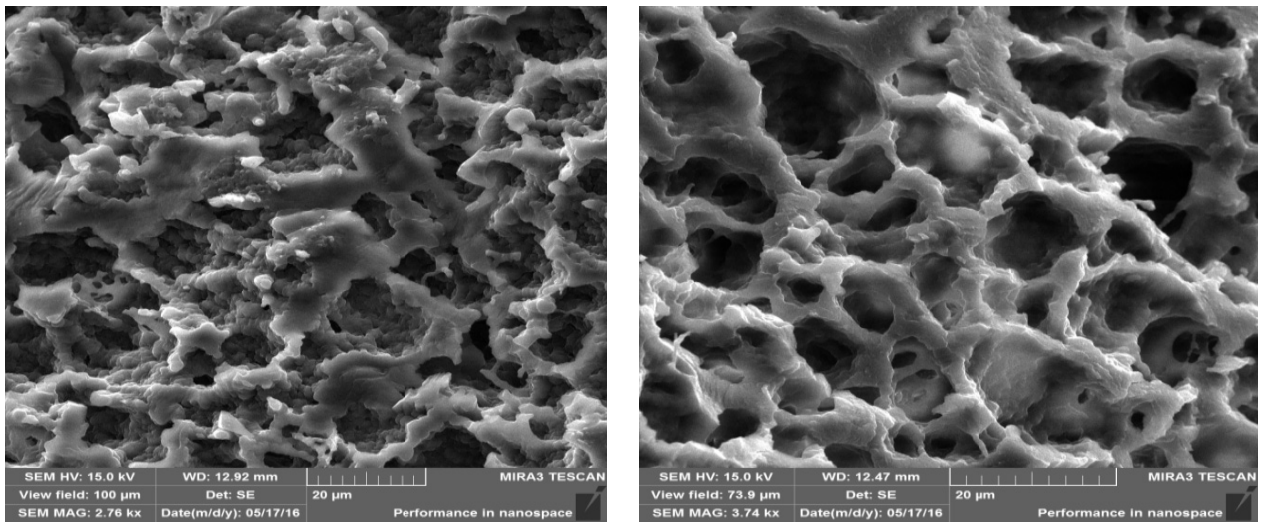
Гидрлеуде пайданылатын белсенді катализаторларды жасау маңызды мәселе. Өндірісте кеңінен қолданылып жүрген катализаторлардың кемшілігі — нақты беттік ауданының төмендігі. Сондықтан қазіргі уақытта наноөлшемді катализаторлар бірегей туындыларға айналып отыр. Нанобөлшектерді тасымалдаушы және тұрақтандырғыш ретінде полимерлер қолданылады. Металл-полимерлі нанокомпозиттер металдар мен полимерлердің ерекше қасиеттерін өз бойынан көрсетеді [2–4].

Аталған реакторларды алудағы тиімді материалдардың алдыңғы қатарын тор құрылымды, су сіңіруге және ұстап тұруға бейімді полимерлі гидрогельдер алады. Сонымен қатар аталған гидрогельдер қоршаған орта өзгерістеріне жоғары сезімталдық көрсететіндіктен, ғылым мен техниканың әр саласында қолданыс тауып отыр [5, 6].

Тәжірибелік бөлім

Қанықпаған полиэфирлі шайырлардың қасиеттері мен олардың негізіндегі гидрогельдер металл нанобөлшектерінің арзан және қолжетімді тасымалдауышы екендігі [7, 8] жұмыстарында анықталған. Шайырлардың құрамына сополимеризация әдісімен енгізілген карбон қышқылдары (АҚ және МАҚ) алынған жаңа гельдерге сіңіруші қасиет беретіндігі алдыңғы жұмыстарда қарастырылған.

Алынған гидрогельдердің құрамдық мәліметтері және құрылымы электронды-расторлық микроскоп арқылы зерттеліп, оның торлы құрылымды және металл бөлшектерін орнықтыруда «нанореактор» болатыны дәлелденді (1, 2-сур.) [9].



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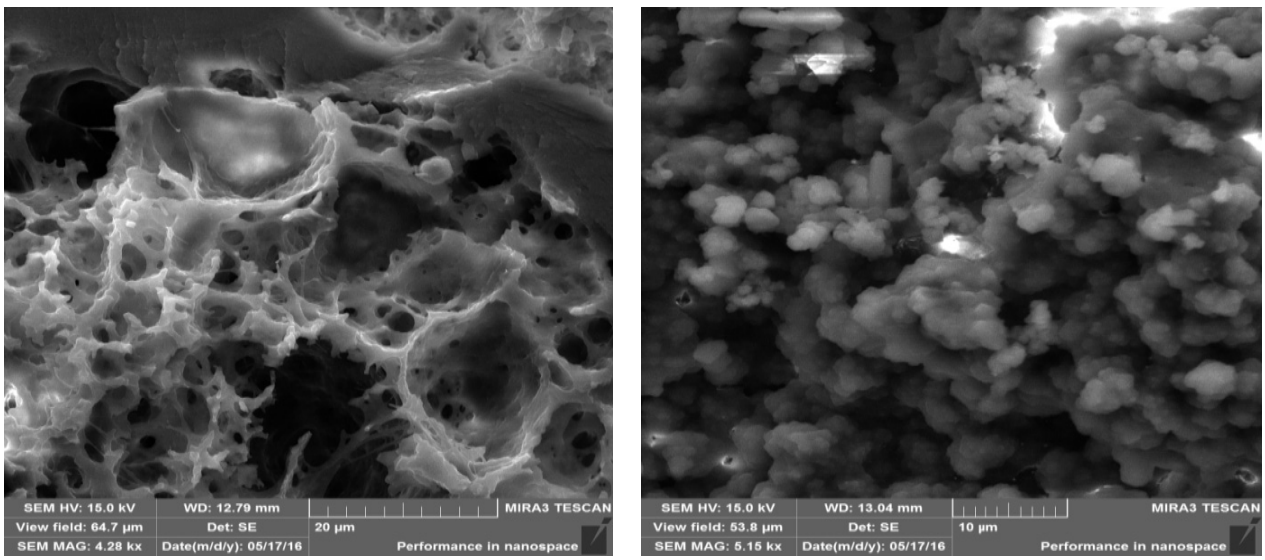
1-сурет. *n*-ЭГМ: АҚ (*1*) және МАҚ (*2*) сополимерлерінің электронды-расторлық микроскоптық бейнелері



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2-сурет. *n*-ПГМ:АҚ (*1*) және МАҚ (*2*) сополимерлерінің электронды-расторлық микроскоптық бейнелері

Жұмыстарымыздың жалғасы ретінде [10] полиэтилен- және полипропиленгликольмалеинат (*n*-ПГМ) пен акрил қышқылы (АҚ) және метакрил қышқылы (МАҚ) гидрогельдері негізіндегі жаңа металл-полимерлі комплекстер (МПК) алынған.

Зерттеу жұмыстары алынған металл-полимерлі комплекстердің қасиеттерін кеңінен зерттеумен және оларды органикалық қосылыстарды алуда қолданумен жалғасын тапты.

Бұл мақалада қоршаған орта факторларының, атап айтқанда, температура, ортаның pH мәнінің жаңа металл-полимерлі комплекстерге әсері қарастырылады. Температура МПК-дің әрекетіне едеуір әсер ететін факторлардың бірі. Электрокатализ үрдісінде каталитикалық ұяшықтағы ерітінділер бөлме температурасынан жоғары қыздырылады. Осыған орай ісінген МПК-ге температураның әсері зерттелді. Төмендегі 1-кестеден температураның жоғарлауымен МПК-тің ісіну дәрежесі аса өзгермейтіні көрінді.

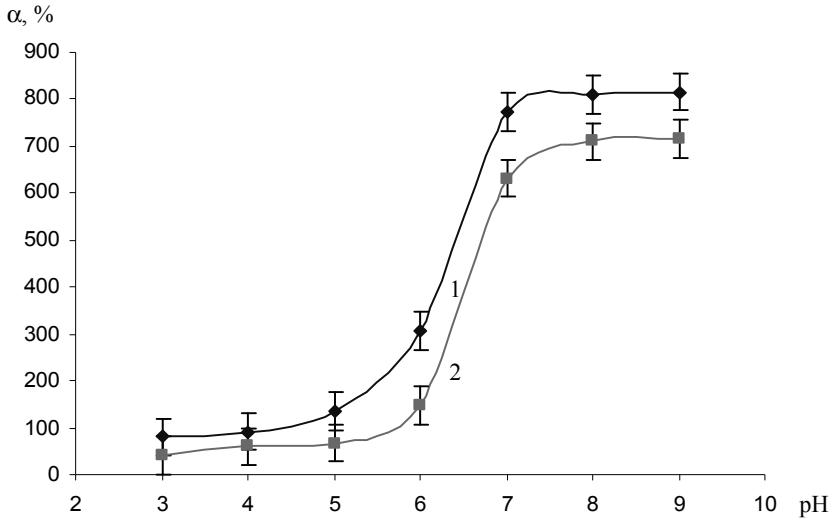
1 - к е с т е

Металл-полимерлі комплекстердің ісіну дәрежесіне температураның әсері

n-ЭГМ-АҚ негізіндегі МПК				
Температура, ºС	25	30	35	40
α, %	845 864 836	847 868 844	850 869 846	910 901 903
Орташа көрсеткіш	848±16	853±15	855±14	905±5
n-ЭГМ-МАҚ негізіндегі МПК				
Температура, ºС	25	30	35	40
α, %	650 663 642	654 667 651	657 677 669	690 704 705
Орташа көрсеткіш	652±11	657±10	668±1	701±4
n-ПГМ-АҚ негізіндегі МПК				
Температура, ºС	25	30	35	40
α, %	726 733 718	731 742 722	746 759 737	800 802 806
Орташа көрсеткіш	726±7	732±10	747±12	803±2
n-ПГМ-МАҚ негізіндегі МПК				
Температура, ºС	25	30	35	40
α, %	610 624 609	625 633 617	636 648 623	672 651 680
Орташа көрсеткіш	614±10	625±8	636±12	668±12

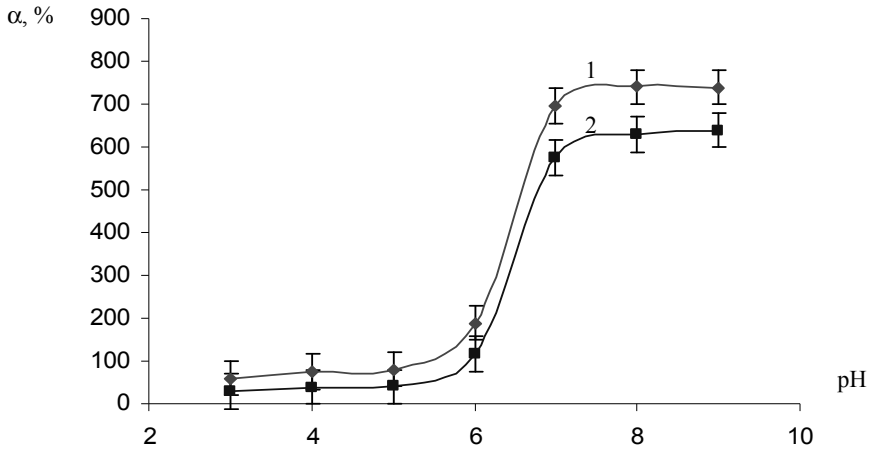
Жоғарыда көрсетілген кесте мәліметтерінен МПК-тің ісіну дәрежесіне температураның әсері мардымсыз екенін байқауға болады. Алайда гель көлемінің аздап өзгергені көрінді. Бұл көрініс полимерлі гель көлеміндегі металл бөлшектерінің каталитикалық белсенділігіне синергетикалық әсер көрсетуі мүмкін.

Үрдіс кезінде ортаның pH көрсеткіші де өзгеріске ұшырайды, себебі гидрлеу сілтілік ортада өтеді. Сондықтан МПК-ң ісінуіне ортаның pH әсерін зерттедік (3, 4-сур.).



Сополимерлердің құрамы, сәйкесінше *n*-ЭГМ: *1* — АҚ 22,8:77,2 мас. %; *2* — МАҚ 29,2:70,8 мас.%

3-сурет. МПК-ның ісінуіне ортаның pH әсері



Сополимерлердің құрамы, сәйкесінше *n*-ПГМ: *1* — АҚ 22,8:77,2 мас.%; *2* — МАҚ 29,2:70,8 мас.%

4-сурет. МПК-ның ісінуіне ортаның pH әсері

Тәжірибелік мәліметтерден (сур. 3, 4) қисықтардың қанықпаған полиэфирлі шайырлар негізіндегі гидрогельдердің ісіну заңдылығына ұқсас екенін байқауға болады. Сілтілік ортада МПК-тің ісіну дәрежесінің жоғары болуы электркаталитикалық гидрлеу үрдісінде оңтайлы нәтиже береді, себебі комплекстің ісіну қабілетінің жоғарлауымен субстраттың катализаторға қолжетімділігі де өседі.

Зерттеулеріміз еріткіш табиғатының МПК-тің ісіну дәрежесіне әсерін зерттеумен жалғасты. Еріткіштің полярлығы ұлғайған сайын ондағы полимер мен МПК соғұрлым жақсы ісінеді. Физикалық сипаттамалардан диэлектрлік өткізгіштік ерітіндінің полярлығы бастапқы маңыздылықта болады (2-кесте) [11].

2 - к е с т е

Металл-полимерлі комплекстердің ісіну дәрежесіне еріткіштердің әсері

Еріткіш	Диэлектрлік өтімділік, ε	Дипольдік сәт, μ	Донорлық мән	Акцепторлық мән	α, %			
					1	2	3	4
Су	78,5	1,8	18	54,8	845	650	726	610
ДМСО	48,9	3,9	28,9	19,3	768	543	623	432
ДМФА	36,7	3,8	26,6	16,0	756	539	599	445
Этанол	24,3	1,7	19,6	37,9	566	365	278	189
Ацетон	20,7	2,7	17,0	12,5	214	198	123	87
Пиридин	12,3	2,2	33,1	14,2	132	111	96	65

Ескерту. 1 — *n*-ЭГМ:АҚ; 2 — *n*-ЭГМ:МАҚ; 3 — *n*-ПГМ:АҚ; 4 — *n*-ПГМ:МАҚ.

Диэлектрлік өтімділік пен полимерлердің ісіну дәрежелері арасында, нақтырақ айтқанда, орта полярлы ерітінділерден пиридинге қарай корреляция байқалады. Алайда ісіну дәрежесінің төмендеуі байқалмайды.

Пиридиннің әлсіз негізге жататынын (K_n=1.7·10^{-9}) атап өткен жөн. Пиридинннің химиялық қасиеттерін ескере отырып, оның донорлы еріткіштерге жататынын және бұның, өз кезегінде, сулы-пиридинді ортада полиэлектролиттердің (*n*-ЭГМ, *n*-ПГМ пен АҚ, МАҚ сополимерлері) ісіну дәрежесіне әсер ететінін атап өткен жөн. Сонымен қатар пиридинді гидрлеу кезінде күшті негізге жататын пипиридин түзіледі. Зерттелген электркаталитикалық жүйе үшін органикалық ерітінділердің 0,5 об.% дейінгі аралықта полимердің ісіну дәрежесі біркалыпты болатындығын ескерген жөн. Бізге қажетті үрдіс жағдайында ерітіндегі пиридиннің мөлшері 0,3 об.%-тен аспайды және пиридин:су қатынасы тек қана азая береді.

Қорытынды

Осылайша, жүргізілген тәжірибелер нәтижесі металл-полимерлі комплекстердің ісіну дәрежесіне температураның ықпалы мардымсыз екенін көрсетеді. Полиэтилен(пропилен)гликольмалеинат негізіндегі жаңа металл-полимерлі комплекстер сілтілік ортада ісіну дәрежесінің жоғары мәнге ие болып, еріткіштердің полярлығы өскен сайын ісіну дәрежесі де артатындығы байқалады.

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Моделирование условий реакции синтеза органических соединений и поведения в этих условиях полимерного комплекса

Структура и состав гидрогелей на основе ненасыщенных полиэфирных смол с ненасыщенными карбоновыми кислотами были изучены на электронно-растровом микроскопе. Доказаны их пористая структура и использование их в качестве матрицы для иммобилизации частиц металла. Далее приведены результаты влияния таких внешних факторов, как температура, pH среды и природа растворителей на новые металл-полимерные комплексы на основе полиэтилен-(пропилен)гликольмалеинатов. Экспериментальные результаты показали, что влияние температуры на степень набухания металл-полимерных комплексов незначительно. Данные комплексы показывают высокую степень набухания в щелочной среде, а с увеличением полярности растворителей наблюдается возрастание степени набухания. Высокие показатели набухающей способности металл полимерного комплекса в щелочной среде положительно скажутся на результатах электрокаталитического гидрирования, так как с ростом набухающей способности МПК увеличится и доступность молекул субстрата катализатору. Наблюдается определенная корреляция между диэлектрической проницаемостью и степенью набухания полимеров, в частности, при переходе от растворителей со средней полярностью к пиридину. Однако столь значительного уменьшения степени набухания нет.

Ключевые слова: полиэтиленгликольмалеинат, полипропиленгликольмалеинат, ненасыщенная полиэфирная смола, катализ, наночастицы, нанореактор, катализатор, металл-полимерный комплекс, полимерная матрица, электрокаталитическое гидрирование.

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Simulation of the synthesis reaction conditions of organic compounds and the behavior of the polymer complex under these conditions

The structure and composition of the hydrogels on the basis on unsaturated polyester resins with unsaturated carboxylic acids have been studied by scanning electron microscope. It was proved that their porous structure and their use as a matrix for immobilization of the metal particles. The results of the influence of external factors such as temperature, pH and the nature of the solvent on the new metal-polymer complexes on the basis of polyethylene (propylene) glycol maleate are shown in the article. The experimental data showed that the effect of temperature on the degree of swelling of the polymer-metal complexes are insignificant. These complexes exhibit a high degree of swelling in alkaline medium, and with increasing solvent polarity increase the degree of swelling is observed. High indexes of swelling ability of metal-polymeric complex in an alkaline medium have a positive impact on the results of the electrocatalytic hydrogenation, as with increasing swelling ability of MPC availability of substrate molecular to catalyst increases. There is a definite correlation between the dielectric constant and the degree of polymers swelling, in particular during the transition from solvents with an average polarity to pyridine. However, there is not such a significant reduction in the swelling degree.

Keywords: poly (ethylene glycol maleate), poly (propylene glycol maleate), unsaturated polyester resins, catalysis, nanoparticles, nanoreactor, catalyst, metal-polymeric complex, polymer matrix, electrocatalytic hydrogenation.

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УДК 547.823:615.212

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Направленный синтез С- и N-замещенных фенилоксипропинилпиперидинов с противоинфекционным действием

Конденсацией 1-(метил-, пропил-, бензил- и 2-фенилэтил)пиперидин-4-онов с феноксипропаргилом в условиях реакции Фаворского в абсолютном бензоле в присутствии пятикратного избытка порошкообразного технического КОН при соотношении пиперидон-4: феноксипрорпаргил=1:1,5 получены соответствующие 4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-олы. При ацилировании третичных феноксипропиниловых пиперидолов циклопропанкарбонилхлоридом в диоксане при комнатной температуре или нагревании образуются соответствующие гидрохлориды сложных эфиров. Строение синтезированных соединений подтверждено данными спектроскопии ЯМР и ИКС. Показано, что гидрохлорид 1-метил-4-(3-феноксипропин-1-ил)-4-циклопропанкарбонилоксипиперидина) проявил противомикробную активность *in vitro* в отношении *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC-BAA-196, *Klebsiella pneumoniae* ATCC 10031, *Klebsiella pneumoniae* ATCC 700603, *Staphylococcus aureus* ATCC 6538-P, *Staphylococcus aureus* ATCC-BAA-39, *Candida albicans* ATCC 10231. Гидрохлорид 1-пропил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина подавлял рост музейных штаммов микроорганизмов, кроме *Klebsiella pneumoniae* ATCC 700603.

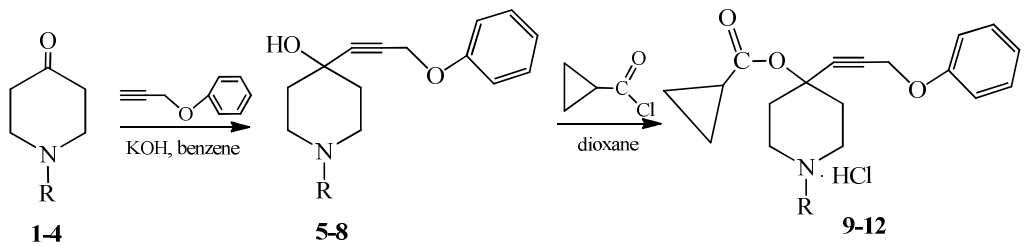
Ключевые слова: феноксипропаргилпиперидин-4-ол, циклопропанкарбонилхлорид, сложные эфиры, противомикробная активность, реакция Фаворского.

Поиск новых соединений с антимикробным и вирулицидным действием, в том числе обладающих способностью вызывать реверсию лекарственной чувствительности, относится к приоритетному направлению в области разработки новых противоинфекционных препаратов. Актуальность НИР, несмотря на большой ассортимент антибактериальных лекарственных средств, связана, в первую очередь, с высокой приспособляемостью патогенных организмов к ним, включая антибиотики [1–3].

Рациональным путем поиска эффективных биологически активных соединений (БАС) признано направленное конструирование новых молекул из фармакофорных структурных фрагментов, среди которых лидирующие позиции занимают насыщенные азотистые гетероциклы, являющиеся синтетическими аналогами природных алкалоидов. Разнообразные по строению алкилокси-, арилокси- и гетераарилоксипропинилкарбинолы [4–7] зарекомендовали себя как удобные реакционноспособные «строительные» блоки в органическом синтезе, в том числе и для БАС.

Основанием для проведения настоящих исследований явилась высокая биологическая активность синтезированных ранее сложных эфиров 1-(2-этоксиэтил)-4-гидрокси-4-[3-(арилокси)пропин-1-ил]-пиперидинов [8]. Цель НИР заключается в направленном синтезе новых феноксипропаргилпиперидинов с потенциальной антибактериальной активностью варьированием природы заместителя у атома азота и введением в молекулы дополнительного фармакофора — циклопропанкарбонила [9–12].

Конденсация 1-метил-, 1-пропил-, 1-бензил-, 1-(2-фенилэтил)-4-оксопиперидинов (**1–4**) с феноксипропаргилом в условиях реакции Фаворского [13, 14] приводит к третичным феноксипропаргиловым спиртам (**5–8**).



1-4 **5-8** **9-12**

R= CH_3 (**1, 5** [13]**, 9**); C_3H_7 (**2, 6, 10**); CH_2—C$_6$H$_5$ (**3, 7** [14]**, 11**); H_2CH_2C—C$_6$H$_5$ (**4, 8, 12**)

Оптимальными параметрами реакции оказались соотношение пиперидон:фенилоксипропин =1:5, абсолютный бензол, пятикратный избыток технического едкого калия, при которых фенилоксипропинилпиперидолы получены с хорошими выходами (табл. 1).

Ацилирование феноксипропиниловых пиперидолов (**5–8**) взятым в избытке циклопропанкарбонилхлоридом проводят при комнатной температуре или нагревании в диоксане. Сложные эфиры циклопропанкарбоновой кислоты (**9–12**) представляют собой белые кристаллические порошки, хорошо растворимые в воде, этаноле и ацетоне.

Состав и строение синтезированных соединений (**6**, **8**, **9–12**) подтверждены данными элементного анализа, ИК спектроскопии, спектроскопии ЯМР ^{13}C, индивидуальность — тонкослойной хроматографией (табл. 1).

Таблица 1

Выходы и физико-химические характеристики соединений 6, 8, 9–12

№ соединения	Выход, %	R_f	$t_{пл.}$, °C	Найдено, % / Вычислено, %		Брутто-формула	ИК спектр, $см^{-1}$	
				C	H		OH	C=O
6	70,3	0,48	масло	75,01 / 74,69	7,91 / 8,48	$C_{17}H_{23}NO_2$	3574	–
8	95,0	0,51	112–114	78,91 / 78,70	7,89 / 7,51	$C_{22}H_{25}NO_2$	3605	–
9	66,4	0,83	181–183	64,92 / 65,23	7,24 / 6,91	$C_{19}H_{24}NO_3Cl$	–	1738
10	29,6	0,91	167–169	67,01 / 66,68	7,09 / 7,41	$C_{21}H_{28}NO_3Cl$	–	1732
11	83,0	0,82	163–165	70,20 / 70,49	6,91 / 6,62	$C_{25}H_{28}NO_3Cl$	–	1731
12	61,6	0,81	143–144	71,22 / 70,91	6,53 / 6,82	$C_{26}H_{30}NO_3Cl$	–	1727

В ИК-спектрах пиперидолов (**6, 8**) проявляются полосы поглощения валентных колебаний гидроксильной группы в области 3574–3605 $см^{-1}$, ароматического кольца 688–752 $см^{-1}$. Интенсивные полосы поглощения при 1727–1738 $см^{-1}$, обусловленные колебаниями С=О сложноэфирной группы, свидетельствуют об образовании целевых эфиров 4-феноксипропинил пиперидол-4-ов циклопропанкарбоновой кислоты (**9–12**).

В таблицах 2 и 3 приведены значения химических сдвигов протонов и атомов углерода, которые полностью подтверждают углеводородный состав сложных эфиров 4-феноксипропинил пиперидол-4-ов циклопропанкарбоновой кислоты (**9–12**). В сильнопольной части спектров ЯМР ^1H (0,78–1,63 м.д.) наблюдаются сигналы протонов циклопропильного фрагмента, а в слабопольной области спектров **9–12** (6,93–7,31 м.д.) резонируют протоны фенильного радикала (OPh), для N-бензильного (**11**) и N-фенилэтильного (**12**) производных появляется дополнительный набор сигналов метиновых протонов еще одного фенильного кольца. Оксиметиленовые протоны проявляются в виде синглетов в области 4,83–4,84 м.д., протоны пиперидинового цикла резонируют при 2,09–3,57 м.д. в виде неразрешенных мультиплетов.

Таблица 2

Значения химических сдвигов протонов в спектрах ЯМР ^1H эфиров 4-феноксипропинилпиперидол-4-ов циклопропанкарбоновой кислоты (9–12)

№ соединения	Химические сдвиги ($CDCl_3$), δ, м.д.							
	H-2,6a	H-2,6e	H-3,5a	H-3,5e	O-CH_2	H cyclopropan	OPh	N-R
9	2.92 dm	3,31 dm	2,32 m	2.46 m	4,83 d	0,78–0,87 m; 1,60 d	6,93–7,28 d	2,60 **N-CH_3**
10	3,34 dm	3,43 dm	2,09 m	2,35 m	4,84 d	0,87–0,99 m; 1,59	6,91–7,31d	2,91; 1,68; 1,63 **N-$CH_2CH_2CH_3$**
11	2,89 m	3,18 m	2,35 dm	2,46 m	4,88 d	0,77–0,86 m; 1,59 m	6,90–7,41	4,22; 6,92–7,62 **N-CH_2Ph**
12	3,52 m	3,57 m	2,33 m	2,46 m	4,84 d	0,78–1,02 m; 1,63 m	6,93–7,31	2,99;3,75; [6,93–7,33] **N-CH_2CH_2Ph**

Таблица 3

Значения химических сдвигов атомов углерода в спектрах ЯМР ^{13}С эфиров 4-феноксипропинилпиперидол-4-ов циклопропанкарбоновой кислоты (9–12)

№ соединения	Химические сдвиги ($CDCl_3$), δ, м.д.										
	$C_{3,5}$	$C_{2,6}$	C_4	CH (cyclopropan)	CH_2 (cyclopropan)	C=O	≡C-CH_2	C_4-C≡	O-CH_2	OPh	N-R
9	33,16; 33,89	50,86; 48,74	71,22	13,61	8,99	172,62	81,88	85,97	56,06	115,5; 115,68; 121,8;129,9; 129,9; 157,7	42,24 N-CH_3
10	32,97; 33,70	47,02; 49,08	71,60	13,61	8,99	172,62	84,06	85,07	56,11	115,49; 115,65; 121,82; 129,94; 130,04; 157,5	57,18; 17,20;13,31 N-$CH_2CH_2CH_3$
11	33,55; 33,88	48,77; 48,95	71,61	13,30	8,99	172,55	81,87	85,93	56,06	(115,32; 129,95; 130,05); 157,75	58,75; (115,32; 129,95; 130,05); 132,05 N-CH_2Ph
12	33,09; 33,82	47,15; 49,19;	71,58	13,33	9,01	172,64	85,07	85,97	56,47	(115,49; 121,8; 130,1) 157,8	56,02;29,95; (115,49; 121,8; 130,1);137,72 N-CH_2CH_2Ph

В спектрах ЯМР ^{13}С (табл. 3) циклопропанкарбонилоксипроизводных (**9–12**) присутствуют синглетные сигналы атомов углерода сложноэфирного карбонила в области 171,55–172,64 м.д., синглетный сигнал C_4 резонирует в области 71,22–71,61 м.д., атом углерода метиленовой группы пропинового фрагмента проявляется в области 56,06–56,47 м.д. Слабопольная область (115–137 м.д.) спектров «населена» сигналами ароматических углеродов. Сильнопольные сигналы при 8,99–9,01 и 13,30–13,61 отнесены к углеродам циклопропанового кольца. Кроме того, наблюдается дублетный набор сигналов углеродов $C_{3,5}$ и $C_{2,6}$ соответственно при 32,97–33,89 м.д. и 47,02–50,86 м.д. пиперидинового цикла, связанных с замедленной инверсией последнего из-за объемных заместителей при C_4.

Экспериментальная химическая часть

Ход реакции и индивидуальность соединений контролировали методом ТСХ на Al_2O_3 II степени активности с проявлением пятен парами иода, элюент — бензол:диоксан — 4:1 или 3:2. ИК-спектры записаны на спектрометре «Nicolet 5 700 FT-IR» в таблетке с KBr. Спектры ЯМР в $CDCl_3$ записаны на спектрометре JNM-ECA400 производства компании «Jeol» (Япония) с рабочей частотой 400 МГц (^{1}H) и 100 МГц ($C^{13}C$).

1-пропил-4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-ол (**6**). В плоскодонную колбу, снабженную магнитной мешалкой, вносят 3,92 г (0,07 моль) порошкообразного едкого калия в 10 мл абсолютного бензола и через 10 мин при перемешивании прикапывают 9,03 мл (0,07 моль) 3-феноксипропина-1 в 15 мл абсолютного бензола. При этом наблюдается незначительное разогревание и изменение цвета раствора. Через 30 мин прикапывают 2,14 мл (0,014 моль) 1-пропилпиперидин-4-она (**2**) в 15 мл абсолютного бензола. Реакционную смесь перемешивают в течение 24 ч. В реакционную смесь добавляют 50 мл воды, хорошо встряхивают раствор, затем разделяют слои. Водный слой экстрагируют бензолом (5×30 мл). Органические слои объединяют, сушат сульфатом магния. Отфильтровывают осушитель, упаривают растворитель, остаток перекристаллизовывают из гексана. Получают 2,72 г (70,3 % от теоретического) 1-пропил-4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-ола (**6**) в виде масла светло-желтого цвета, R_f 0,48 (элюент — бензол:диоксан — 4:1).

1-(2-фенилэтил)-4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-ол (**8**). В плоскодонную колбу с магнитной мешалкой вносят 1,65 г (0,0295 моль) порошкообразного едкого калия в 10 мл абсолютного бензола и через 10 мин при перемешивании прикапывают 3,79 мл (0,0295 моль) 3-феноксипропина-1 в 15 мл абсолютного бензола. При этом наблюдается незначительное разогревание и изменение цвета раствора. Через 30 мин прикапывают 2 г (0,0098 моль) 1-(2-фенилэтил)-пиперидин-4-она (**4**) в 15 мл абсолютного бензола. Реакционную смесь перемешивают в течение 7–8 ч при комнатной температу-

ре. В реакционную смесь добавляют 50 мл дистиллированной воды, разделяют слои. Водный экстрагируют бензолом. Органические слои объединяют, сушат сульфатом магния. Отфильтровывают осушитель, упаривают растворитель, остаток перекристаллизовывают из гексана. Получают 1,88 г (95 % от теоретического) спирта (**8**) в виде белых кристаллов с т. пл. 112–114 ºС, R_f 0,51 (элюент — бензол:диоксан — 4:1).

Гидрохлорид 1-метил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**9**). Раствор 0,83 мл (0,0092 моль) циклопропанкарбонилхлорида в абсолютном диоксане медленно при перемешивании приливают к раствору 1,5 г (0,0061 моль) 1-метил-4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-ола (**5**) в абсолютном диоксане. При этом наблюдается разогревание реакционной смеси. Смесь выдерживают 24 ч при комнатной температуре. Отгоняют растворитель. Остаток промывают диэтиловым эфиром, перекристаллизовывают из изопропанола. Получают 1,42 г (66,4 % от теоретического) гидрохлорида 1-метил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**9**) в виде кристаллов с т. пл. 181–183 ºС, R_f 0,83 (Al_2O_3, элюент — бензол:диоксан — 3:2).

Гидрохлорид 1-пропил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**10**). Раствор 1,66 мл (0,0183 моль) циклопропанкарбонилхлорида в абсолютном диоксане медленно при перемешивании прикапывают к раствору 2,5 г (0,0091 моль) 1-пропил-4-(3-феноксипроп-1-ин-1-ил)-пиперидин-4-ола (**6**) в абсолютном диоксане. При этом наблюдается разогревание реакционной смеси. Смесь выдерживают в течение 3-х суток при комнатной температуре. Ход реакции контролируют по ТСХ. Отгоняют растворитель. Остаток промывают диэтиловым эфиром, перекристаллизовывают из изопропанола. Получают 0,74 г (29,60 % от теоретического) гидрохлорида 1-пропил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**10**) с т.пл. 167–169 ºС, R_f 0,91 (Al_2O_3, элюент — бензол:диоксан — 3:2).

Гидрохлорид 1-бензил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**11**). К раствору 1,5 г (0,0047 моль) 1-бензил-4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-ола (**7**) в абсолютном диоксане при перемешивании медленно прикапывают раствор 0,84 мл (0,0093 моль) циклопропанкарбонилхлорида в абсолютном диоксане. При этом наблюдается незначительное разогревание реакционной смеси, реакционную смесь нагревают при температуре ~50 ºС в течение 30 мин и выдерживают 24 ч при комнатной температуре. Отгоняют растворитель. Остаток промывают диэтиловым эфиром и перекристаллизовывают из изопропанола. Получают 1,64 г (83,0 % от теоретического) гидрохлорида 1-бензил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**11**) с т. пл. 163–166 ºС, R_f 0,82 (Al_2O_3, элюент — бензол:диоксан — 3:2).

Гидрохлорид 1-(2-фенилэтил)-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**12**). Смешивают горячие растворы 0,62 мл (0,0068 моль) циклопропанкарбонилхлорида в абсолютном диоксане с раствором 1,5 г (0,0045 моль) 1-(2-фенилэтил)-4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-ола (**8**) в абсолютном диоксане. Смесь продолжают перемешивать в течение 1 ч и выдерживают 24 ч при комнатной температуре. Отгоняют растворитель. Остаток промывают диэтиловым эфиром. Перекристаллизовывают из изопропанола. Получают 1,22 г (61,62 % от теоретического) гидрохлорида 1-(2-фенилэтил)-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**12**) с т. пл. 143–144 ºС, R_f 0,81 (Al_2O_3, элюент — бензол:диоксан — 3:2).

Исследование биологической активности

Гидрохлориды 1-метил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**9**, ПИП-36), 1-пропил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**10**, ПИП-37) и 1-(2-фенилэтил)-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина (**12**, ПИП-35) изучены на антимикробную активность в лаборатории микробиологии АО «Научный центр противоинфекционных препаратов». Результаты биологических испытаний представлены в таблице 4.

Оказалось, что ПИП-36 (**9**, гидрохлорид 1-метил-4-(3-феноксипропин-1-ил)-4-циклопропанкарбонилоксипиперидина) [15] обладает антимикробной активностью ко всем семи взятым в эксперимент музейным штаммам микроорганизмов: *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 10031, *Candida albicans* ATCC 10231 в концентрации (МИК 1000 мкг/мл), а в отношении *Escherichia coli* ATCC-BAA-196, *Klebsiella pneumoniae* ATCC 700603, *Staphylococcus aureus* ATCC 6538-P, *Staphylococcus aureus* ATCC-BAA-39 в концентрации (МИК 2000 мкг/мл). ПИП-37 (**10**, гидрохлорид 1-пропил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипипе-

ридина) подавляет рост 6 штаммов микроорганизмов, а в отношении *Klebsiella pneumoniae* ATCC 700603 оказался не активен.

Таблица 4

Антимикробная активность ПИП-35 – ПИП-37

Шифр соединения	Штамм						
	Escherichia coli ATCC 25922	*Escherichia coli* ATCC-BAA-196	*Klebsiella pneumonia* ATCC 10031	*Klebsiella pneumonia* ATCC 700603	*Staphylococcus aureus* ATCC 6538-P	*Staphylococcus aureus* ATCC-BAA-39	*Candida albicans* ATCC 10231
	МИК, мкг/мл						
9, ПИП-36	1000	2000	1000	2000	2000	2000	1000
10, ПИП-37	2000	2000	2000	НА	2000	2000	1000
12, ПИП-35	НА	НА	НА	НА	НА	НА	НА

Примечание. НА — не активен.

ПИП-35 (**12**, гидрохлорид 1-(2-фенилэтил)-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидина) не проявил противомикробную активность.

Экспериментальная биологическая часть

Синтезированные соединения (**9, 10, 12**) под шифрами ПИП-35, ПИП-36 и ПИП-37 изучены на противомикробную активность в отношении музейных штаммов микроорганизмов, оценены действия данных препаратов *in vitro* в отношении *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC-BAA-196, *Klebsiella pneumoniae* ATCC 10031, *Klebsiella pneumoniae* ATCC 700603, *Staphylococcus aureus* ATCC 6538-P, *Staphylococcus aureus* ATCC-BAA-39, *Candida albicans* ATCC 10231. Модель исследования включает в себя необходимый минимум тестов с различной степенью чувствительности *in vitro* [14]. Схема исследования проводится в соответствии с действующими на территории Республики Казахстан методическими рекомендациями, утвержденными Государственным Фармакологическим комитетом Республики Казахстан [16, 17].

Подготовка музейных культур к исследованию: реактивация, проверка жизнеспособности и контроль физиолого-биохимических свойств. Перед началом эксперимента микроорганизмы подверглись реактивации (оживлению) с последующим субкультивированием. Для определения жизнеспособности взятых в эксперимент микроорганизмов использовали метод Коха. Установлено, что все штаммы обладают хорошей жизнеспособностью, превышающей 10^{11} КОЕ/мл.

Определение минимальной ингибирующей концентрации (МИК) препаратов ПИП. Оценку минимальной ингибирующей концентрации (МИК) в отношении взятых в эксперимент микроорганизмов проводили по общепринятому методу двукратных серийных разведений в бульоне Мюллера-Хинтона. Для приготовления базовых растворов ПИП-35, ПИП-36 и ПИП-37 в концентрации 4000 мкг/мл, навеску 0,2 г растворили в 50 мл 0,9 %-ного раствора хлорида натрия. Далее готовили двукратные серийные разведения от 2000 мкг/мл до 2 мкг/мл (2000 мкг/мл, 1000 мкг/мл, 500 мкг/мл, 250 мкг/мл, 125 мкг/мл, 63 мкг/мл, 31 мкг/мл, 16 мкг/мл, 8 мкг/мл, 4 мкг/мл, 2 мкг/мл). В приготовленные разведения вносили свежеприготовленную суспензию микроорганизма в концентрации 10^6 КОЕ/мл. Контролем служила пробирка, содержащая питательную среду с тестируемым штаммом. Посевы инкубировали в термостате при 37 ºС в течение 18–24 ч. По истечении времени инкубации с каждого разведения произведен высев на чашки Петри, содержащие агар Мюллера-Хинтона. Чашки Петри с посевами инкубировали при температуре 37 ºС в течение 18–24 ч. МИК определяли по наименьшей концентрации ПИП-35, ПИП-36 и ПИП-37 которая подавляла видимый рост тестируемого микроорганизма.

В контрольном опыте наблюдался обильный рост тестируемых штаммов.

Заключение

Таким образом, показано, что направленное введение циклопропанкарбонильного фрагмента в структуру феноксипропинилпиперидина привело к соединениям с притотивоинфекционной активностью. Замена метильной группы у атома азота препарата ПИП-36 на пропильную (препарат

ПИП-37) приводит к ослаблению антимикробной активности, а замена на фенилэтильную группу (препарат ПИП-35) — к полной потере антимикробной активности.

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Инфекцияға қарсы әсерлі С- және N-орынбасқан фенилоксипропинилпиперидиндердің бағытты синтезі

Фаворский реакциясы жағдайында абсолютті бензолда бес есе артық мөлшерде алынған ұнтақ тәрізді техникалық КОН қатысында пиперидон-4:феноксипрорпаргил=1:1,5 қатынасында [1-метил-, 1-пропил-, 1-бензил-, 1-фенилэтил-]-пиперидин-4-ондарды феноксипропаргилмен конденсациялау арқылы сәйкес 4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-олдар синтезделініп алынды. Үшіншілік феноксипропинилді пиперидолдарды циклопропанкарбонилхлоридпен диоксанда бөлме температурасында немесе қыздырып ацилдеу барысында сәйкес күрделі эфирлердің гидрохлоридтері түзілді. Синтезделініп алынған қосылыстардың құрылысы ЯМР және ИҚС спектроскопия мәліметтері бойынша дәлелденді. 1-метил-4-(3-феноксипропин-1-ил)-4-циклопропанкарбонилоксипиперидин гидрохлоридінің *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC-BAA-196, *Klebsiella pneumoniae* ATCC 10031, Klebsiella pneumoniae ATCC 700603, *Staphylococcus aureus* ATCC 6538-P, *Staphylococcus aureus* ATCC-BAA-39, *Candida albicans* ATCC 10231 қатысты микробқа қарсы *in vitro* белсенділік

көрсететіні анықталды. 1-Пропил-4-(3-феноксипроп-1-ин-1-ил)-4-циклопропанкарбонилоксипиперидин гидрохлориді, *Klebsiella pneumoniae* ATCC 700603 басқа микроағзалардың мұражайлық штаммдарының өсуін тежеді.

Кілт сөздер: феноксипропаргилпиперидин-4-ол, циклопропанкарбонилхлорид, күрделі эфирлер, микробқа қарсы белсенділік, Фаворский реакциясы.

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Target synthesis of C- and N-subsituted phenyloxypropynylpiperidines possessing an anti-infective action

Several 1-(methyl- propyl-, benzyl and 2-phenethyl)-4-(3-phenoxyprop-1-yn-1-yl)piperidin-4-ols had been prepared by the condensation of corresponding piperidin-4-ones with phenoxypropargyl in the Favorsky reaction conditions in absolute benzene in the presence of a fivefold excess of powdered technical KOH at the piperidone-4:phenoxypropargyl ratio = 1:1,5. The acylation of phenoxypropynylpiperidols by cyclopropanecarbonyl chloride in dioxane at room temperature or by heating led to the esters as hydrochlorides. The structure of the synthesized compounds was confirmed by NMR and IR spectroscopy data. It had been found *in vitro* antimicrobial activity of 1-methyl-4-(3-phenoxypropin-1-yl)-4-cyclopropanecarbonyloxypiperidine hydrochloride against *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC-BAA-196, *Klebsiella pneumoniae* ATCC 10031, *Klebsiella Pneumoniae* ATCC 700603, *Staphylococcus aureus* ATCC 6538-P, *Staphylococcus aureus* ATCC-BAA-39, *Candida albicans* ATCC 10231. Hydrochloride of 1-propyl-4-(3-phenoxyprop-1-yn-1-yl)-4-cyclopropanecarbonyloxypiperidine inhibited growth Museum strains of microorganisms except *Klebsiella pneumoniae* ATCC 700603.

Keywords: Phenoxypropynylpiperidin-4-ol, cyclopropanecarbonyl chloride, esters, an anti-infective activity, Favorsky reaction.

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UDC 548.512+546.05

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Determination of the nature of the interaction of calcium ions with amino acids by potentiometric titration

In work on the basis of potentiometric titration, the features of interaction of Ca^{2+} calcium ions with amino acids (AC), which are involved in biochemical processes in the human body, are established. The regularities of the complexes formed in the «Ca^{2+}-AC» system are studied theoretically by the example of mixtures of calcium nitrate with isoleucine (Ile), arginine (Arg), aspartic acid (Asn), glycine (Gly), alanine (Ala). The conditions for titration are chosen, under which the destruction of the complex occurs. By results, semi-quantitative characteristics of the interaction of Ca^{2+} and the studied AC were established. It was shown that the stability of the complexes increases with increasing number of carboxyl groups –COOH and nitrogen-containing groups in the AC molecule (especially NH_2 groups in the α-position), and with the increase in the length of the carbon skeleton of the molecule and the appearance of bulky substituents — decreases. Also, on the base of insertion of the new criteria δ are established comparative rates of lability of complexes. According to their lability, complexes of Ca^{2+} with these amino acids are located in the next order: δ (Ca^{2+} – Asp) < δ (Ca^{2+} – Ile) < δ (Ca^{2+} – Ala) < δ (Ca^{2+} – Arg) < δ (Ca^{2+} – Gly).

Keywords: complexation, amino acids, bioorganic ligands, potentiometric titration, modeling, stability constants, calcuim, lability.

Nowadays, the trend that matches with the studying of the principles of processes which are happening in the alive systems, becomes one of the most leading in the current scientific reaserches. It's exactly, because actual negative factors of the technosphere (social risks, conflicts and stresses, impact of noise, vibrations, malnutrition, ecological risks, manufacture hazards, physical inactivity etc.) could disengage complex system of organic and inorganic substances that exist in the human body in a certain balance [1–7]. At the same time, the growth of the number of diseases which are linked with the formation of, for example, pathogenic organomineral aggregates (POA) in the human body is 0,5–5,5 % per year [1; 8–10].

The key role in the processes that are characteristic for the human body is allotted for the calcium ions. In the ionic forms, the content of calcium in the human body is nearly 1 %. It takes fifth place by the abundance in vivo among chemical elements after carbon, nitrogen, oxygen and hydrogen. In the human and mammalian bodies 95 % of calcium is contained in the solid tissues: bones and tooth, where he stands in the form of fluorapatite $Ca_5(PO_4)_3F$ and hydroxylapatite $Ca_5(PO_4)_3OH$; in the birds and mollusk organism prevailing type of form is calcuim carbonate. On the surface of the blood vessel wall and arteries calcium can be found in the form of calcium carbonate or in the complex with the cholesterol, and in the kidneys — in the forms of oxalate or urates (salts of uric acids) [11]. Calcium ion is primary component not only in quantitative, but even in functional relation. He takes part in the processes of the transferring of nerve impulses, provides equilibrium between processes of excitation and stopping in the cortex, participates in the regulation of contractility of skeletal muscles and heart muscle, takes influence on acid-base equilibrium in organism and on activity of some enzimes [1; 6–10].

It must be noted that in the human body Ca^{2+} stands in the continuous interaction between thw organic and inorganic constitutions of biofluids, including the amino acids. At the time of impaction of negative factors which are highlighted before, interaction between the ions of calcium and amino acids could be disrupted. In particular, researches [1, 8–10, 12–18 etc.] confirm that POA have organic constituents in their own composition. Authors [19] in their work try to find out possible conditions of dissolution of amino acids which were previously adsorbed on biological substrate. Also, interaction between Ca^{2+} with the biological enzimes, which are accelerate processes of reaction of calcium ions with the organic constituents of the human body, was researched on the molecular level [20]. We have understanding of behavior of amino acids in the solution with the organic salts of sodium, potassium and calcium [21]. However, to prevent human body from the possible repercussions which are related with the pathogenic mineral aggregation and another diseases, disturbance of musculoskeletal system, fragility of bones, weakening of immunity and increased fatigue of organism, on the first stage we should now semi-quantitative and quantitative characteristics of interaction of components which are taking part in the functioning of the vital activity, in particular, between such a components as biogenic calcium-ion and amino acid.

Because most of the POA are introduced by the salts of calcium, a lot of investigators are noting that just specificity of organic constituent, partially, Ca^{2+} and amino acid, mostly controls the process of phase formation in the human body [9, 10, 12–18 etc.]. But, nowadays there is no unified theory which could explain the nature of interaction between organic and inorganic constituents of POA.

According to this, the aim of present work is development of methodology for the establishment of the behavior of the interaction between Ca^{2+} and amino acid which are take part in the metabolism. Also, very important thing is to find out pattern between the structure of the majority of amino acids and their specific interaction with the calcium ions.

Experimental part

General issues. Quantitative criteria of the interaction of these components is overall stability constant which can be calculated by the following formula:

$$M + nL \rightleftarrows [ML_n];$$

$$\beta_n = \frac{[ML_n]}{[M][L]^n}, \quad (1)$$

where β — overall stability constant of all complexes in all existing forms; $[ML_n]$ — equilibrium concentration of the formed complex of calcium and amino acid; $[M]$ — equilibrium concentration of free metal in the ionic form in the solution; $[L]^n$ — equilibrium concentration of free ligand in the solution.

To determine its value, in the most of the cases are used spectrophotometric, ion-exchange and polarographic methods [6, 22]. But, as it was said before, the object of analysis is difficult and little-learned system, and format of interaction «Ca^{2+} – Amino acid» is not obvious as in the most cases of complexion. There must be created methods which would be sensitive, precise, quick and selective for another components of the system. Possible way of such a evaluating could become using of potentiometric titration of mixes of Ca^{2+} and amino acids by the solution of sodium hydroxide NaOH with the following decoding of experimental data.

Materials and methods. In the present study were used aminoacetic acid (glycine, Gly), aminopropanoic acid (alanine, Ala), 2-amino-3-carbamoylpropanoic acid (aspartic acid, Asn), 2-amino-5-(diamino-methylideneamino) pentanoic acid (arginine, Arg), 2-amino-3-methylpentanoic acid (isoleucine, Ile) (all are «chemically pure»), their main characteristics are introduces in the Table 1, calcium chloride $CaCl_2$ («ch.p.»). Researchment of interaction between Ca^{2+} and amino acid was conducted at the $T = 298$ K by the potentiometric titration with the ion-selective electrode *ЭЛИС-121Ca*, the possibility of its applying as a selective for calcium ions is pointed in the work [23].

Silver/silver chloride electrode *ЭСр-10103* in this work was used as a reference electrode. The measuring electrode was Ionomer *И-160-МИ*, whose precision of measuring e.m.f. is ± 0.1 mV. Precision of potentiometric titration as a method is enough (overall error of determination is 0.5–1.0 %) to define nature of interaction of amino acids and calcium ions [24].

Before and after every series of titration potentiometric unit was calibrated by dint of the standard aqua solutions of calcium nitrate ($C_{Ca(NO_3)_2} = 10^{-2}$, 10^{-3}, 10^{-4} mole per liter) under the fixed value of ionic strength $I = 0.5$ mole per litre (KNO_3 was an ionic medium).

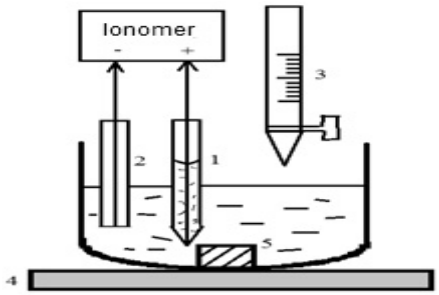
The stock solutions of amino acids and $CaCl_2$ were prepared from samples of solid substances, which were selected with the precision to 10^{-4} g; the samples were completely transferred in the volumetric flask and were dissolved, after that flask was filled by the distill water to the label. The mass of the samples were determined with a view to reach concentrations $C_{\text{amino acid}} = 10^{-2}$ mole per litre, $C_{Ca(NO_3)_2} = 10^{-3}$ mole per litre — it's optimum concentrations of salt and amino acid under which titration jumps have more obvious form. These values of concentrations were established experimentally by the authors.

In the case when solubility of amino acid in water is limited, the solution, before filling to the label, was heated till the full dissolution of precipitation.

During the titration, aliquot with the $V = 10.0$ ml of stock solutions of amino acid and $Ca(NO_3)_2$ consistently were placed in the volumetric flask with the volume $V = 100.0$ ml, then flask was filled by the distill water to the label. After that, content of the flask undergo mixing by dint of the apparatus of mixing of fluids during the 30 minutes. Finally, from the content of the flask was selected precise volume (20.0 ml) of process solution and was transferred in pure beaker. Content of the beaker was acidified to pH = 3 by dint of glass electrode.

Then, in the content of the beaker was immersed connected to ionomer И-160-МИ electrodes: calcium-selective electrode, reference electrode and temperature sensor. The first clean measure of e.m.f. of the solution was established in the range of ±0.1 mV during 3 minutes. The titration was conducted with the 0.5 ml-step from the burette, as titrant was used fresh solution of 0.10 M NaOH (its was standardized by the solution of HCl with the acid-base indicator phenolphthalein), the analytical signal was the value of e.m.f. in mV. The value of this criteria before every measure was established during 45 seconds. Titration was continued before the moment of starting of precipitation of $Ca(OH)_2$. The titration was conducted under intensive mix by dint of magnetic stirrer.

The principle scheme of potentiometric unit is depicted on Figure 1.



1 — Silver/silver chloride electrode; *2* — Glass electrode; *3* — Burette; *4* — Magnetic stirrer; *5* — Magnet

Figure 1. The principal scheme of potentiometric unit for titration aims

It was carried out 3 duplicating titrations, the values of e.m.f. were averaged [25]. Every amino acid was titrated separately from the other amino acids.

Results and discussion

According to these methodology, we have received potentiometric titration curves for highlighted amino acids (Table 1). To find out the form of amino acid in stock solution at constant pH, we have drawn ion percentage diagrams of studied amino acid, where along the abscissa is pointed pH, along the ordinate — shares of forms of amino acids (Table 2, Fig. 2).

For the aspartic acid ion diagram is drawn at the Figure 3, for the arginine — at the Figure 4. As values of $pKa_{(acid.)}$, except arginine, are standing in the range to pH < 3, amino acids in the aqua solutions before titration will stay predominantly in the form of zwitter-ion:

$$R - CH_2 - NH_2 - COOH \rightleftarrows R - CH_2 - NH_3^+ - COO^- \quad (2)$$

Arginine, besides α-NH_3^+ group, has in its composition guanidine group at the δ-carbon atom, and that's why arginine will stay predominantly in the cationic form at this pH in the aqua solutions [25]:

$$R^+ - CH_2 - NH_2 - COOH \rightleftarrows R^+ - CH_2 - NH_3^+ - COO^- \quad (3)$$

Table 1

The most common characteristics of amino acids, including the dissociation constants and the isoelectrical points

AA	Reduction	Formule	Structure
Glycine	Gly	$C_2H_5NO_2$	$H_2N–CH_2–COOH$
Alanine	Ala	$C_3H_7NO_2$	$CH_3–CH(NH_2)–COOH$
Aspartic acid	Asp	$C_4H_7NO_4$	$HOOC–CH_2–CH(NH_2)–COOH$
Isoleucine	Ile	$C_6H_{13}NO_2$	$CH_3–CH_2–CH(CH_3)–CH(NH_2)–COOH$
Arginine	Arg	$C_6H_{15}N_4O_2$	$H_2N–C(=NH)–NH–(CH_2)_3–CH(NH_2)–COOH$

Table 2

δ-values for all amino acids

Amino acid	δ
Glycine	6.3
Alanine	3.1
Aspartic acid	2.1
Isoleucine	2.2
Arginine	5.3

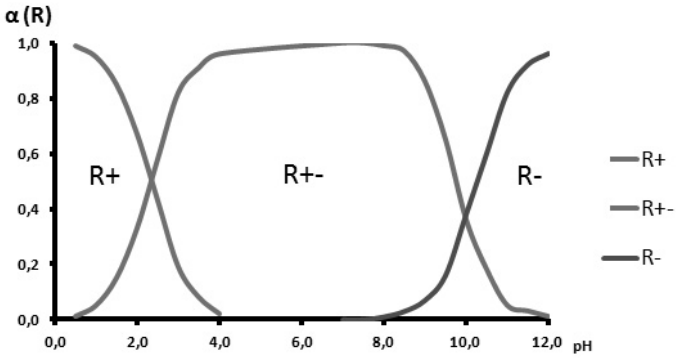


Figure 2. Ion diagram of forms at the different pH for amino acids, which don't have ionized links in the side groups (Isoleucine, Alanin, Glycine)

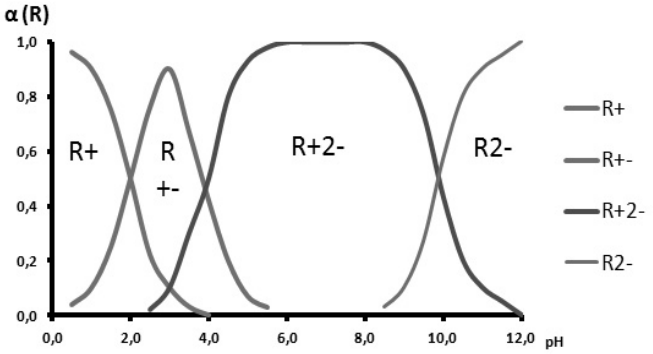


Figure 3. Ion diagram of forms of «acidic» amino acids

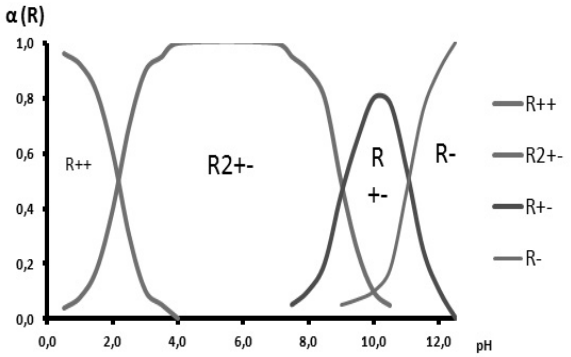


Figure 4. Ion diagram of forms of «basic» amino acids

To understand basic regularities of complexion of Ca^{2+} with amino acids, it will be needed to classify obtained curves into smaller groups which will be created by virtue of the structure of studied amino acids. Based on the experience of later researches [1, 8, 26, 27], we can predict that system in the system are formed complexes with the ratio Ca^{2+}:Amino acid — 1:1.

On the Figure 5 are introduced titration curves of $Ca(NO_3)_2$ and first group of amino acids (Isoleucine, Arginine, Aspartic Acid) by the aqua solution of sodium hydroxide.

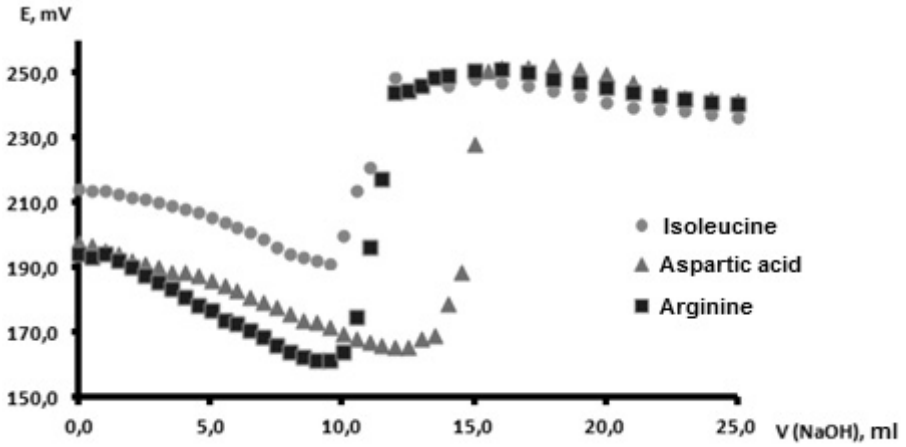


Figure 5. Potentiometric titration curves of calcium nitrate ($C_{Ca(NO_3)_2} = 10^{-3}$ mole per liter) and amino acids ($C_{\text{amino acid}} = 10^{-2}$ mole per liter)

Proceeding the form of curves, it could be predicted, that in system are flowing the following reactions:

On the first step, where is happening the mixing of solutions of $Ca(NO_3)_2$ with the solutions of the amino acids, usually form complexes, where Ca^{2+} perform a role of complexing agent and amino acids are playing a role of ligands (4, 5):

$$R - CH_2 - NH_3^+ - COO^- = L^{\pm};\ Ca^{2+} + L^{\pm} \rightleftarrows [CaL^{\pm}]^{2+} \quad (4)$$

For arginine

$$R^+ - CH_2 - NH_3^+ - COO^- = L^{\pm+};\ Ca^{2+} + L^{\pm+} \rightleftarrows [CaL^{\pm+}]^{2+} \quad (5)$$

In the start of titration adding of titrant causes small decrease of e.m.f. It is all because of the increasing of ionic strength, which reduces acivity of free ions of calcium. At the same time $[CaL^{\pm}]^{2+}$ and $[CaL^{\pm+}]^{2+}$ are staying stable.

At a certain moment, after another adding of portion of titrant, there is a sharp increase of e.m.f. It can be corresponded to the increase of concentration of unbounded calcium ions, which are releasing in the solution during the destruction of complex:

$$[CaL^{\pm}]^{2+} \rightleftarrows Ca^{2+} + L^{\pm} \quad (6)$$

For the arginine:

$$[CaL^{\pm+}]^{2+} \rightleftarrows Ca^{2+} + L^{\pm+} \quad (7)$$

It could be expected that in the equivalence point (eq.p.) 50 % of complex molecules are stable, 50 % — are destroyed, so, they have formation function $\bar{n} = 0.5$ [28].

After full destruction of the complex, e.m.f. starts to undergo small decrease again because of the increasing of ionic strength, which reduces acivity of free ions of calcium.

At a certain moment, pH of the solution increases to the 10–10.5, which leads to precipitation of insoluble calcium hydroxide (pSP = 5.26):

$$Ca^{2+} + 2OH^- \rightarrow Ca(OH)_2 \quad (8)$$

As in the eq.p. 50 % of molecules of previously formed complexes are destroying, volume of sodium hydroxide solution which was wasted on the titration to attain eq.p. can be some sort of semi-quantitative criteria of interaction between calcium ions and every of the amino acids. So, the more volume we have wasted, the more we need this to destroy complex and more stable the complex is. To explain the obtained results, we should return to the table 1. It should be noted that structural formulas of three amino acids above are differ between each other by: a) the number of carbon atoms in the structural formula; b) the nature of functional groups; c) location of the functional groups.

The molecule of isoleucine has 5 atoms of carbon in the main chain, contains one carboxyl (–COOH) group, one aminogroup ($–NH_2$), at α-position one methyl ($CH_3–$) group; the molecule of arginine has the same structure, but instead of methyl group, on another from carboxyl group ending of molecule is located

guanidine group NH_2–C(NH)–NH_2. Molecule of aspartic acid has smaller number of carbon atoms (4) in the structure and it doesn't have another group as previous two amino acids, but it contains two –COOH groups and one –NH_2 group at the same time.

On the Figure 5 seems obvious the fact that eq.p., if look on it from the side of volume of wasted titrant, eq.p. of the amino acids line up in the following row: $V_{Ile} < V_{Arg} < V_{Asn}$, what is more, V_{Ile} and V_{Arg} are slightly different from each other, and V_{Asn} is more different from previous volumes row.

According to the investigation of K.B. Yatsimirsky [29], calcium ions concerns to first group of cations for which complexing is carried out, predominantly, on account of oxygen atoms — –COOH-group of amino acid. Impaction of donor atoms of nitrogen for creating of coordinating bonds with calcium (II) is possible, although insignificant.

As values of volumes of sodium hydroxide, which are wasted on titration of complexes of Ca^{2+} with isoleucine and arginine, are approximately equal, it should be predicted that stability constants of present complexes have the similar values. At the same time, eq. p. on the titration curve of $Ca(NO_3)_2$ and aspartic acid is located far away from the origin than for first two amino acids, moreover, for the molecule of aspartic acid two –COOH groups at the same time. As it said before, coordination of hard ions of metals in reactions of complexing with the amino acids is carried out on account of oxygen atoms of carboxyl groups. Also, –COOH-group there is bidentate and forms a cyclic or bridge structures [30]:

Because the molecule have two carboxyl groups, it considered to be more strong ligand, and complex of Ca^{2+} with the aspartic acid is more stable than with previous amino acid, which is consisted with our data. In the second group of amino acids (Isoleucine, Alanine, Glycine) are observing next tendencies, which are submitted on the Figure 6.

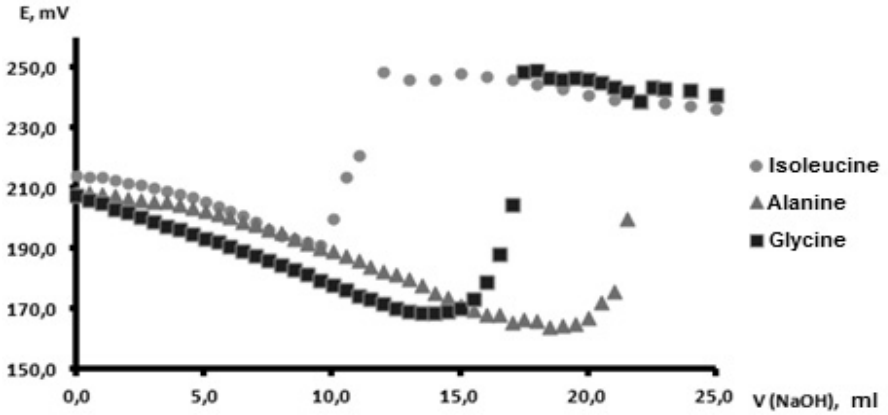


Figure 6. Potentiometric titration curves of calcium nitrate
($C_{Ca(NO_3)_2} = 10^{-3}$ mole per liter) and amino acids ($C_{\text{amino acid}} = 10^{-2}$ mole per liter)

All stages of the curves are the same as first group of amino acids. It is seen that eq. p. of titration curve of mix of Ca^{2+} and isoleucine is located significantly closer to the origin than for mixes of Ca^{2+} with alanine and glycine. In contrast to isoleucine, molecules of alanine and glycine are consisted from smaller number of atoms of carbon and they don't have big CH_3-alternates, which can come the steric obstacles for transferring of free s-orbitales of complexing agent Ca^{2+} to the electronic pairs of ligand. That's why complexes of Ca^{2+} with amino acids AK without any steric obstacles are more stable than those who have in its composition big alternates and more atoms of carbon in the main chain. Besides the investigation of titration curves of complexes, the experimental data were processed mathematically and we have obtained first and second derivatives of curves titration and derivative curves, which were described according to the Gran method.

In the Gran method eq.p. usually determines on graph in the coordinates: $V/\Delta E - V$, where ΔV is the step of titiration, ΔE — difference of the utmost points of e.m.f.; V — the volume of added titrant. Before eq. p. and after it curve of Gran is linear. Eq.p. serves as the point of the intersection of these lines. Advantages

and facilities of Gran method are especially obvious in the time of analysis of dilute solutions; they allow to obtain eq.p. with the require precise because of the linearity of the graph and in the cases, when curve isn't have a typical form [31].

As our experimental data are different from the classical potentionmetric titration curves, the Gran method was modified by the changing of criteria of axis of ordinates — there were a difference between the current e.m.f. value and the volume of the spent titrant and their values before the start of titration, respectively. This type of processing allows to avoid the misinterpretation of curves from the collateral processes, it's very convenient for analysis. For example, on the Figure 7 are illustrated differentiated titration curves for mixtures of $Ca(NO_3)_2$ with isoleucine and arginine.

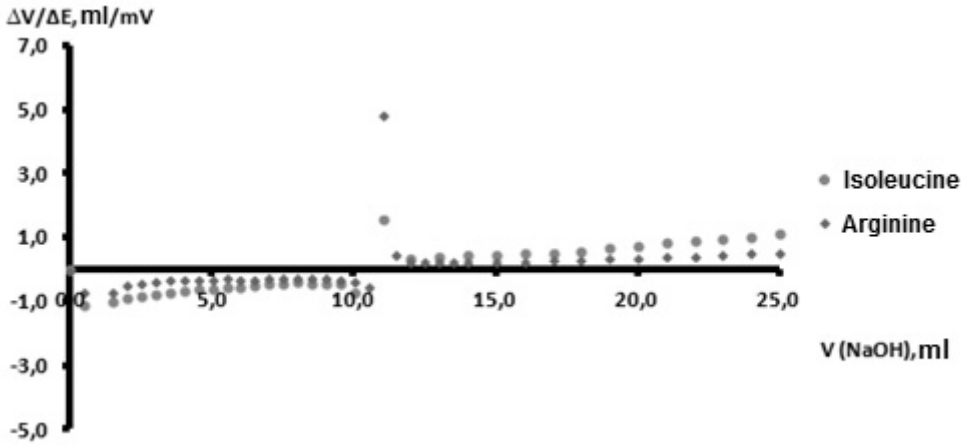


Figure 7. Differentiated titration curves, proceeded by the Gran method* of mixtures of $Ca(NO_3)_2$ ($C_{Ca(NO_3)_2} = 10^{-3}$ mole per liter) and amino acids ($C_{\text{amino acid}} = 10^{-2}$ mole per liter) by the solution of sodium hydroxide ($C_{NaOH} = 10^{-1}$ mole per liter)

The obtained curves as such could be used for semi-quantitative description of lability of complexes. To determine the degree of lability, we suggest semi-quantitative criteria, which can describe the behavior of the collapsing complex — δ, which is described by the following equation:

$$\delta = \frac{\Delta V}{\Delta E} \text{ after the eq.p.;} \quad -\frac{\Delta V}{\Delta E} \text{ before the eq.p.,} \tag{9}$$

where the first term is the relation of the above differences for the point, which is next after the eq.p., the second term — similarly for a point immediately up to the eq.p. So, the less δ is, the faster complex destroys and forms, so it's more labile, and on the turnover.

For every amino acid, according to its curve, was obtained the value of δ, all values were matched with each other. As we see, according to their lability, complexes of Ca^{2+} with these amino acid are formed the following row: δ (Ca^{2+} – Asp) < δ (Ca^{2+} – Ile) < δ (Ca^{2+} – Ala) < δ (Ca^{2+} – Arg) < δ (Ca^{2+} – Gly), so, the most labile complex is complex with the aspartic acid, with the isoleucine — the most stable.

Finally, the obtained results are in good agreement with the theoretical data of other studies [8; 25–27], which makes it possible to use this laboratory unit as a basic model for further complication and varying the experimental conditions for establishing the character of the interaction between calcium ions and amino acids.

Conclusions

1. A technique of potentiometric titration of amino acids and calcium salts is proposed.

2. The nature of all potentiometric titration curves is explained, possible processes, occurring in solutions with titrant addition, consistent with the theoretical data, are indicated.

3. On the example of solutions of calcium nitrate with a raw of amino acids (isoleucine, arginine, aspartic acid, alanine, glycine), the principal possibility of ranking by their potentiometric titration curves is shown.

4. Semiquantitative characteristics of the interaction of calcium ions and some amino acids, which can indicate: a) the stability of the complexes formed; b) their lability, are established.

Acknowledgments

The present study was carried out with the partial financial support of the Russian Foundation for Fundamental Research (№ 15–29–04839 офи_м and № 16–33–00684 project мол_а).

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Потенциометрлік титрлеу арқылы амин қышқылдары мен кальций иондарының өзара іс-қимыл сипатын құру

Мақалада потенциометрлік титрлеу негізінде адам ағзасындағы биохимиялық үрдістерге қатысатын кальций иондары (Ca^{2+}) және амин қышқылдарының (АС) өзара әрекеттесу ерекшеліктері қарастырылды. «Ca^{2+} – АС» жүйесінде пайда болатын кешен сипаты теориялық тұрғыда кальций нитраты изолейцин (Ile), аргинин (Arg), аспарагин қышқылы (Asn), глицин (Gly), аланин (Ala) қоспалары мысалында зерттелді. Кешен ыдырауына септесетін титрлеу шартттары талданды. Олардың нәтижелері бойынша зерттеліп отырған АС мен Ca^{2+} өзара әрекеттесуінің жартылай сандық сипаттары алынды. Амин қышқылы молекуласында карбоксилді топтар –COOH және азот құраушы топтар (әсіресе NH_2 тобының α-жағдайындағы) саны жоғарлаған сайын кешен тұрақтылығы артатыны, ал молекуланың көміртек қанқасының ұзындығы артқан сайын және көлемді орынбасушылардың пайда болуынан — азаятындығы белгілі болды. Сондай-ақ δ жаңа көрсеткіштерін енгізу негізінде комплекстер тұрақсыздығының салыстырмалы көрсеткіштері белгілі болды. Олардың қозуы тұрақсыздығына байланысты Ca^{2+} мен $\delta(Ca^{2+} – Asp) < \delta(Ca^{2+} – Ile) < \delta(Ca^{2+} – Ala) < \delta(Ca^{2+} – Arg) < \delta(Ca^{2+} – Gly)$ кешендері осы тәртіп бойынша тізбектелген.

Кілт сөздер: кешендер, амин қышқылдары, биоорганикалық лигандтар, потенциометрлік титрлеу, модельдеу, тұрақтылық, кальций, қозғыштық, тұрақсыздық.

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Установление характера взаимодействия ионов кальция с аминокислотами с помощью потенциометрического титрования

В статье на основе потенциометрического титрования установлены особенности взаимодействия ионов кальция (Ca^{2+}) с аминокислотами (АС), которые участвуют в биохимических процессах в организме человека. Характеристики комплексов, образующихся в системе «Ca^{2+} – АС», теоретически изучаются на примере смесей нитрата кальция с изолейцином (Ile), аргинином (Arg), аспарагиновой кислотой (Asn), глицином (Gly), аланином (Ala). Выбраны условия титрования, при которых происходит разрушение комплекса. По их результатам были установлены полуколичественные характеристики взаимодействия Ca^{2+} и изучаемых АС. Было показано, что стабильность комплексов возрастает с увеличением в молекуле аминокислоты числа карбоксильных групп –COOH и азотсодержащих групп (особенно группы NH_2 в α-положении), а с увеличением длины углеродного скелета молекулы и появлением объемных заместителей — уменьшается. Кроме того, на основе введения новых критериев δ установлены сравнительные показатели лабильности комплексов. Согласно их лабильности комплексы Ca^{2+} с этими аминокислотами расположены в следующем порядке: $\delta (Ca^{2+} – Asp) < \delta (Ca^{2+} – Ile) < \delta (Ca^{2+} – Ala) < \delta (Ca^{2+} – Arg) < \delta (Ca^{2+} – Gly)$.

Ключевые слова: комплексообразование, аминокислоты, биоорганические лиганды, потенциометрическое титрование, моделирование, константы устойчивости, кальций, лабильность.

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UDC 678.7–139

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Processing of hydrogel isotermic data on the base of polymethyl vinyl ether of maleic acid cross linked with polypropylene glycol under thermogravimetric data

Comparative kinetic analysis by NPK method

Analysis of different computational methods for kinetic parameters of hydrogel thermal degradation on the base of polymethyl vinyl ether of maleic acid cross linked with polypropylene glycol under thermogravimetric data is presented. Researches were made in a nitrogen and air atmosphere at different heating rates: 6, 10, 12 and 16 K/min. It was demonstrated that it makes sense to apply approaches of Friedman, Ozawa-Flynn-Wall, related to group of isoconversion methods. Obtained data indicate decentish coincidence between values of activation energy obtained by different methods. To get complete kinetic analysis, it is necessary to process data applying the method of non-parametric kinetics. Non-parametric kinetics method (NPK) is a special approach for processing of kinetic data. Method is a new viewpoint to kinetic analysis, which is based upon rounding of results of single-stage process kinetics. Experimental values of response time are located in the matrix, which is expressed as multiplication of two vectors, containing the information on $f(T)$ and $g(\alpha)$.

Keywords: dynamic thermogravimetry, thermal analysis, thermal destruction, hydrogel.

Introduction

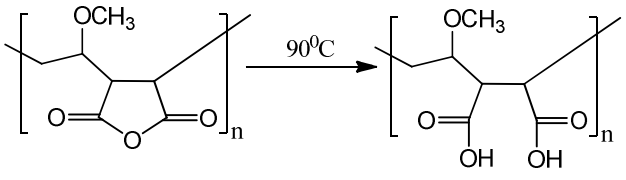
Using the method of differential thermal analysis, we can identify such important parameters of polymers as phase transitions, radiation damages in polymeric materials, the heat of absorption and polymerization of the cross-linking, oxygenation and decomposition processes, concentration of the registered components of impurities etc [1].

High accuracy and sensitivity of the differential scanning calorimeter allow us to determine phase transitions of oxygenation and decomposition processes and etc., when we use samples of high-molecular composition which masses are equal to a few milligrams [2]. Of course, that the determination of kinetic parameters of decomposition reactions of polymers in isothermal conditions gives more accurate and valid results, but this method is labor consuming and requires considerable time and the use of large number of samples.

Goal of this work is to study and compose the academic kinetic model of hydrogel thermal decomposition on the basis of polymethyl vinyl ether of maleic acid cross linked with polypropylene glycol by nonlinear regression of thermo gravimetric analysis (TGA) isothermal curves.

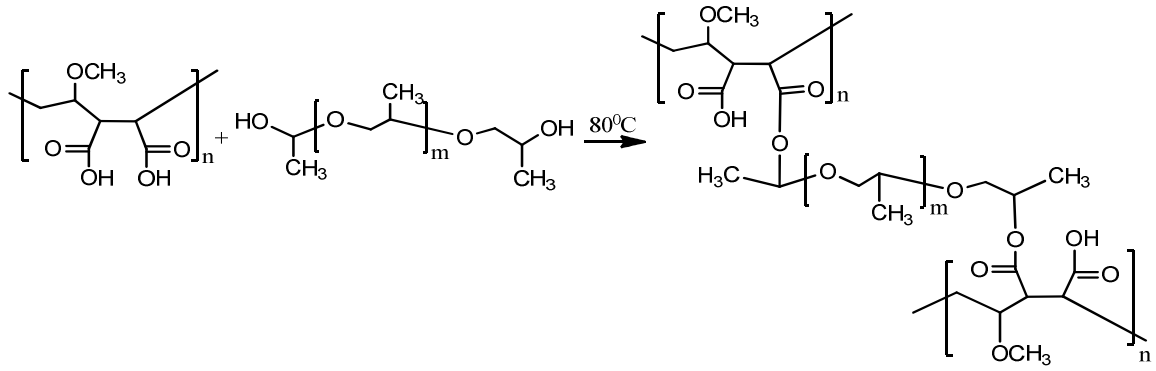
Experimental

Poly(methyl-vinyl-co-maleic acid) or polymethylvinyl maleic acid ether (PMVE-MA) was obtained by hydrolysis polymethylvinyl ether of maleic anhydride (PMVE-MAH):



Process was held on assembly of round-bottomed flask with volume of 100 ml and backflow condenser. Base mixture was prepared of 0.6500 g of PMVE-MAH and 20 ml of distilled water. Hydrolysis was carried at the temperature of 90 ºC during 2 hours. Gradually water solution of polypropylene glycol (PPG) was added to generated polymethylvinyl maleic acid ether (PMVE-MA) up to obtaining of homogenic mixture. Excess water was drained with rotary evaporator. Reaction mixture was firmed for 24 hours at 80 ºC. In the

result of etherification reaction between polymethylvinyl maleic acid ether and polypropylene glycol gel PMVE-MA with PPG was formed:



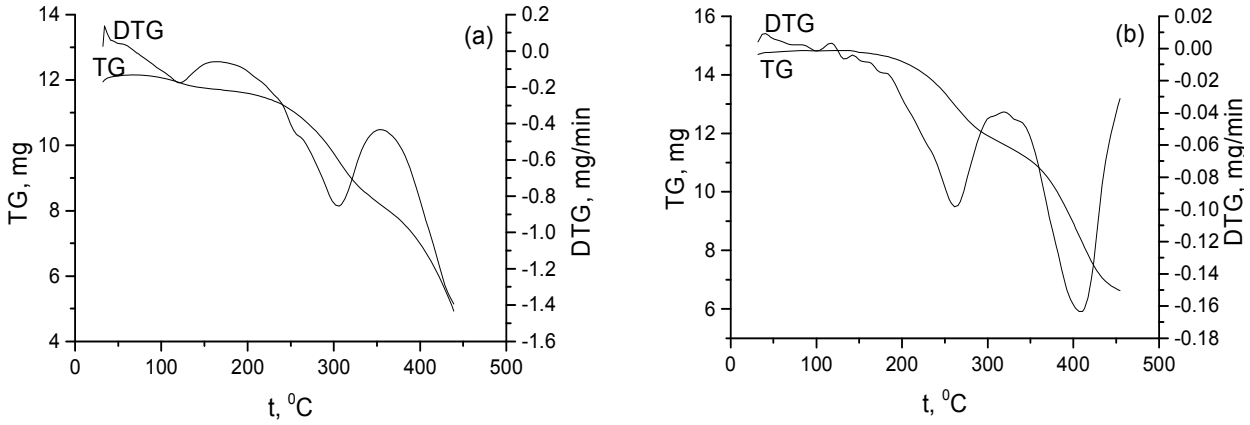
Study of hydrogel thermal properties was made with differential scanning calorimeter Labsys Evolution DTA/DSC of «Setaram» brand in dynamic regime with temperature range of 0–500 ^{0}C with heating rate of 6, 10, 12 и 16 K/min in atmosphere of air and nitrogen in melter Al_2O_3.

All these calculations were performed with the use of the program MATLAB.

Results and discussion

Active substances were obtained by TGA analysis at heating rates β=6, 10, 12 and 16 K/min in a nitrogen and air atmosphere. Kinetic analysis was held, applying isoconversion methods of Friedman (FR) [3] and Ozawa-Flynn-Wall (OFW) [4] for objective estimation of complex processes running parallel to thermal destruction, non-parametric kinetics method (NPK) was applied [5].

Thermal analytical values of hydrogel PMVE-MA with PPG decomposition are represented with thermal analytical curves TG (thermogravimetric), DTG (differential thermogravimetric) (Figs. 1, *a* and *b*). According to figures 1, a and b, thermal decomposition of examined hydrogel PMVE-MA with PPG in a nitrogen atmosphere appears at the temperature of 265–335 ºC with peak DTG=304 ºC, and in air atmosphere at 347–443 ºC with peak DTG=405 ºC.



a — in a nitrogen atmosphere; *b* — in air

Figure 1. The TG and DTG curves of the sample at a heating rate of 10 K/min

At temperature of 100–110 ºC weight loss in all samples amounts 5–10 %, which corresponds to the first decomposition process. Analysis of DTG curves (Figure 1, *a*, *b*) showed that desorbtion of associated water takes place up to temperature of 150 ºC. This fact may be explained by obstructivity of hydrogen bonds abruption between water molecules and polar function groups of gel PMVE-MA with PPG.

Second decomposition process includes the destruction of gel and reason of selected kinetic analysis. Isoconversion method is one of the methods for definition of activation energy; this method does not require knowledge on analytical form of conversion function, and gives the possibility to define the activation energy against conversion degree as well.

Application of abovementioned models allowed defining of thermodynamic parameters of thermal decomposition of hydrogel PMVE-MA with PPG graphically at different heating rates and conversion levels (Fig. 2, table 1, *a* and *b*). Significant dependence of change of activation energy on transformation level should be mentioned (Fig. 2, *a*). This fact indicates that decomposition process of hydrogel PMVE-MA with PPG happens according to more than one process. In this case it is necessary to apply another kinetic method of research, more developed in the attempt to define and separate these processes, still unknown as Figure 2, *b*.

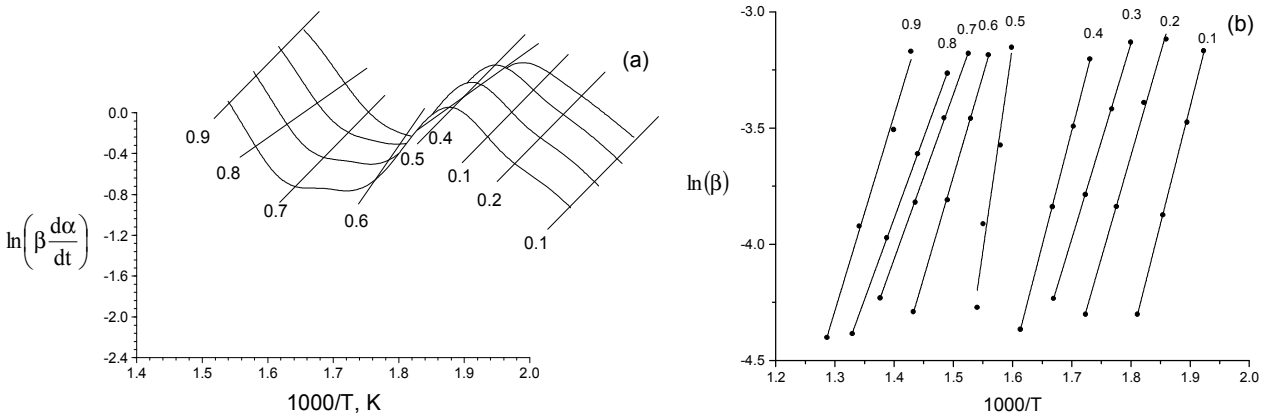


Figure 2. Graphic results of analysis, defined by methods of Friedman (*a*), Ozawa-Flynn-Wall (*b*) for hydrogel PMVE-MA with PPG

Attained values of dependence of activation energy on conversion level corresponds the second decomposition process and are shown in Table 1.

Table 1

Thermodynamic parameters of thermal decomposition of PMVE-MA with PPG, calculated with methods of Friedman (FR) and Ozawa-Flynn-Wall (OFW)

a) in nitrogen atmosphere

α	Friedman method				Ozawa–Flynn–Wall method			
	E_a, kJ/mol	$\delta_{(E)}$	ln $A\times10^3$, min^{-1}	r	E_a, kJ/mol	$\delta_{(E)}$	ln $A\times10^3$, min^{-1}	r
0.1	60.70	0.02	13.06	0.99	66.20	0.02	13.15	0.99
0.2	60.45	0.01	11.61	0.96	66.95	0.12	12.20	0.96
0.3	70.05	0.02	8.87	0.98	77.05	0.02	8.16	0.98
0.4	79.21	0.14	9.59	0.97	76.20	0.18	6.88	0.97
0.5	68.53	0.02	7.08	0.99	64.05	0.12	8.37	0.99
0.6	81.15	0.11	4.71	0.98	99.15	0.01	5.00	0.98
0.7	76.35	0.05	3.70	0.99	84.35	0.02	3.99	0.99
0.8	87.95	0.12	2.65	0.98	87.95	0.11	2.94	0.98
0.9	93.55	0.05	1.64	0.99	93.55	0.10	1.21	0.99

b) in air atmosphere

α	Friedman method				Ozawa–Flynn–Wall method			
	E_a, kJ/mol	$\delta_{(E)}$	ln $A\times10^3$, min^{-1}	r	E_a, kJ/mol	$\delta_{(E)}$	ln $A\times10^3$, min^{-1}	r
0.1	66.32	0.02	14.66	0.99	61.32	0.02	15.71	0.99
0.2	72.27	0.16	13.11	0.96	72.27	0.12	12.29	0.96
0.3	77.12	0.02	11.27	0.98	77.12	0.02	10.17	0.98
0.4	72.77	0.17	8.99	0.97	72.77	0.18	9.12	0.97
0.5	78.87	0.02	9.48	0.99	78.87	0.12	6.10	0.99
0.6	77.77	0.90	6.11	0.98	79.77	0.01	7.09	0.98
0.7	89.97	0.02	5.10	0.99	89.97	0.02	2.11	0.99
0.8	97.77	0.10	2.05	0.98	97.77	0.11	4.23	0.98
0.9	106.52	0.02	1.00	0.99	106.52	0.10	2.41	0.99

Use of definite value, defined for activation energy in estimation of thermal stability is risky. Even if standard deviation of values $\delta_{(E)}$ increases 10 % of average value for each composition, it would be logic to avoid the comparison of quantitative values applying modeless values only.

Processing of TG data applying modified NPK method

Non-parametric kinetics method (NPK) [6–8] of Serra, Nomen and Sempere is based upon the suggestion that reaction velocity may be expresses as multiplication of two independent functions, $g(\alpha)$ and $f(T)$. Reaction model $g(\alpha)$ considers the dependence of conversion degree, and $f(T)$ considers the temperature dependence. Reaction velocity $\beta d\alpha/dT$ is measured by several experiments at different heating rates, β, was interpolated as the surface in 3D ($\beta d\alpha/dT$, α, T). This surface is organized as matrix $i \times j$ where the lines correspond to different conversion degrees, from α_1 to α_i and columns correspond to different temperatures from T_1 to T_j. Elements i, j of matrix A, after $A_{i,j} = g(\alpha_i)f(T_j)$. Functions $g(\alpha)$ and $f(T)$ may be sampled and expressed as vector columns, u_0 and v_0, respectively, where elements and sampled values of function $g(\alpha)$ and $f(T)$.

$$u_0 = \{g(\alpha_1)\ g(\alpha_2)...g(\alpha_i)\}; \quad (1)$$

$$\nu_0 = \{f(T_1)\, f(T_2)...f(T_j)\}. \quad (2)$$

Reaction speed may be expressed in the form of matrix as follows:

$$A = u_0 \cdot \nu_0^T. \quad (3)$$

NPK method applied the algorithm of single value decomposition (SVD) for decomposition of matrix A into two vectors u_0 and v_0. These vectors may be further analyzed by check of attained graphs of velocity dependence on α (to define the kinetic model) and velocity dependence on temperature (to define Arrhenius parameters). Vector u_0 is defined by first column of matrix U and v_0 from the first column of matrix V, where:

$$A = U(diag.\ s)V^T \quad (4)$$

and s is the vector of singular value.

Under values α, $\beta d\alpha/dT$ and T taken from data attained by TG, DTG methods, reaction velocity surface was attained in coordinate space (α, T and $\beta(d\alpha/dT)$) (Fig. 3).

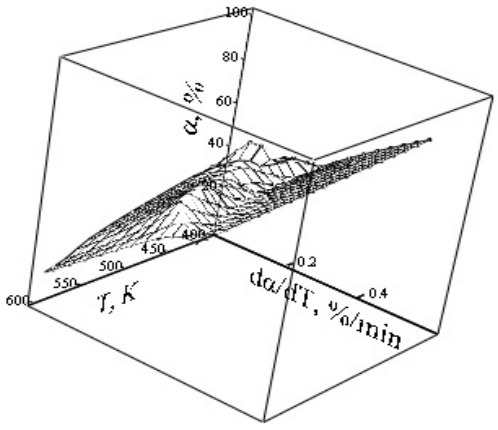


Figure 3. Surface of hydrogel PMVE-MA with PPG in coordinate space:
dependence of reaction velocity ($d\alpha/dT$) on temperature (T) and conversion degree (α)

After application of algorithm of single value decomposition (SVD), matrix A is a vector s with two significant values. In this case matrix A is a sum total of the following:

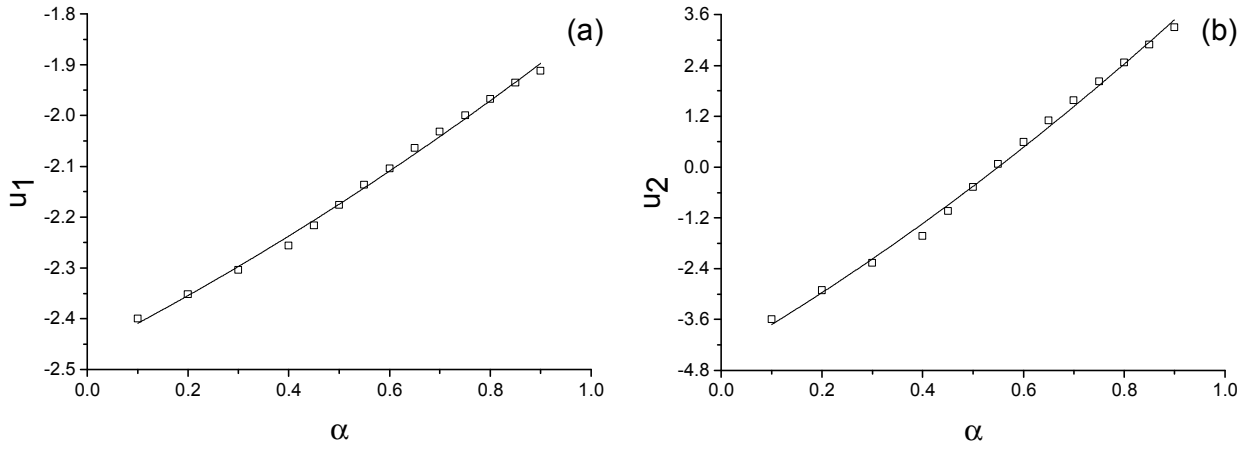
$$A = A_1 + A_2 = u_1 \cdot \nu_1^T + u_2 \cdot \nu_2^T. \quad (5)$$

This means that there are two elementary processes in decomposition level, and discrimination between them is possible by values of explained variance) λ_1 and λ_2 $(\lambda_1 + \lambda_2 \approx 100\,\%)$.

Vectors u_1 and u_2 were checked against the equation of Šestak-Berggren [9] (Fig. 4)

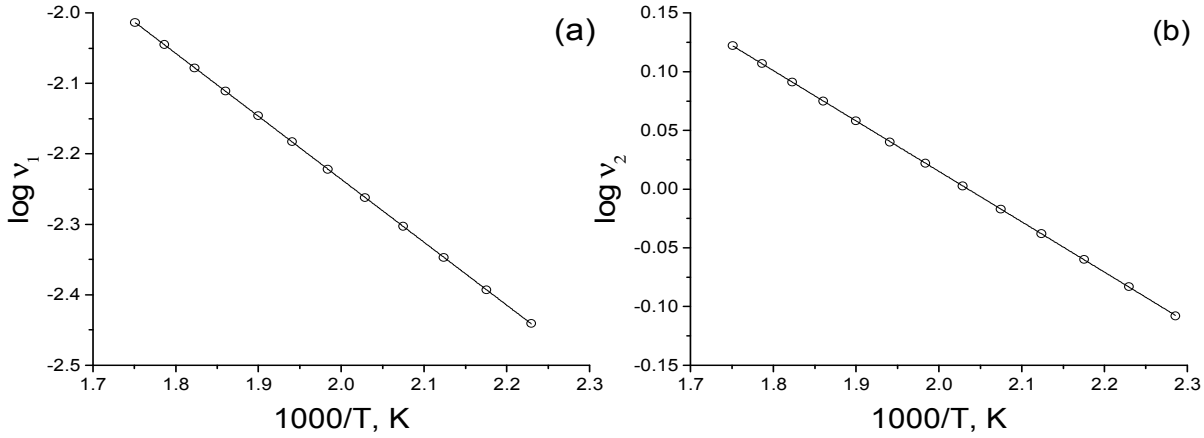
$$g(\alpha) = \alpha^m (1-\alpha)^n \left[-\ln(1-\alpha)\right]^p \quad (6)$$

and vectors ν_1 and ν_2, against the equation of Arrhenius, respectively (Fig. 5). Results of kinetic analysis are shown in Table 2.



a — main process; *b* — secondary process

Figure 4. Simulated and determined values of the normalized vectors *u* for sample PMVE-MA with PPG



a — main process; *b* — secondary process

Figure 5. Linearized Arrhenius equation (ln *v* vs. 1000/*T*)

Table 2

Kinetic parameters of thermal decomposition of hydrogel PMVE-MA with PPG calculated by method of non-parametric kinetics (NPK)

Sample		λ, %	E_a, kJ/mol	A, s^{-1}	n	m	Šestak-Berggren $g(\alpha)=\alpha^m(1-\alpha)^n$	$\sum\lambda\cdot E_a$, kJ/mol
PMVE-MA with PPG	in a nitrogen atmosphere							
	1	57.8	59.56	0.06×10^5	4/5	1/3	$(1-\alpha)^{4/5}\cdot\alpha^{1/3}$	99.47
	2	42.2	92.23	6.42×10^5	–	2	α^2	
	in air							
	1	62.1	60.38	0.12×10^5	4/5	1/3	$(1-\alpha)^{4/5}\cdot\alpha^{1/3}$	115.15
	2	37.9	108.07	4.41×10^5	–	2	α^2	

Values of explained variance make clear that sample, decomposed by us, is met in separate processes ($\lambda_2 \approx 50$ %) and this is related to the lower level of thermal stability (minimum value of activation energy). In comparison with II stage, it represents the significant process of thermal decomposition.

Overrun of this process to TG curve is definitely caused by kinetic influence (of value E_a). Parameter $n = 4/5$ (eq. (6) and table 2) denotes the decomposition of condensed phase, weight loss≈75 % on TG curve. These data correspond to the decomposition after melting of combinations. Values, $m = 1/3$ may be conditioned by diffusion influence on kinetic law.

Conclusions

Thus, to calculate the kinetic parameters of thermal destruction of PMVE-MA with PPG isoconversion models of Friedman, Ozawa-Flynn-Wall may be applied, which proved themselves at thermal analysis of non-organic compositions. Value of kinetic model parameters calculated applying these models, are true enough. However, to our opinion, the most appropriate model is the non-parametric kinetics method, as the advantage of this method of analysis is in the fact that calculation result does not depend on type of kinetic equation g(α).

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Термогравиметрия нәтижелері бойынша полипропиленгликольмен тігілген полиметилвенилэфирмалеин қышқылы негізіндегі гидрогельдің изотермиялық көрсеткіштерін өңдеу

ПЕК әдісі бойынша салыстырмалы кинетикалық талдау

Динамикалық термогравиметрия нәтижелері бойынша полипропиленгликольмен тігілген полиметилвинил эфир малеин қышқылы негізіндегі гидрогельдің термодеструкциясының кинетикалық көрсеткіштерін есептеудің әртүрлі әдістері келтірілген. Зерттеу азот пен ауа атмосферасында қызу жылдамдығы әртүрлі жағдайда жүргізілді: 6, 10, 12 және 16 К/мин. Берілген сополимер үшін изоконверсионды әдіс тобына жататын Фридман, Флинн-Озав-Уолл әдістерін қолдану анағұрлым мақсатты әрекет етеді. Көрінген нәтижелер әртүрлі әдіспен алынған белсенді энергия көрсеткіштерінің сәйкес келуін анық көрсетеді. Толық кинетикалық талдау үшін параметрлік емес (ПЕК), кинетикалық әдісті қолдана отырып зерттеу нәтижелерін өңдеу керек. ПЕК кинетикалық деректерді ерекше өңдеу тәсілін көрсетеді. Бұл әдіс кинетикалық талдауды басқа жағынан сипаттайды, яғни ол бір стадиялық үдерістің нәтижелерін дөңгелектеуіне негізделген. Реакция жылдамдығының эксперименталды мағынасы матрицада орналасқан, ол $f(T)$ және $g(\alpha)$ туралы ақпараттан тұратын екі вектордың туындысымен сипатталды.

Кілт сөздер: динамикалық термогравиметрия, термиялық талдау, термодеструкция, гидрогель.

А.Ж. Сарсенбекова, А.И. Халитова, А.А. Шахабаева

Обработка изотермических данных гидрогеля на основе полиметилвинилового эфира малеиновой кислоты, сшитого полипропиленгликолем по данным термогравиметрии

Сравнительный кинетический анализ методом НПК

В статье представлен анализ различных методов расчета кинетических параметров термодеструкции гидрогеля на основе полиметилвинилового эфира малеиновой кислоты, сшитого полипропиленгликолем по данным динамической термогравиметрии. Исследования были произведены в атмосфере азота и воздуха при различных скоростях нагрева: 6, 10, 12 и 16 К/мин. Показано, что для данного сополимера наиболее целесообразно использовать методы Фридмана, Флинн-Озава-Уолла, относящиеся к группе изоконверсионных методов. Результаты указывают на достаточно хорошее совпадение между значениями энергии активации, полученных разными методами. Для получения полного кинетического анализа необходима обработка данных с использованием метода непараметрической кинетики (НПК). Метод НПК представляет собой особый подход для обработки кинетических данных, а также новую точку зрения на кинетический анализ, который основан на округлении результатов кинетики одностадийного процесса. Экспериментальные значения скорости реакций расположены в матрице, которая выражается как произведение двух векторов, содержащих информацию по $f(T)$ и $g(\alpha)$.

Ключевые слова: динамическая термогравиметрия, термический анализ, термодеструкция, гидрогель.

UDC 577.114:622.24.063

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Development of drilling muds based on anionic and nonionic polysaccharides

The present article is devoted to development of new drilling muds based on anionic (gellan, xanthan) and nonionic (starch) polysaccharides. The results of DSC and viscometric and rheological measurements of gellan, mixtures of gellan — xanthan and gellan-corn starch in absence and presence of NaCl, KCl, $MgCl_2$, $CaCl_2$ and bentonite are presented. The influence of temperature, pH medium, concentration of polysaccharides and salts on the rheological characteristics and conformational transitions of gellan, gellan-xanthan and gellan-starch mixtures was studied. The rheological behavior of 0.2–1.0 wt.% gellan solutions at various temperature, pH medium and content of NaCl, KCl, $MgCl_2$, $CaCl_2$ and bentonite is well described by Ostwald–de Waele and Herschel–Bulkley equations. The coil-helix conformation and sol-gel phase transitions of gellan induced by temperature, salt addition, and pH are key factors to design of drilling muds. Model experiments show that the gellan in combination with xanthan and starch are effective agents to stabilize borehole walls and isolate water inflow. Effective drilling muds based on gellan-starch and gellan-xanthan-starch mixtures in the presence of bentonite and KCl were obtained. The formulated recipes can be used for drilling of wells at unfavorable geological conditions.

Key words: colloids, drilling muds, gellan, interpolymer complexes, viscosity.

Introduction

Low acyl gellan (LAG) which is produced by the bacterium *Pseudomonas elodea* consists of a tetrasaccharide repeating unit of D-glucose, D-glucuronic acid, D-glucose, and L-rhamnose [1, 2]. The review of Morris et al. [3] comprehensively considers the structure, rheology, gelation, topology, and application aspects of LAG. The coil-helix conformational and sol-gel phase transitions of LAG gums induced by temperature, salt addition, pH change and etc. were the main subject of many studies [4, 5].

It is commonly accepted [1; 2; 6] that LAG gum exhibits a conformational change from the disordered state (single chain) to the ordered state (double helix) induced by temperature decrease, while the gelation is considered to be mediated by the double-helix formation and the association of such helices, which is enhanced in the presence of mono- and divalent alkaline and alkaline earth cations [7, 8]. The main difference between the monovalent and divalent cations is that the monovalent cations shield the electrostatic repulsion between the $-COO^-$ while the divalent cations rather suppress electrostatic repulsion and form interchain ionic bonds with carboxylic groups of the glucuronic acid units resulting in the aggregation of the double helices [9].

The sol-gel technology is an effective tool to design materials with unique chemical, physical and mechanical properties. Transformation from sol to gel state proceeds with increasing of either concentration of disperse phase or under the action of external factors (concentration of polymer, temperature, time, pH medium, ionic strength etc.).

Natural polysaccharides like starch, carboxymethyl cellulose, xanthan and others are widely used in formulation of low-clay-content and clay-free polymer drilling fluid for drilling of vertical and lateral wells [10–12]. However, the high price, low thermal and microbiological stability significantly limit the application of polysaccharides for drilling muds [10].

Earlier [13–15] we have demonstrated for the first time that the LAG solution can be successfully used for enhanced oil recovery. The remarkable property of LAG was plugging of high drainage channels in oil reservoirs.

The idea of using LAG as key component of drilling muds is based on its ability to undergo the conformational and phase transitions under the influence of temperature, low molecular salt additives, and pH medium. This should ensure the effective capacity of LAG containing solutions to strength the walls of the well by forming polymer-clay filter cake, to control the adsorption of water and clean the down hole from cuttings.

In the present paper the viscometric, rheological, conformational and phase behavior of LAG and LAG-xanthan mixtures at various concentrations of polysaccharides, salt content, temperature and pH are investi-

gated. Based on these studies novel LAG-containing drilling muds with good rheological, filtration and cake-formational characteristics have been developed.

Experimental part

Materials

LAG is an anionic extracellular bacterial polysaccharide discovered in 1978 [8]. It consists of repeated tetrasaccharide units: 1,3-linked β-D-glucose, 1,4-linked β-D-glucoronic acid, 1,4-linked β-D-glucose, and 1,4-linked α-L-rhamnose.

Xanthan gum is also a microbial exopolysaccharide produced by bacterium *Xanthomonas campestis* [16, 17]. It consists of repeated pentasaccharide units composed of two D-glucopyranosyl units, two mannopyrasonyl units and D-glucopyranosyluronic acid in the molar ratio 2.8:2.0:2.0

Corn starch is commercial product was purchased from «Jarkent corn-molasses plant» (Almaty region, Kazakhstan). Structural formula of corn starch is shown in [18].

Low molecular weight salts: NaCl, KCl, $CaC1_2$ $MgCl_2$ and bentonite $(Na, Ca)_{0.3}(Al, Mg)_2Si_4O_{10}(OH)_2 \cdot nH_2O$ purchased from JSC «Reactiv», Russia, were used without further purification.

Methods

The viscosity of aqueous LAG solutions was measured by Ubbelohde viscometer at 25±0.1 ºC. The rheological behavior of polysaccharide solutions was monitored with the help of Rheolab QC, Anton Paar (Austria). The approximation of results was performed by Ostwald–de Waele and Herschel–Bulkley models to find the rheological and conformational characteristics (shear stress — τ_0, plastic viscosity — η, consistency index — *K* and nonlinearity factor — *n*). The DSC and dDSC characteristics of samples were determined with the help of DSC Eva Setaram (France). Static shear stress (SSS) measurement was performed by means of the instrument SNS-2 (Russian Federation) [10; 19]. Water yield of the drilling muds (WY) was determined by VM-6 instrument (Russian Federation) [19]. The thickness of the filter cake (δ) was measured by the instrument WIKA IV-2 (Russian Federation).

Result and discursion

Thermal and storage stability of LAG [20]

Figure 1 represents the DSC and dDSC curves of LAG within temperature range from –30 to 300 ºC. DSC curve shows the endothermic peak at 95 ºC with melting enthalpy –264.5 $J \cdot g^{-1}$. The second endothermic peak at 251.1 ºC corresponds to LAG decomposition temperature — LAG enthalpy of which is equal to 98.99 $J \cdot g^{-1}$. Thus, LAG is thermally stable polysaccharide, which in solid state melts within the temperature interval at 31–178 ºC.

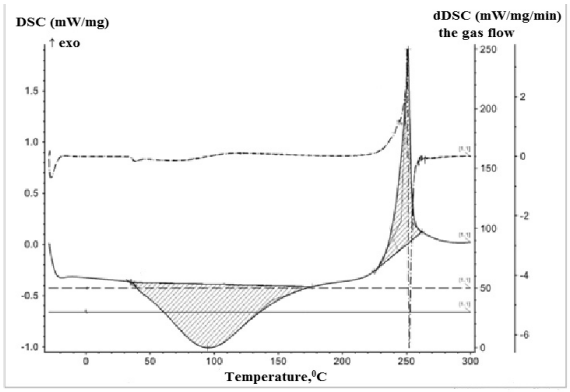

Figure 1. The results of DSC and dDSC analysis of LAG

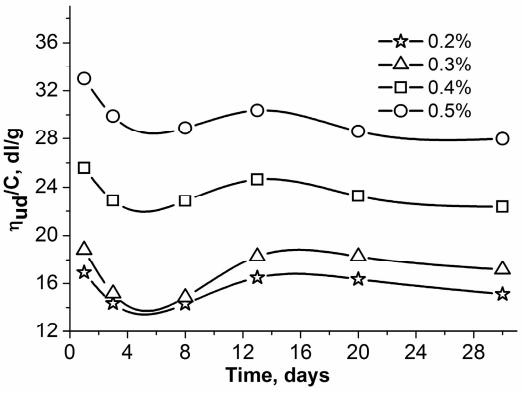

Figure 2. The intrinsic viscosity of LAG solutions versus storage time pH = 6.4; T = 25 ºC

One of the main requirements to drilling muds is the stability of rheological characteristics versus time. Especially it concerns to polysaccharides, which are able to undergo biodegradation [11, 12,19]. In this regard, the viscosity of LAG solutions was studied as a function of storage time. As seen from Figure 2 the viscosity of LAG in concentration range of 0.2–0.5 wt.% decreases up to 15–18 % after 4 days, while the further slightly changes of the viscosity (during the following 30 days) are within the limits of experimental error and may be considered as constant.

Influence of pH medium on rheological behavior of LAG and LAG-xanthan solutions

Influence of pH on the rheological behavior of LAG was studied for 0.5 and 1 wt. % LAG solutions (Fig. 3*a*). The maximal value of shear stress is registered at pH = 7.5. The subsequent increase of pH leads to decrease of the shear stress due to increasing of the ionic strength of solution [20]. The shape of all flow curves is characteristic for pseudoplastic fluid that is common for gel forming structures [21].

Flow curves of LAG-xanthan solutions (Fig. 3*b*) significantly differ from the flow curves of LAG. All flow curves of LAG-xanthan solutions are located in the area of anomalously low shear stress. The average ratio of the shear stress values for solutions of LAG and LAG-xanthan mixture (1:1) with the same shear rate equal to 2.5. Besides the effect of ionic strength at pH above 7.5 is minimal or absent. Such anomaly behavior of LAG-xanthan solutions is apparently caused by the formation of interpolymer complexes (IPC) between macromolecules of LAG and xanthan.

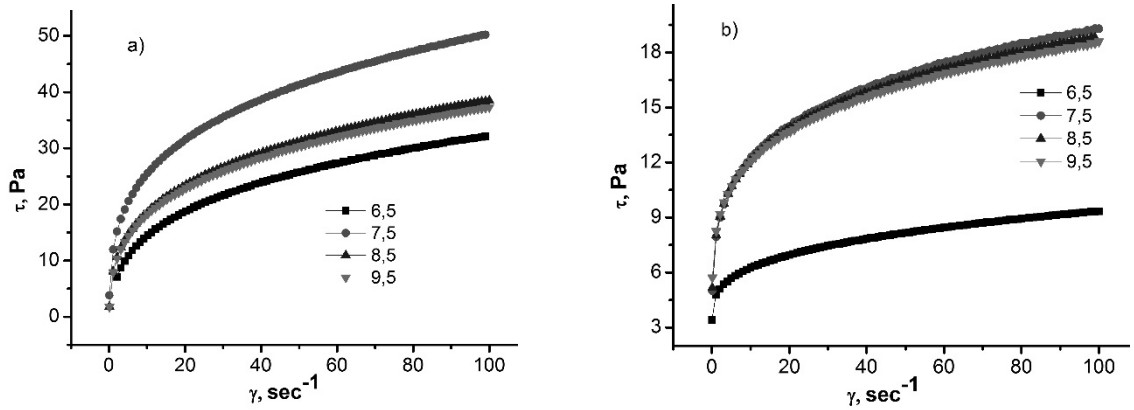

Figure 3. Shear stress versus shear rate curves of 1 wt.% LAG (*a*) and LAG-xanthan (1:1) (*b*) solutions at different pH values; *T*=25 ºC

For detailed analysis of flow curves of LAG and LAG-xanthan solutions shear stress- shear rate dependences were processed by Shvedov-Bingham (1), Ostwald-de Waele (2) and Herschel-Bulkley (3) equations [22]:

$$\tau = \tau_0 + \eta \times \gamma; \quad (1)$$

$$\tau = K \times \gamma^n; \quad (2)$$

$$\tau = \tau_0 + K \times \gamma^n, \quad (3)$$

where τ — shear stress; γ — shear rate; τ_0 — yield point; K — consistency index; n — nonlinearity factor.

Correlation coefficient R was used to match the curves with their corresponding models, R^2 in ideal case should be equal to unity. The results are shown in Tables 1 and 2.

Table 1

The rheological characteristics of LAG and LAG-xanthan solutions at different pH, 1 wt.% total polysaccharide concentration and 25 ºC

pH	LAG/xanthan weight ratio	Rheological parameters of Herschel-Bulkley equation							
		after 1 min of solution immobility				after 10 min of solution immobility			
		τ_0, Pa	K, Pa·s	n	R^2	τ_0, Pa	K, Pa·s	n	R^2
9.5	1/0	0	8.837	0.322	0.995	0	13.092	0.257	0.998
8.5	1/0	0	5.414	0.414	0.996	0	13.173	0.262	0.998
7.5	1/0	0	11.309	0.322	0.999	0	17.5.49	0.253	0.998
6.5	1/0	0.223	0.009	1.138	0.987	0.127	0.158	0.911	0.797
9.5	1/1	0.823	5.821	0.219	0.996	1.973	6.13.	0.216	0.997
8.5	1/1	0.779	5.739	0.226	0.997	0.341	7.528	0.195	0.997
7.5	1/1	1.637	5.285	0.249	0.996	0.384	7.386	0.204	0.997
6.5	1/1	3.862	0.144	0.617	0.988	0	2.273	0.230	0.992

Table 2

The rheological characteristics of LAG and LAG-xanthan solutions at different pH, 1 wt.% total polysaccharide concentration and *T*=25 ºC

pH	LAG/xanthan weight ratio	Rheological parameters of Ostwald–de Waele' equation					
		after 1 min of solution immobility			after 10 min of solution immobility		
		K, Pa·s	*n*	R^2	*K*, Pa·s	*n*	R^2
9.5	1/0	5.654	0.411	0.968	7.241	0.367	0.970
8.5	1/0	4.605	0.448	0.991	7.420	0.368	0.970
7.5	1/0	7.50	0.394	0.988	11.359	0.330	0.984
6.5	1/0	0.053	0.768	0.982	0.012	0.983	0.708
9.5	1/1	6.642	0.201	0.996	8.072	0.179	0.996
8.5	1/1	6.513	0.208	0.996	7.873	0.189	0.996
7.5	1/1	9.851	0.102	0.875	7.769	0.197	0.997
6.5	1/1	2.944	0.161	0.972	1.234	0.336	0.969

As seen from Tables 1 and 2, the flow curves of LAG and LAG-xanthan solutions at pH 7.5, 8.5 and 9.5 are described in the best way by Herschel-Bulkley model, which takes into account the yield stress characteristic of the gelling systems. At pH 6.5 the flow curves of LAG and LAG-xanthan solutions are poorly described by the equations 1–3. The appearance of yield stress (τ_0) for flow curves of LAG solution at pH 6.5 and LAG-xanthan solution in the range of pH 6.5–9.5 confirms the gelation of the system [23]. This is probably due to participation of polysaccharides in complexation reaction. The difference in consistency index of LAG and LAG-xanthan solutions after 1 and 10 minutes of immobility is indicated on the thixotropic behavior of polysaccharide systems. Thixotropic phenomenon is more pronounced for LAG solutions, that is favorable for suspending of drilled cuttings [21].

Temperature dependent rheology of polysaccharides

Comprehensive information on the rheological properties of LAG, xanthan and LAG-xanthan mixture as a function of temperature and salt content is necessary to predict the behavior of drilling muds. In this regard, shear stress-shear rate dependences of polysaccharide solutions at different temperatures and salt concentrations were analyzed using the equations describing the flow curves of Newtonian and non-Newtonian fluids.

The shear stress-shear rate curves of 0.5 wt.% LAG solution registered at temperature interval between 25 and 55 ºC show the pseudoplastic behavior (Fig. 4*a*). Newtonian flow of LAG solution is observed at 60–70 ºC. Step-by-step transformation of LAG solution from pseudoplastic behavior to Newtonian may be explained by «melting» of double stranded structure of LAG and formation of LAG macromolecules in random coil conformation at higher temperature [3].

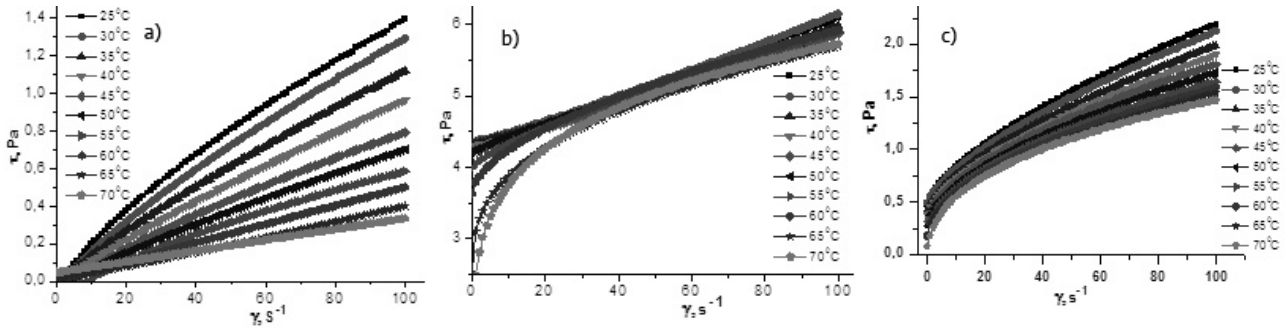

Figure 4. The shear stress-shear rate curves of 0.5 wt.% LAG (*a*), xanthan (*b*) and LAG-xanthan (2:1) (*c*) solutions at the interval of temperature 25–70 ºC

In the temperature range 25÷40 ºC the 0.5 % xanthan solutions are typically viscoelastic fluids. At the interval of 40÷65 ºC the gradual transition from viscoelastic flow to pseudoplastic flow is observed. The mixture of LAG-xanthan throughout the temperature range behaves like a pseudoplastic fluid, further having a yield stress at t<50 ºC. Such behavior 0.5 % solution of LAG-xanthan mixture (2:1) is probably due to formation of IPC.

Influence of salts on rheological behavior and gel formation of polysaccharides [20]

Oilfield water may participate in the formation of a filter cake on the surface of the borehole wall contacting with drilling fluid. This process may occur even in the case of clay-free drilling muds by the hydrogel formation of a filter cake on the well surface. This is particularly actual in the conditions of high permeability and fracturing the rock [21].

The viscometric measurements were performed with 0.2 wt.% LAG solution because the reduced viscosity of 0.5 wt.% LAG is extremely high and difficult to measure. Dependence of the reduced viscosity of 0.2 wt.% LAG on the ionic strength of the solution adjusted by addition of $BaCl_2$, $CaCl_2$, $MgCl_2$ and oilfield water with the salinity 73 $g \cdot L^{-1}$ is shown in Figure 5. According to viscometric data the effectiveness of salts to enhance gelation changes in the following order: $BaCl_2 > CaCl_2 \approx MgCl_2 >$ oilfield water. This order is in good agreement with the results found for LAG by the authors [24].

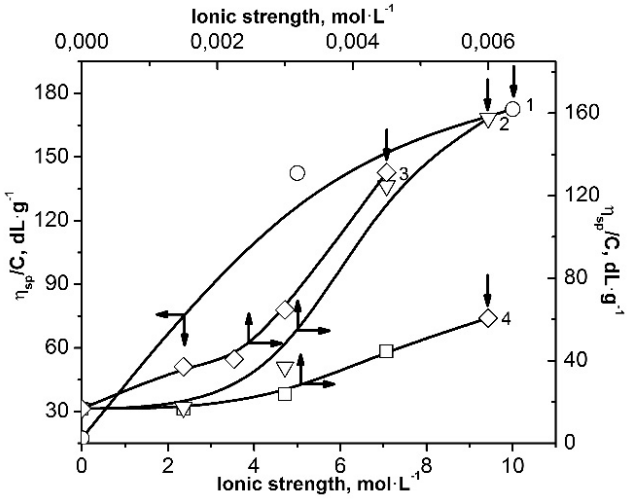

Figure 5. Dependence of reduced viscosity of 0.2 wt.% LAG on the ionic strength of the solution adjusted by addition of oilfield water with the salinity 73 $g \cdot L^{-1}$ (*1*), $CaCl_2$ (*2*), $BaCl_2$ (*3*), $MgCl_2$ (*4*). Arrows show the start of the gelation process. Temperature is 25 ºC

Dependences of shear stress versus shear rate for LAG and LAG-xanthan solutions in the presence of NaCl, KCl, $CaC1_2$, $MgCl_2$ and oilfield water are shown in Figure 6. Increasing of shear stress as a function of shear rate follows by the order: Oilfield water > $CaC1_2$ > $MgCl_2$ > KCl > NaCl (Fig. 6*a*).

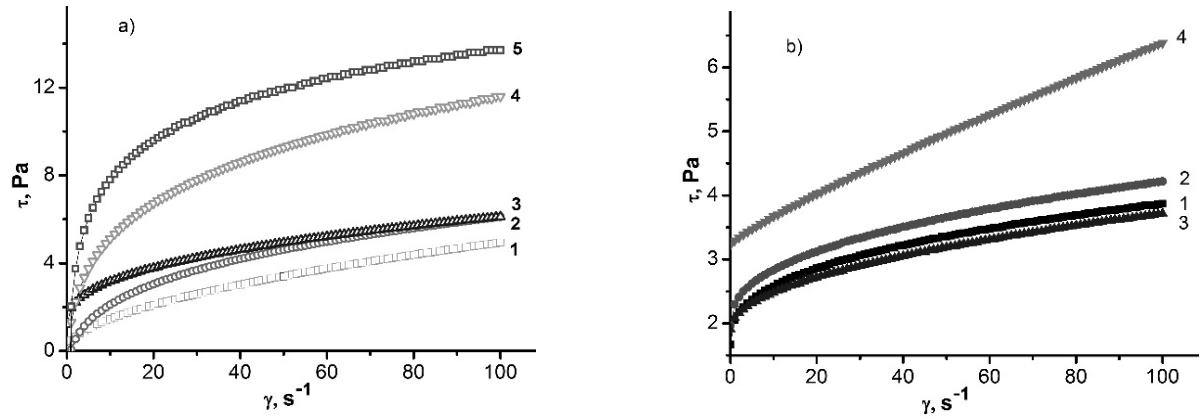

Figure 6. The shear stress-shear rate curves of 0.5 wt.% LAG (a) and 0.5 wt.% LAG-xanthan (2:1) solutions (b) at the ionic strength μ = 0.01 adjusted by addition of NaCl (1), KCl (2), $MgCl_2$ (3), $CaC1_2$ (4) and oilfield water (5)

This sequence is in good agreement with the effectiveness of salts to enhance LAG gelation. It is seen that the effect of oilfield water is more substantial compared to solutions of individual salts. This may be due to combined effect of alkaline and alkaline earth metal ions with respect to coil-helix conformation of LAG.

In case of LAG-xanthan (2:1) mixture, the shear stress increases in the sequence: $CaCl_2$ > KCl > NaCl > > $MgCl_2$ (Fig. 6*b*). Changes in the rheological behavior of solutions during the transition from a LAG to LAG-xanthan mixture (decrease values τ_0, the transition from viscoelastic to the pseudoplastic flow), are apparently due to the formation of ternary complexes such as LAG-xanthan-Me^{2+}.

Influence of dispersed phase on the rheological behavior of LAG solutions [20]

Evaluation of the influence of bentonite on rheological characteristics of LAG solution is necessary for simulation of drilling mud ability to carry up the cuttings from the bottom hole of the well to the surface. Influence of dispersed phase on the rheological and conformational characteristics of 0.5 wt.% LAG solutions in the presence of bentonite was studied by rotational viscometry. The obtained results are summarized in Table 3. The values of correlation coefficient (R^2) show, that the model of Ostwald-de Waele good describes the rheological behavior of LAG solution and the colloid-dispersed systems LAG-bentonite excepting for 8 wt.% of bentonite concentration.

Table 3

Rheological parameters of 0.5 wt.% LAG solutions in the presence of bentonite at 25 ºC

$C_{bentonite}$, %	pH	Rheological parameters of Ostwald–de Waele equation					
		after 1 min of solution immobility			after 10 min of solution immobility		
		K, Pa·s	*n*	R^2	*K*, Pa·s	*n*	R^2
0	6.34	0.371	0.829	0.958	0.43	0.739	0.968
2	9.94	8.038	0.243	0.997	9.69	0.242	0.999
4	9.97	9.754	0.218	0.992	11.36	0.263	0.986
6	10.01	10.781	0.288	0.989	12.38	0.247	0.964
8	10.05	11.445	0.298	0.972	9.50	0.192	0.693

Rheological parameters of LAG/xanthan mixture were determined in presence of bentonite and KCl. As seen from Table 4, the rheological behavior of disperse systems obeys Ostwald-de-Waale' equation. The optimal values of *K* and *n* were obtained for the rations 1/1, 1/2 and 1/4. For the compositions 1/0, 2/1 and 4/1 the value of n>0.3, this worsens the flowing properties of the solutions [21].

Table 4

Rheological parameters of 0.5 wt.% LAG-xanthan mixtures in the presence of 1,5 wt.% bentonite and 1 wt.% KCl at 25 ºC

LAG/xanthan weight ratio	pH	Rheological parameters of Ostwald–de Waele' equation					
		after 1 min of solution immobility			after 10 min of solution immobility		
		K, Pa·s	*n*	R^2	*K*, Pa·s	*n*	R^2
1/0	9.9	4.482	0.238	0.968	3.273	0.322	0.960
1/1	9.2	2.780	0.268	0.978	3.293	0.226	0.994
1/2	9.7	2.731	0.235	0.998	1.779	0.499	0.978
1/4	9.1	3.123	0.206	0.994	3.719	0.161	0.986
2/1	9.2	2.301	0.335	0.830	2.303	0.279	0.887
4/1	9.1	1.357	0.344	0.949	1.539	0.331	0.958

Properties of Drilling Muds

On the basis of obtained results several drilling formulations were prepared by selecting the different concentration and composition of polysaccharides with and without addition of bentonite and/or KCl. The structural-mechanical, filtration and filter cake forming properties of these compositions are summarized in Table 5.

Table 5

Characteristics of drilling muds obtained on the basis of polysaccharides, bentonite and KCl

DM	Composition of DM*, wt.%					Characteristics of DM					
	LAG	Starch	Xanthan	Bentonite	KCl	pH	ρ, g/sm^3	η_{rel}, sec	WY, sm^3	δ, mm	SSS_1/SSS_{10} dPa
1	0.4	3	0	1	3	10	1.04	41	4	0.2	2.7/3.3
2	0.4	3	0	2	1	10.1	1.04	40	3	0.4	3.1/4.2
3	0.4	3	0	1	0	10.2	1.04	40	4	0.5	3.0/4.5
4	0.34	0	0.1	1.75	0.05	9.8	1.02	36	5.6	0.5	2.5/2.9
5	0.25	0.75	0.1	0.5	0	11	1.01	29	10	0.2	0.6/0.6
6	0.17	0	0.33	0.5	3	9.4	1.02	30	10	0.5	1.6/1.6
7	0.17	0.5	0.33	1	3	9.6	1.03	35	10	0.6	3.0/7.0
8	0.17	1	0.33	0.5	3	9.5	1.02	30	10	0.5	1.7/1.6
9	0.15	0	0.45	3	3	9.8	1.03	39	10	0.5	3.5/2.8
10	0.13	0	0.37	1	2	9.7	1.01	41	10	0.5	2.8/2.7

Note: * The rest — water.

Analysis of the data shows that the samples 1–3 at LAG/corn starch ratio around of 1:7 possess good structural-mechanical and filtration characteristics. The thickness of filter cake may be increased by adding 2 wt.% of bentonite or deleting KCl from the mud composition.

The samples 4, 6, 9 and 10 exhibit good filter cake forming and filtration properties but not good thixotropic characteristics because $SSS_{10}/SSS_1 < 1$. This condition will decrease the efficiency of cuttings suspension by the drilling mud.

The best structural-mechanical, filtration and filter cake forming properties exhibit the sample 7 consisting of the mixture of LAG/corn starch /xanthan at the weight ratio 1:3:2 with total polysaccharide concentration 1 wt.%.

Conclusions

The rheological behavior of LAG and LAG/xanthan mixtures at a wide range of concentrations, temperatures, pH, salt content and dispersed phase can be described by Ostwald-de Waal or Herschel-Bulkley equations. In solutions of LAG — xanthan mixtures interpolymer complexes stabilized by hydrogen bonds are formed. The structural-mechanical, filter cake forming and filtration properties of drilling muds based on LAG-xanthan-corn starch mixture can be successfully controlled by changing of composition of polysaccharide mixture and concentration of bentonite and KCl. The developed drilling muds can be used for drilling of wells having unfavorable geological conditions.

Acknowledgements

Authors thank the Ministry of Education and Science of the Republic of Kazakhstan for financial support (Grant No.4410/GF4 2015–2017).

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В.Б. Сигитов, Ж.А. Нурахметова, Я.Ю. Песириди, С.Е. Кудайбергенов

Аниондық және иондық емес полисахаридтер негізінде бұрғылау ерітінділерін әзірлеу

Мақала аниондық (геллан, ксантан) және иондық емес (крахмал) полисахаридтер негізінде жаңа бұрғылау ерітінділерін әзірлеуге арналған. Геллан, геллан–ксантан, геллан–жүгері крахмалы қоспаларының NaCl, KCl, $MgCl_2$, $CaCl_2$, бентонит қатысында және қатысынсыз вискозиметрлік, реологиялық және механикалық қасиеттері және ДСК нәтижелері көрсетілген. Температура, pH орта, тұздар және полисахаридтер концентрацияларының геллан, геллан–ксантан, геллан–крахмал қоспаларының реологиялық қасиеттері мен конформациялық ауысуларына әсері зерттелген. NaCl, KCl, $MgCl_2$, $CaCl_2$, бентонит қатысында және қатысынсыз әртүрлі температура, pH ортада 0.2–1.0 % геллан ерітінділерінің реологиялық қасиеттерін нақтырақ Оствальда-Де Ваале және Хершеля-Балкли теңдеулері сипаттайды. Гелланның шиыршық-шумақ конформациясына және золь-гель фазалық ауысуына температураның, тұздардың және pH ортаның әсері бұрғылау ерітінділерін жобалауда негізгі факторлар болып табылады. Модельді эксперименттер гелланның ксантан және крахмалмен қоспасы ұңғыма қабырғаларын тұрақтандыру және судың келуін тоқтатуда тиімді агент болып табылатынын көрсетті. KCl және бентонит қатысында геллан–крахмал және геллан–ксантан–крахмал қоспалары негізінде тиімді бұрғылау ерітінділері алынды. Бұл рецептер күрделі таулы-геологиялық жағдайларда ұңғымаларды бұрғылау үшін қолданылуы мүмкін.

Кілт сөздер: коллоидтар, бұрғылау ерітінділері, геллан, интерполимерлі кешендер, тұтқырлық.

В.Б. Сигитов, Ж.А. Нурахметова, Я.Ю. Песириди, С.Е. Кудайбергенов

Разработка буровых растворов на основе анионных и неионных полисахаридов

Статья посвящена разработке новых буровых растворов на основе анионных (геллан, ксантан) и неионогенных (крахмал) полисахаридов. Приведены результаты ДСК, вискозиметрические и реологические свойства геллана, смесей геллана–ксантана и геллан–кукурузного крахмала в отсутствии и присутствии NaCl, KCl, $MgCl_2$, $CaCl_2$ и бентонита. Изучены влияния температуры, pH среды, концентрации полисахаридов и солей на реологические характеристики и конформационные переходы смесей геллана, геллан–ксантан и геллан–крахмал. Более точное описание реологического поведения растворов геллана 0.2–1.0 мас.% при варьировании температуры, pH среды в присутствии NaCl, KCl, $MgCl_2$, $CaCl_2$ и бентонита описывают уравнения Оствальда-Де Ваале и Хершеля-Балкли. Влияние температуры, солей и pH на конформации спираль-клубок и золь-гель фазовые переходы геллана являются ключевыми факторами при проектировании буровых растворов. Модельные эксперименты показывают, что комбинации геллана с ксантаном и с крахмалом являются эффективными агентами для стабилизации стенок скважины и изолирования притока воды. Получены эффективные буровые растворы на основе смесей геллан–крахмал и геллан–ксантан–крахмал в присутствии бентонита и KCl. Сформулированные рецепты могут быть использованы для бурения скважин в сложных горно-геологических условиях.

Ключевые слова: коллоиды, буровые растворы, геллан, интерполимерные комплексы, вязкость

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УДК 519.242.7+ 519.233.4

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Использование многофакторной переменной в методе вероятностно-детерминированного планирования эксперимента

В статье показано, что в качестве как минимум одного из факторов в плане ВДПЭ может выступать переменная, объединяющая несколько величин путём группировки в гнездовой план. На примере четырёхфакторного плана с тремя уровнями варьирования и «составного фактора», содержащего четыре компонента, показан способ построения математической модели многокомпонентной системы. Оговорены некоторые ограничения предлагаемой методики расчётов. Установлено, что влияние на результат только одного компонента «составного фактора» позволяет использовать метод ВДПЭ без видоизменений. На примере показано, что парное влияние компонентов «составного фактора» может быть обнаружено с помощью перебора вариантов по росту коэффициента нелинейной множественной корреляции. В качестве необходимых условий построения математической модели влияния каждого из компонентов «составного фактора» на результат указано равенство числа уровней компонента общему числу уровней варьирования факторов в плане эксперимента. При тестировании метода использованы «искусственные данные», точные значения которых известны. Для имитации ошибки эксперимента расчётные значения умножались на случайное число, близкое к единице. Оценку точности полученных моделей провели с помощью общепринятого в литературе критерия — средней ошибки, и с помощью принятого в методе ВДПЭ коэффициента нелинейной множественной корреляции. Метод позволяет значительно сократить число опытов, необходимых для изучения сложных систем с применением ВДПЭ. Разработанный в статье подход предлагается, главным образом, для применения в спектральном анализе многокомпонентных систем и в других случаях, когда результат зависит лишь от одного из компонентов «составного фактора».

Ключевые слова: вероятностно-детерминированное планирование эксперимента, факторный эксперимент, искусственные данные, частная зависимость, составной фактор, среднее отклонение, спектральный анализ.

Роль математического планирования эксперимента в различных областях науки и техники непрерывно возрастает. В химии и химической технологии планирование эксперимента широко используется для получения математических моделей сложных многофакторных процессов, оптимизации их параметров и одновременной статистической оценки достоверности получаемых результатов. Удобным методом математического планирования эксперимента является вероятностно-детерминированное планирование (ВДПЭ). Этот метод, появившийся в 1960-х гг. [1], был развит в работах В.П. Малышева, его учеников, сподвижников [2, 3] и последователей.

Ядром метода ВДПЭ является план эксперимента, основанный на использовании латинских квадратов. Применение латинских квадратов позволяет добиться сочетания каждого из уровней каждого из факторов с остальными один и только один раз. Это обеспечивает равноценность вклада всех факторов в получаемую математическую модель, и, как следствие, статистическую достоверность результатов использования плана. Существенное преимущество метода ВДПЭ перед другими разновидностями планирования эксперимента заключается в сравнительно небольшом числе требуемых опытов и получении математической модели в единственной серии экспериментов. Немаловажными являются также простота математической обработки результатов и возможность ее автоматизации.

Изучение многокомпонентных химических систем с помощью ВДПЭ при традиционном подходе начинается с определения факторов и уровней их варьирования. При этом каждый из рассматриваемых компонентов системы назначается отдельным фактором. Предположим, изучается закаливание четырехкомпонентного сплава. Рассматривается влияние количественного соотношения компонентов, температуры и времени нагрева, теплоемкости охлаждающей среды, длительности процесса «отпуска» на твердость получаемого материала. Для уменьшения числа факторов содержание компонентов сплава может быть задано в виде массовых долей в основном компоненте или весовых отношений к одному из компонентов. Тогда 4 компонента сплава дадут всего три фактора. В итоге число рассматриваемых факторов составит 7, с вакантным — 8. Придется планировать эксперимент, состоящий из 49 испытаний. Конечно, это не очень много, особенно, если учесть возможность обойтись без повторных опытов, которую предоставляет метод ВДПЭ, однако уменьшить число опытов без

снижения качества получаемой модели представляется весьма заманчивым. А если число компонентов сплава будет не четыре, а больше? Такие случаи нередки, особенно если учесть не только основные компоненты, но и легирующие добавки.

В практике спектрального анализа часто приходится сталкиваться с многокомпонентными системами. При разработке методов анализа этих систем требуется учесть влияние на качество анализа настроек прибора и состава пробы. Минимизация числа опытов в этой области также представляется весьма желательной [4].

Возможность уменьшения числа испытаний в рассматриваемых примерах и в похожих случаях может быть реализована путем включения химического состава системы в план в качестве единого (составного) фактора. Каждый компонент состава (точнее — его концентрация), таким образом, будет и компонентом составного фактора. При этом представляется возможным получить оценки влияния на результат каждого из рассматриваемых компонентов составного фактора и, в перспективе, их комбинаций. Общее число факторов в плане уменьшится на два. Число единичных испытаний составит шестнадцать или двадцать пять с вакантным фактором (вместо сорока девяти!). Проиллюстрируем эти возможности с помощью плана эксперимента с меньшей размерностью. Воспользуемся традиционным планом, состоящим из четырех факторов на трёх уровнях варьирования (табл. 1).

Таблица 1

План эксперимента с участием составного фактора

№	F_1	F_2	F_3	V
1	1	1	1	1
2	1	2	2	2
3	1	3	3	3
4	2	1	2	3
5	2	2	3	1
6	2	3	1	2
7	3	1	3	2
8	3	2	1	3
9	3	3	2	1

Позицию первого фактора (F_1) занимает составной фактор, условно обозначенный как «состав системы». Придерживаясь общей тенденции ВДПЭ, используем в качестве уровней компонентов составного фактора неповторяющиеся значения. Общее число вариаций «состава системы» будем задавать равным числу уровней остальных факторов. Таким образом, один «состав» и будет являться одним уровнем варьирования составного фактора. Значения уровней компонентов составного фактора объединим в таблице 2. Сами значения могут быть произвольными, но не повторяющимися для одного компонента. Забегая вперед, отметим, что если для какого-либо компонента значения уровней будут повторяться, это не помешает вычислениям частных зависимостей, вызванных варьированием уровней остальных компонентов.

Таблица 2

Составной фактор (F_1)

Уровень	K_1	K_2	K_3	K_4
1	4	6	9	12
2	6	9	12	4
3	9	12	4	6

Значения, сгруппированные в таблице 2, выбраны такими исключительно для визуального отличия от цифр 1, 2, 3, из которых сформирован план эксперимента.

Чтобы в полной мере оценить точность получаемой с помощью ВДПЭ модели, воспользуемся «искусственными данными» — данными, сгенерированными по заданной формуле. Чтобы избежать деления на ноль при оценке погрешности модели, а также для имитации 5 %-ной ошибки экспери-

мента, каждое из рассчитанных значений умножим на случайное число в диапазоне 0,975–1,025. Для генерации данных применим формулы (1–4). Результаты вычислений с поправками на «ошибку эксперимента» сгруппируем в таблице 3. Данные, непосредственно вычисленные по формуле, помечены знаком (ф), а данные с поправками — знаком (э). Результат, рассчитанный по полученной методом ВДПЭ модели, отмечен знаком (в). Для расчётов по методу ВДПЭ использованы цифры, округлённые до второго знака после запятой, поэтому результаты вычислений, кроме КНМК, приведены округлёнными. Все коэффициенты в формулах выбраны наугад и не имеют какого-либо физического смысла. Намеренно значения результатов описаны как сумма, чтобы упростить последующую обработку, можно использовать только среднее арифметическое и не применять другие способы усреднения.

$$Y_1 = 1,99 * F_2^{1,7} + \exp(F_3 * 0,68); \quad (1)$$

$$Y_2 = K_2 * 8,5 + 1,5 * F_2^{1,9} + \exp(F_3 * 0,8); \quad (2)$$

$$Y_3 = K_4 * 5 + 1,5 * F_2^{1,9} + \exp(F_3 * 0,8); \quad (3)$$

$$Y_4 = K_1 * K_4 * 0,87 + 1,5 * F_2^{1,9} + \exp(F_3 * 0,8). \quad (4)$$

Точность получаемых методом ВДПЭ математических моделей оценивали как по значению коэффициента нелинейной множественной корреляции (5) и его значимости (6), так и с помощью среднего отклонения (7).

$$R = \sqrt{1 - \frac{(N-1)\sum_1^N (Y_Э - Y_T)^2}{(N-K-1)\sum_1^N (Y_Э - Y_{Cp})^2}}. \quad (5)$$

$$t_R = \frac{R\sqrt{N-K-1}}{1-R^2}. \quad (6)$$

$$\overline{A} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{y_{iв.} - y_{iф.}}{y_{iф.}}\right|. \quad (7)$$

Таблица 3

Результаты вычислительного эксперимента

№ п/п	Y_1(ф)	Y_1(э)	Y_1(в)	Y_2(ф)	Y_2(э)	Y_2(в)	Y_3(ф)	Y_3(э)	Y_3(в)	Y_4(ф)	Y_4(э)	Y_4(в)
1	3,96	4,06	4,06	54,73	55,60	56,89	63,73	65,06	64,73	45,49	45,49	43,81
2	10,36	10,48	10,32	61,55	62,41	63,11	70,55	69,21	69,97	52,31	52,63	51,3
3	20,57	20,80	20,72	74,12	75,30	76,54	83,12	81,37	81,82	64,88	64,81	62,5
4	5,89	5,85	6,24	80,23	81,11	82,17	23,73	24,06	25,16	24,61	24,33	23,9
5	14,16	13,97	13,99	87,05	86,53	88,39	30,55	30,73	30,38	31,43	31,43	31,39
6	14,86	14,78	14,87	99,62	98,52	101,82	43,12	43,25	44,55	44,00	44,31	42,59
7	9,68	9,73	9,91	105,73	108,26	107,97	33,73	32,88	33,79	50,71	49,79	48,85
8	8,44	8,28	8,14	112,55	112,78	114,19	40,55	41,32	41,33	57,53	56,38	56,34
9	16,78	16,73	17,05	125,12	127,25	127,62	53,12	54,18	53,2	70,10	68,49	67,54

Результаты вычислений, приведённые в таблице 3, далее обрабатывались способом, принятым в методе ВДПЭ, как результаты обычного лабораторного эксперимента. Обработка и интерпретация результата Y_1, заданного независимым от составного фактора, никак не отличались от принятых в рамках метода, за исключением того, что вместо каких-либо значений использовались порядковые номера уровней.

В таблице 4 представлены выборки для построения частных зависимостей Y_1 от рассматриваемых факторов.

Таблица 4

Выборки для построения частых зависимостей Y_1

от F_1						от F_2					
№		№		№		№		№		№	
1	3,96	4	5,98	7	9,87	1	3,96	2	10,44	3	20,41
2	10,44	5	14,28	8	8,23	4	5,98	5	14,28	6	14,72
3	20,41	6	14,72	9	17,08	7	9,87	8	8,23	9	17,08
Ср.	11,6		11,66		11,73	Ср.	6,6		10,98		17,4
X_1	1		2		3	X_2	1		2		3
от F_3						от F_4					
№		№		№		№		№		№	
1	3,96	2	10,44	3	20,41	1	3,96	2	10,44	3	20,41
6	14,72	4	5,98	5	14,28	5	14,28	6	14,72	4	5,98
8	8,23	9	17,08	7	9,87	9	17,08	7	9,87	8	8,23
Ср.	8,97		11,17		14,85	Ср.	11,77		11,68		11,54
X_3	1		2		3	X_4	1		2		3

Аппроксимирующая функция для каждой из частных зависимостей выбиралась по максимуму коэффициента нелинейной множественной корреляции (КНМК) из семи часто применяемых формул: $y = a + bx$ (8); $y = a + b/x$ (9); $y = \dfrac{1}{a + bx}$ (10); $y = a + b\ln x$ (11); $y = ax^b$ (12); $y = ab^x$ (13); $y = ae^{bx}$ (14); $y = ae^{bx}x^c$ (15).

Функцию (15) при аппроксимации не применяли, так как она описывает любые три точки со стопроцентной точностью (так же, как полином второго порядка) и является частой причиной ошибочного описания значимости функций при числе экспериментов менее 25.

На рисунке 1 (*а–г*) приведены графики функций, описывающих частные зависимости Y_1 от рассматриваемых факторов. Несложно заметить, что зависимость результата от F_1 описывается прямой, практически совпадающей с линией среднего значения. Следовательно, составной фактор не оказывает влияния на результат. Что и было задано соответствующей функцией генерации данных.

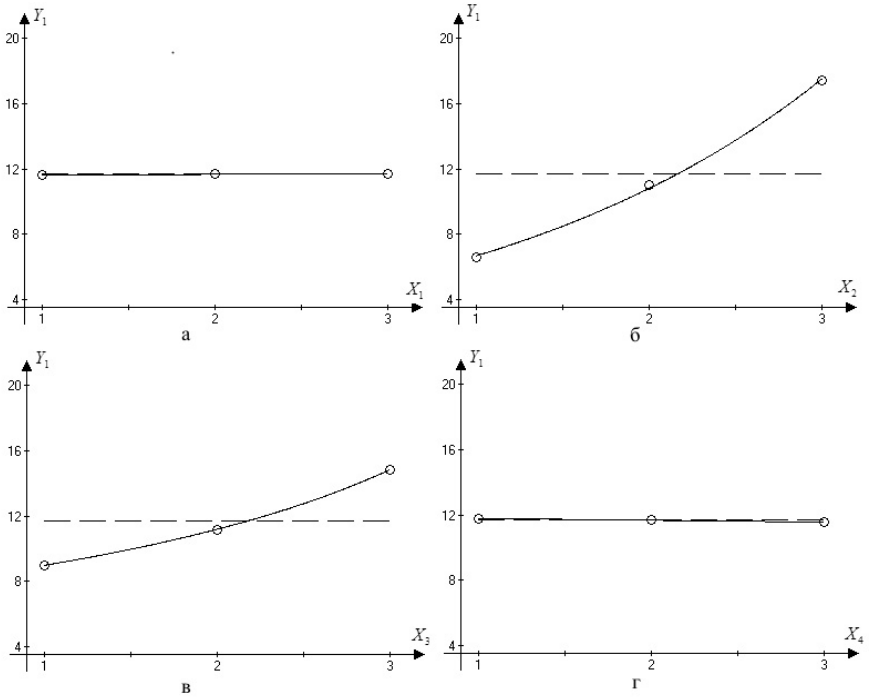

Рисунок 1. Частные зависимости Y_1 от F_1 (*а*), F_2 (*б*), F_3 (*в*) и вакантного фактора (*г*)

Как видно из рисунка 1(*г*) и соответствующей частной функции, вакантный фактор почти идеально описывается прямой, близкой к линии среднего значения. Когда речь идёт о специально сгенерированных данных и правильно подобранном виде среднего, иного ожидать не приходится [5 и др.]. Поэтому на остальных рисунках, иллюстрирующих выборки на частные зависимости, вакантный фактор удалён. Итоговое уравнение, полученное методом ВДПЭ (16), описывает систему (1) с $R = 0{,}9991$; $t_R = 1360{,}215$; $\overline{A} = 0{,}0204$.

$$Y_1 = 4{,}101 * 1{,}623^{X_2} + \frac{1}{0{,}1336 - 0{,}02209 X_3} - 11{,}6633. \qquad (16)$$

Y_2 и Y_3 заданы заведомо зависимыми от компонентов составного фактора K_2 и K_4. Наличие зависимости можно наблюдать уже при использовании порядковых номеров, однако описать такую зависимость функциями 5–11 оказывается невозможным из-за ярко выраженного экстремума. При замене номеров на значения уровней обнаруживается закономерность, близкая к зависимости, заданной формулой синтеза данных. В таблицах 5 и 6 приведены выборки для аппроксимации функций, описывающих частные зависимости Y_2 и Y_3 от рассматриваемых факторов (рис. 2, 3).

Таблица 5

Выборки для построения частых зависимостей Y_2

От F_1(K$_2$)						От F_2					
№		№		№		№		№		№	
1	55,6	4	81,11	7	108,26	1	55,6	2	62,41	3	75,3
2	62,41	5	86,53	8	112,78	4	81,11	5	86,53	6	98,52
3	75,3	6	98,52	9	127,25	7	108,26	8	112,78	9	127,25
Ср.	64,4367		88,72		116,0967	Ср.	81,6567		87,24		100,3567
$X_1(K_2)$	1(6)		2(9)		3(12)	X_2	1		2		3
От F_3						От F_4					
№		№		№		№		№		№	
1	55,6	2	62,41	3	75,3	1	55,6	2	62,41	3	75,3
6	98,52	4	81,11	5	86,53	5	86,53	6	98,52	4	81,11
8	112,78	9	127,25	7	108,26	9	127,25	7	108,26	8	112,78
Ср.	88,9667		90,2567		90,03	Ср.	89,7933		89,73		89,73
X_3	1		2		3	X_4	1		2		3

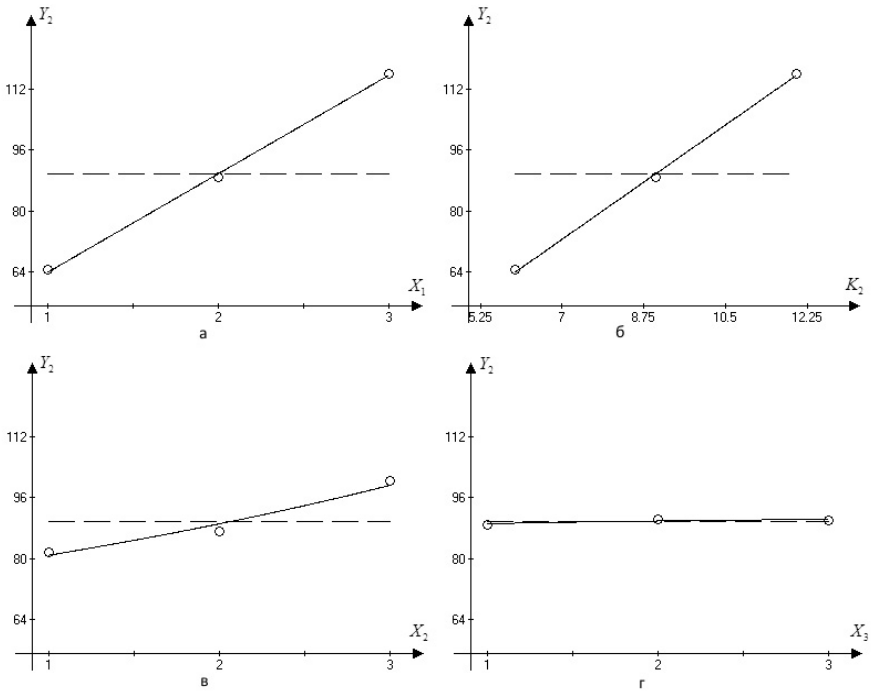

Рисунок 2. Частные зависимости Y_2 от F_1 (*а*), K_2 (*б*), F_2 (*в*) и F_3 (*г*)

Формула (17) отображает описание системы (2), полученное с помощью ВДПЭ. $R = 0{,}9964$; $t_R = 310{,}005$; $\overline{A} = 0{,}0239$.

$$Y_2 = 12{,}26 + 8{,}61K_2 + \frac{1}{0{,}01351 - 0{,}001143X_2} + 89{,}11X_3^{\,0.01189} - 179{,}5022\,. \qquad (17)$$

При использовании X_1, заданного порядковым номером, точность уравнения не изменяется, поскольку закономерность изменения порядкового номера совпадает с таковой для K_2.

Таблица 6

Выборки для построения частых зависимостей Y_3

От $F_1(K_4)$						От F_2					
№		№		№		№		№		№	
1	65,06	4	24,06	7	32,88	1	65,06	2	69,21	3	81,37
2	69,21	5	30,73	8	41,32	4	24,06	5	30,73	6	43,25
3	81,37	6	43,25	9	54,18	7	32,88	8	41,32	9	54,18
Ср.	71,88		32,68		42,7933	Ср.	40,6667		47,0867		59,6
$X_1(K_4)$	1(12)		2(4)		3(6)	X_2	1		2		3
От F_3						От F_4					
№		№		№		№		№		№	
1	65,06	2	69,21	3	81,37	1	65,06	2	69,21	3	81,37
6	43,25	4	24,06	5	30,73	5	30,73	6	43,25	4	24,06
8	41,32	9	54,18	7	32,88	9	54,18	7	32,88	8	41,32
Ср.	49,8767		49,15		48,3267	Ср.	49,99		48,4467		48,9167
X_3	1		2		3	X_4	1		2		3

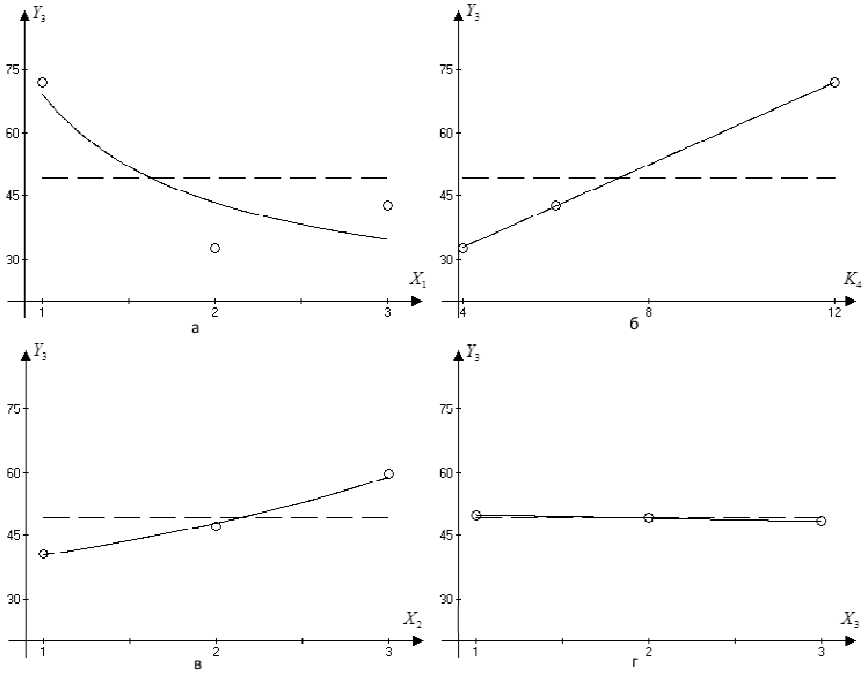

Рисунок 3. Частные зависимости Y_3 от F_1 (*а*), K_4 (*б*), F_2 (*в*) и F_3 (*г*)

Уравнение (18) учитывает зависимость Y_3 от K_4 и имеет $R = 0{,}9979$; $t_R = 531{,}8375$; $\overline{A} = 0{,}0179$. Если вместо значений K_4 использовать их порядковые номера, точность уравнения резко падает ($R = 0{,}8326$; $t_R = 6{,}0687$).

$$Y_3 = 13{,}27 + 4{,}888K_4 + \frac{1}{0{,}02868 - 0{,}003905X_2} + 50{,}67 - 0{,}775X_3 - 98{,}2356\,. \qquad (18)$$

Результат Y_4 получен при использовании в качестве действующей переменной произведения значений K_1 и K_4. Поскольку значения произведения не повторяются, оно полностью подходит по требованиям и может рассматриваться как отдельный компонент составного фактора. Выборки на частные зависимости представлены в таблице 7. Рисунок 4 описывает полученные частные функции графически.

Таблица 7

Выборки для построения частых зависимостей Y_4

От $F_1(K_1*K_4)$						От F_2					
№		№		№		№		№		№	
1	45,49	4	24,33	7	49,79	1	45,49	2	52,63	3	64,81
2	52,63	5	31,43	8	56,38	4	24,33	5	31,43	6	44,31
3	64,81	6	44,31	9	68,49	7	49,79	8	56,38	9	68,49
Ср.	54,31		33,3567		58,22	Ср.	39,87		46,8133		59,2033
$X_1(K_1K_4)$	1(48)		2(24)		3(54)	X_2	1		2		3
От F_3						От F_4					
№		№		№		№		№		№	
1	45,49	2	52,63	3	64,81	1	45,49	2	52,63	3	64,81
6	44,31	4	24,33	5	31,43	5	31,43	6	44,31	4	24,33
8	56,38	9	68,49	7	49,79	9	68,49	7	49,79	8	56,38
Ср.	48,7267		48,4833		48,6767	Ср.	48,47		48,91		48,5067
X_3	1		2		3	X_4	1		2		3

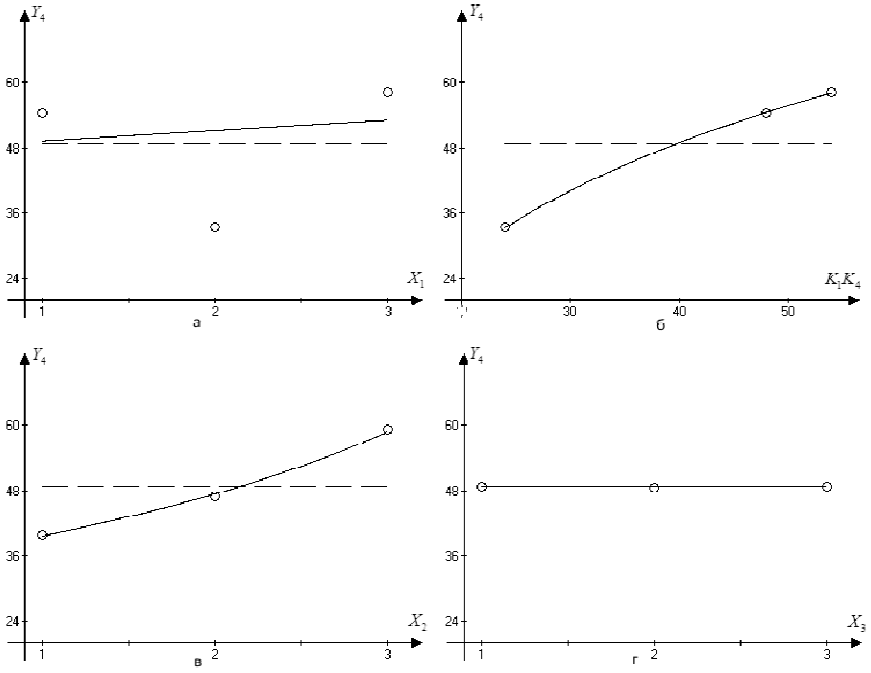

Рисунок 4. Частные зависимости Y_4 от F_1 (*а*), K_1*K_4 (*б*), F_2 (*в*) и F_3 (*г*)

Уравнение (19) отлично описывает Y_4, если учитывать значения произведения K_1*K_4 ($R = 0{,}9988$; $t_R = 931{,}1356$; $\overline{A} = 0{,}0277$). При использовании номеров фактора картина существенно ухудшается ($R = 0{,}5051$; $t_R = 1{,}7941$).

$$Y_4 = -63{,}64 + 30.51\ln(K_1K_4) + \frac{1}{0{,}0293 - 0{,}004095X_2} + 48{,}68 - 0{,}025X_3 - 97{,}2578\,. \qquad (19)$$

При анализе приведённых рассуждений и данных возникает вопрос: как поведут себя частные зависимости от двух и более компонентов составного фактора в случае, если их уровни зависят от номеров сходным образом: например, возрастают или убывают от первого к последнему? Действи-

тельно, только математическими приёмами ВДПЭ различить, какой из факторов вызывает наблюдаемый результат, не получится. Рассмотрим частные зависимости Y_2 от K_1 и K_3 (табл. 8, рис. 5 *а*, *б*).

Таблица 8

Выборки для построения частной зависимости Y_2 от K_1 и K_3

От $F_1(K_1)$						От $F_1(K_3)$					
№		№		№		№		№		№	
1	55,6	4	81,11	7	108,26	1	55,6	4	81,11	7	108,26
2	62,41	5	86,53	8	112,78	2	62,41	5	86,53	8	112,78
3	75,3	6	98,52	9	127,25	3	75,3	6	98,52	9	127,25
1	64,4367		88,72		116,0967	Ср.	64,4367		88,72		116,0967
X_1	1(4)		2(6)		3(9)	X_2	1(9)		2(12)		3(4)

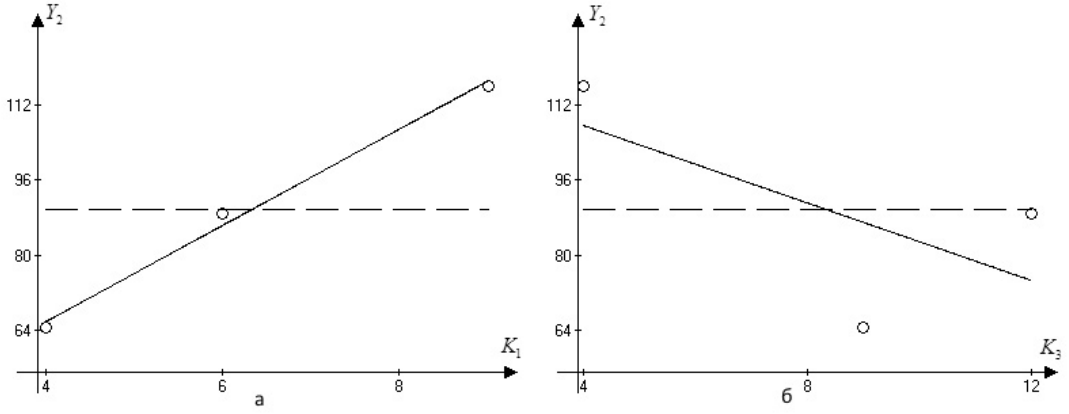

Рисунок 5. Частные зависимости Y_2 от K_1 (*а*), K_3 (*б*)

В целом возрастающая зависимость Y_2 от K_1 похожа на зависимость Y_2 от K_2. Показатели точности для такой модели довольно высоки: $R = 0{,}9916$; $t_R = 132{,}5379$. В то же время для остальных компонентов составного фактора значимую зависимость по формулам (5–11) подобрать не удаётся. Например, при попытке использовать значение K_3 модель получается полностью неадекватной ($R = 0{,}2873$; $t_R = 0{,}7671$).

Резюмируя изложенное выше, можно заключить, что составной фактор может быть использован в планировании эксперимента с применением ВДПЭ. Для успеха расчётов необходимо соблюдение ряда условий.

1. Число уровней варьирования исследуемых компонентов фактора должно быть равно числу уровней факторов в плане ВДПЭ. Это требование соблюдается путём добавления вакантных факторов в основной план или же, наоборот, добавлением «вакантного компонента» в составной фактор.

2. Зависимость значения уровня от его номера должна быть различной для всех изучаемых компонентов составного фактора. Это требование легко соблюдается при использовании латинского квадрата, получаемого сдвигом строки на одну позицию и добавлением «выпавшей цифры» в начало строки.

3. Сведения о возможности или невозможности зависимости результата от данного компонента составного фактора, полученные из других источников, могут быть использованы для выбора итогового уравнения. При этом соблюдение пункта 2 становится необязательным.

4. Поиск парных, тройных и т.д. зависимостей от компонентов составного фактора может быть осуществлен путем перебора возможных вариантов.

Метод предлагается использовать для калибровки спектральных приборов с применением специально составленных смесей. Модификации методов калибровки, в которых предполагается использовать данную методику, не сложнее других современных методов калибровки атомно-эмиссионных спектрометров, для которых настоятельно рекомендуется использовать планирование эксперимента [6] и часто применяются «изощрённые методы статистической обработки спектров» [7, 8]. Применение методики представляется возможным и в других областях науки и техники.

Идея метода возникла при обработке экспериментальных данных, полученных в рамках работы по теме «4371/ГФ4 — Изучение совместного осаждения солей дикарбоновых кислот элементов, образующих многоэлементные оксиды с высокотемпературной сверхпроводимостью».

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Тәжірибені ықтималды-детерминді жоспарлау әдісінде көпфакторлы айнамалыны қолдану

Мақалада тәжірибені ықтималды-детерминді жоспарында (ТЫДЖ) бірнеше мәндерді ұялы жоспарға топтау арқылы біріктіретін бір ғана айнымалы шама бола алатындығы көрсетілді. Үш деңгейдегі түрлендірудің төрт факторлы жоспарлау мен «құрамды фактор» мысалында көпкомпонентті жүйенің математикалық үлгісін құру әдісі көрсетілді. Ұсынылатын есептеу әдістемесінің кейбір шектеулері ескерілген. «Құрамды фактордың» бір ғана компонентінің нәтижеге әсер беруі ТЫДЖ әдісін түр өзгерісінсіз қолдануға мүмкіндік беретіндігі көрсетілген. «Құрамды фактордың» компоненттерінің жұпты әсері сызықты көптік корреляция коэффициенттерінің өсуі бойынша нұсқаларды іріктеу көмегімен анықталатындығы мысал ретінде көрсетілген. Математикалық үлгіні құрудың қажетті жағдайы — «құрамды фактордың» әрбір компонентінің әсері тәжірибе жоспарындағы факторлардың түрлену деңгейлер санының компонент деңгейінің санына тепе-тең болады. Әдісті сынамалау барысында нақты мәндері белгілі болатын «жасанды мәліметтер» пайдаланылды. Тәжірибе қателігін ұқсату үшін есептік мәндер бір санына жақын кез келген санға көбейтілді. Алынған үлгінің дәлділігін бағалау — әдебиеттерде жалпы мақұлданған критерийлер — орташа мән және ТЫДЖ әдісінде қабылданған сызықты көптік корреляция коэффициенті көмегімен жүргізілді. Әдіс ТЫДЖ пайдалану арқылы күрделі жүйелерді зерттеуге қажетті тәжірибелер санын қысқартуға мүмкіндік берді. Авторлардың ойынша ұсынылған тәсілдемені көпкомпонентті жүйенің және «құрамды факторлардың» бір ғана компонентіне тәуелді болатын спектралды талдауға қолдануға мүмкіндік туады.

Кілт сөздер: тәжірибені ықтималды-детерминді жоспарлау, факторлы тәжірибе, спектралды талдау.

V.N. Fomin, A.A. Kovaleva, S.K. Aldabergenova

Use of a multifactorial variable in the method of the stochastic-determinated design of experiment

The article shows that, as at least one of the factors in the SDDE plan, a variable that unites several quantities by grouping into a nesting design can act. An example of a four-factorial plan with three levels of variation and a «composite factor» containing four components shows the way to construct a mathematical model of a multicomponent system. Some limitations of the proposed calculation methodology are stipulated. It is shown

that the influence on the result of only one component of the «composite factor» makes it possible to use the SDDE method without modifications. The example shows that the pair effect of the components of the «composite factor» can be detected by looking through the options for increasing the coefficient of nonlinear multiple correlation. As necessary conditions for constructing a mathematical model of the influence of each of the components of the «composite factor» on the result, the equality of the number of levels of the component to the total number of levels of factor variation in the experimental plan is indicated. When testing the method, «artificial data» is used, the exact values of which are known. To simulate the experimental error, the calculated values were multiplied by a random number close to unity. Estimation of the accuracy of the obtained models was carried out with the help of the commonly accepted criterion in the literature — the mean error, and using the coefficient of nonlinear multiple correlation adopted in the SDDE method. The method makes it possible to significantly reduce the number of experiments needed to study complex systems using the SDDE. The approach developed in the article is proposed mainly for application in the spectral analysis of multicomponent systems and in other cases when the result depends only on one of the components of the «composite factor».

Keywords: stochastic-determinated design of experiment, factor experiment, synthetic data, partial dependence, combined factor, mean deviation, spectral analysis.

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UDC 543:615.2/.3

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About quantitative determination of flavonoids in vegetative raw materials

Numerous researches show that the medicines created on the basis of flavonoids are high performance antineoplastic tools, have antioxidatic properties, reduce risk of diseases of cardiovascular system. Currently physical and chemical methods of the analysis, such as spectrophotometry, absorption spectroscopy are widely used for the identification and quantitative determination of flavonoids in medicines. However, combined methods involving various variants of chromatographic separation of the investigated components are increasingly spreading. Wide use of physicochemical and combined methods of analysis is primarily due to the fact that these methods have a much greater sensitivity and selectivity in comparison with modern chemical and electrochemical methods. Literary data on researching new, and also development and exploitation of existing methods for quantitive determination of flavonoids in vegetative raw were generalized and analyzed. Special attention is paid to such analyzing methods as method of high-performance liquid chromatography, spectrophotometry and chromato-mass-spectrometry. The HPLC method is a fast, highly reproducible method that requires a small amount of analyte and is used for quantitative, qualitative analysis and preparative release. The most accessible and objective method for controlling biologically active compounds in plant raw materials is the chromato-mass-spectrometric method of analysis, which makes it possible to identify individual flavonoids, regardless of the presence of extraneous or related compounds. It is established that most of the studies are based on the methods for the quantitative determination of flavonoids, set out in the European and British pharmacopoeias, and are widely used to standardize many types of raw materials containing flavonoids.

Keywords: flavonoids, quercetin, high-performance liquid chromatography, spectrophotometry, complexometric titration.

Introduction

Currently pharmacologists are interested in substances of flavonoids group. Flavonoids are a group of widespread natural antioxidants in which moleculestwo benzene rings linked by a three carbon fragment containing oxygen. These compounds are a part of many medicines and dietary supplements (DS) and have a number of beneficial properties for the human body. Numerous researches have shown that the medicines created on the basis of these substances are highly effective antineoplastic means, have antioxidant properties, reduce risk of diseases of cardiovascular system [1–8].

It should be noted that valuable feature of flavonoids, along with high biological activity, is their low toxicity.

Depending on the structure of the oxygen-containing fragment flavonoids are classified into several classes (see Fig.). Depending on the number and the nature of substituents on the benzene rings flavonoids subdivide also into subclasses [3, 9]. Flavonoids are widespread in flora, particularly in higher plants belonging to the bean, Rosacea, Asteraceae, buckwheat families [3, 9].

Quercetin — 5,7,3′,4′-tetrahydroxyflavonol — one of the most widespread natural antioxidants of a series of flavonoids which is a part of many medicinal preparations and DS. It possesses a wide range of biological effect on a human body, in particular, anticancerogenic, anti-inflammatory, antioxidatic, antihistamine action, slows down processes of cell aging of a skin, cornea, myocardium [3, 9–12].

Materials and methods

Along with quercetin the reare relatively large amounts of individual flavonoids in plant facilities. So the task of the selective isolation of their raw materials and their subsequent determination requires the use of different methods of analysis of natural objects, which give the opportunity to fully characterize complex composition and low content of flavonoids.

Currently, physical and chemical methods of analysis, such as spectrophotometry, absorption spectroscopy widely used for identification and quantification of flavonoids in drugs. However, increasingly used the combined methods, including various options for the chromatographic separation of the investigated components. Wide use of the physical and chemical and combined analysis methods, first of all, is bound to the fact

that these methods have considerably larger sensitivity and selectivity in comparison with the modern chemical and electrochemical methods.

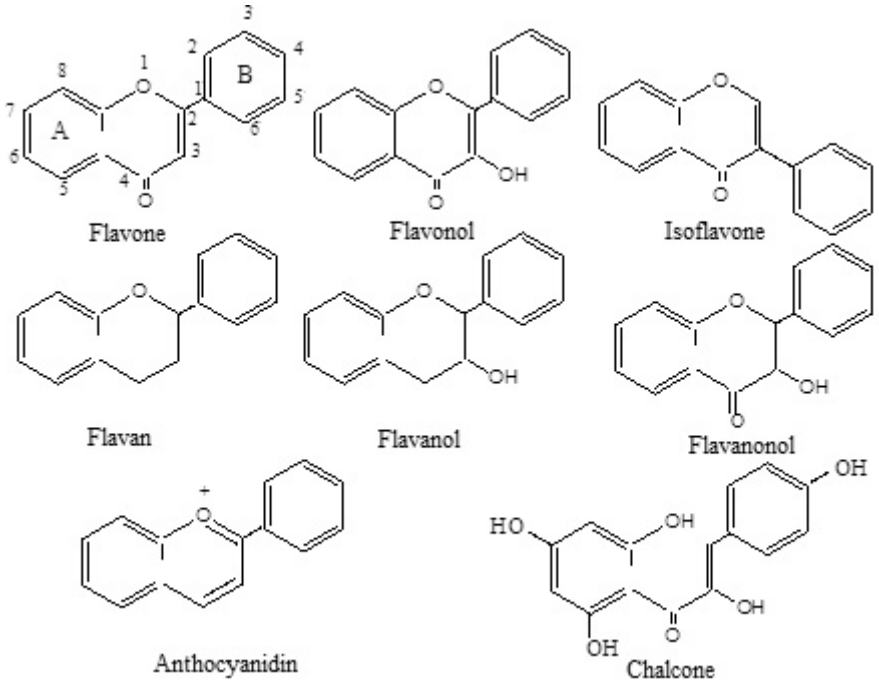

Figure. Members of the main classes of natural flavonoids

The adsorption and chromatographic method is used for division of flavonoids among themselves and separations from the accompanying substances [7].

Results and discussion

For determination of flavonoids in extracts from plants as well as in foods often use high-performance liquid chromatography (HPLC) after pre-concentration of flavonoids using solid phase extraction. In this case the selection or group identification of flavonoids is complicated by restriction of quantity of sorbents.

The HPLC method is a rapid, highly reproducible method which requires a small amount of an analyte and is used for quantitative and qualitative analysis of preparative selection[13].

For flavonoids columns with versed and phase sorbents and detection with a UV-visible detector with variable wavelength are more used. Currently widely used photodiode detector, which allows to obtain UV-visible spectrum of the substance simultaneously with the release of the peak in the chromatogram. This experimental reception considerably facilitates a problem of identification of substances. Mobile phases (eluent systems) tend to be binary and contain acidic polar component (aqueous solutions of acetic, per chloric acid, phosphoric acid or formic acid) and a less polar organic solvent (acetonitrile or methanol) [13, 14].

Gradient mode is most suitable for the separation of complex mixtures of flavonoids. For columns with reversed-phase sorbents typical gradient programs are based on the use of mobile phases with prevalence at the start of the proportion of polar solvent with a further gradual increase in the proportion of a less polar solvent. Correlation peaks in the chromatogram is the most difficult task. A convenient technique is the use of parallel chromatography of standard samples and compare them with the chromatogram of the investigated object. Standard substance should ideally be more akin flavonoids and have similar chromatographic properties. When standard substance is chromatographed under the same conditions, but in parallel, it is called an external standard. Internal standard (added to the investigated sample before putting into the chromatograph) must meet the following conditions: in the mixture should not contain analogous substance and peakof standard must not overlap with any compound in the mixture. Such restrictions are absent in the case of using an external standard.The advantages of an internal standard is the validation of extraction, sample preparation, chromatographic procedures. Rutinum is often used as a standard substance for flavonoids, it is a commercial available product. It is well suited for quantitative analysis of flavonol glycosides. For other flavonoids which are contained in mixture such commercially available standards as apigenin-7-glucoside —

for flavone glycosides, catechin — for flavan-3-ols, naringenin — for dihydroflavons, dihydroquercetin — for dihydroflavonols, daidzein — for isoflavones can be used [13, 14]. For the quantitative analysis the graph of concentration of the flavonoid versus the area of peak for each standard is constructed. The corresponding calibration curves can be used for calculation of quantity of the flavonoid represented by each peak of HPLC chromatogram. Currently, almost disappeared need for the construction of calibration curves due to provision of chromatographs with computer system which is calculated area of peaks [14].

For the quantitative determination of flavonoids using volumetric methods of analysis. So the method of complexometric titration of excess lead acetate, is not entered in the deposition reaction with flavonols, has sufficient selectivity and allows the determination of flavonols in the presence of acetylsalicylic acids, anthraquinones, coumarins. The method of oxidation of flavonoids with potassium ferrocyanide on p-phenyl — aptronilic acid also belongs to a titrimetric method of the analysis. However the method is long and has no selectivity.

Potentiometric titration of the quantitative determination of flavonoids relates to a method of electrochemical analysis, based on the measurement of change during the titration of the electrochemical potential of the electrode immersed in the test solution. Quantitative determination of flavonoids in non-aqueous solvent medium, for example, acetone, dimethylformamide, dimethylsulfoxide by a potentiometric method perhaps with use as titrant of a hydroxide of a tetraethylammonium or sodium. This method gives more accurate results, and does not require standard substances for quantifying compared with optical methods. Low sensitivity (required for analysis 0.0005–0.001 g of substance) and poor selectivity for each of the classes difficult to identify without prior separation of substances in raw materials and total preparations [15].

Reduction of flavonoids on a mercury dropping electrode is the basis for a highly sensitive polarographic method of the analysis. The method allows to analyze the amount of flavonoids, in terms of one of connections chosen as the standard. The method gives results more close to the true cooperative contents for flavonoids unlike a spectophotometery of the colored complexes Flavonoids (flavanols) can be defined against the background of 0.4 M ammonium chloride solution at a half-wave potential of 1.5 V. Polarographic method allows the presence of intramolecular bonds, the identification largest half-wave potential, evaluate the reactivity of the individual groups in the molecule. In practice of the pharmaceutical analysis and in particular industrially the polarographic analysis has difficulties as demands keeping of rigorous conditions of the accident prevention during the work with Hydrargyrum. The disadvantages of the method are its low selectivity because of the close values of half-waves of potentials, in connection with what is required, as in the case of spectral methods, preliminary separation of substances [16].

In modern science, for the detection and quantification of flavonoids in the plant material is also used capillary electrophoresis method [17]. The method of a capillary electrophoresis is based on division of components of the complex mixture in a quartz capillary under the influence of the enclosed electric field. The microvolume of the analyzed solution is entered into the capillary beforehand filled with the suitable buffer — electrolyte. After supplying a high voltage to the ends of the capillary (30 kV), the components of the mixture begins to move through the capillary at different rates, depending primarily on charge and mass (or rather — ionic radius) and, respectively, at different times reach the detection zone. The resulting sequence of peaks called electrophoregrams. Qualitative characteristic of the substance is the retention parameter (during migration), and quantitative — height or peak area, which is proportional to the concentration of the substance. The advantages of capillary electrophoresis are: high separation efficiency, economy (low consumption of reagents) and expressivity.

Quantitative determination of the investigated flavonoid compound in the UV- and visible spectra based on measurement of an optical density at a wavelength in maxima of absorption both solutions of the analyzed substances, and solutions of their painted complexes. Spectrophotometric determination of the maxima of the intrinsic absorption is one of the most common methods for the analysis of flavonoids. At the same time serve as working ranges of lengths of waves as long-wave maxima for flavonoids — 330–370 nm, and shortwave. Shortwave maxima, although more intense, but in many cases less suitable for analytical purposes due to the small «area» top peak, which leads to large errors in the determination. The relative error of the direct spectrophotometric determination is ± 2–5 % and can be reduced in the differential analysis technique to 0.5–1.0 %. The working range of concentrations of alcohol, water-alcohol solutions is from 5 to 20 g substance in 1 ml. With its high sensitivity, the method is not selective because they do not control the content of each of the substances of the class of compounds [18].

Spectrophotometric or photometric determination by diazotization reaction were previously widely distributed in the analysis. The reaction is sensitive, but not selective, because along with flavonoids phenolic

connections, pyrazyl ketones and other classes of connections give this reaction. Even total determination with this reactant do not show the true content of the studied substances, both in cooperative phytochemical medicines, and in vegetable raw materials.

Techniques of determination of flavanols on color complex compounds with aluminum chloride, zirconium oxychloride (zirconyl chloride), gallium nitrate have larger specificity. The colored solutions have maxima in intervals: 385–460 nm with aluminum chloride, 385–500 nm with zirconyl chloride, 400–455 nm with gallium nitrate. Method using gallium nitrate, allowing quantification of 0.5 μg in 1 mL of the solution, then zirconium oxychloride — 0.9–1.0 μg and aluminum chloride — 1–2 μg has the greatest sensitivity [19, 20].

Methods of the analysis of flavonoids with cobalt nitrite in the medium of an acetic acid at a wavelength of 575 nm, and also with zinc and arsenic are described. It is possible to receive the true cooperative maintenance of flavonoids by training of color complexes with metals only in the presence at connections of identical quantity of the complexing centers. Despite these drawbacks, a method has been widely used in determining total flavonoid content in raw materials and total phytochemical preparations. As a standard used quercetin, kaempferol and their glycosides [9].

A photometric method for determining the complexation reaction with boric acid at a wavelength of 470 nm is widely used in determining the total amount of flavonoid compounds in plants. The technique has the same disadvantages as the method of complexation with metal salts, and gives higher results but the simplicity and availability of reagent allowed to use them for indicative determinations. As samples are used aglycones, glycosides of flavones, flavonols, chalcones. Working concentration of solutions 1–10 μg/ml. The relative error of determination is ± 3.35 %.

Borohydride method is most sensitive in the range of spectrophotometric methods for the analysis of flavanones (up to 0.5–1 μg/mL at wavelengths of 535–560 nm). Despite considerable selectivity, it is not widely used because of the short time stability of the colored complex and poor reproducibility of results.

Fluorometric method is based on the complexone-forming properties of flavonoids, which is more sensitive than spectrophotometric. It is possible to determine flavonoids quantitatively by this method, if in 1 ml of solution — 0.05–1 μg of substance. The high sensitivity of fluorometric method allows us to use it for the preliminary identification of biologically active substances in plant tissues. However, to obtain the correct results in the analysis of raw materials and phytochemical preparations is possible only after separation of substances by using various kinds of chromatography.

Chromato-mass spectrometers — method for analysis of mixtures, mainly organic substances and determination of trace amounts of substances in the volume of liquid. The method is based on a combination of the two independent methods — chromatography and mass spectrometry. With the first method, is performed on the separation of the mixture, using a second — identification and determination of structure of the substance, quantitative analysis. There are two options of chromato-mass spectrometers: a combination of mass spectrometry with a gas-liquid chromatography (GC) or HPLC.

The paper contains idea of quantification of flavonoids in elderberry extract, enriched in phenolic acids, polyphenolic flavonoids and other compounds through the use of mass spectrometry DART (Direct Analysis in Real Time), which differs from the conventional mass spectrometry in that the ionization of low molecules from the surface of the liquid or solid objects in the gas allows to do without stages of sample preparation and chromatographic separation [21].

Conclusions

Flavonoids are extremely multifaceted. Equally, they are interesting as objects of study in Botany, Pharmacognosy, Phytochemistry, and especially in pharmacy and medicine.

In this paper flavonoids mainly studied from chemical positions. Namely, the basic methods of quantitative determination of flavonoids in herbal drugs are considered. Particular attention is paid to such methods of analysis as a method of high performance liquid chromatography, spectrophotometry and gas chromatography-mass spectrometry. The basis of most of the research is the method of quantitative determination of flavonoids as set out in the European and British Pharmacopoeia, and is widely used for the standardization of many raw materials containing flavonoids [22, 23]. It was established that the most reasonable and objective method for monitoring of biologically active compounds in plant material and summary of phytochemical preparations is chromato-mass-spectrometric analysis method that allows the identification of individual flavonoids is not dependent on the presence of extraneous or related compounds.

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Өсімдік шикізаттағы флавоноидтерді сандық анықтау әдістері туралы

Көптеген зерттеулер бойынша флавоноидтерге негізделген препараттар жоғары деңгейде ісікке қарсы құралдар болып табылады, тотығуға қарсы қасиеттері бар және жүрек қан-тамыр жүйесінің ауруларының қауіпін азайтады. Флавоноидтердің құнды ерекшелігі — олардың уыттылығы төмен. Қазіргі кезде дәрілік құралдардағы флавоноидтерді анықтау үшін спектрофотометрия, абсорбциялық спектроскопия сияқты, физика-химиялық талдау әдістері кеңінен қолданылады. Зерттелетін компоненттерді хроматографиялық бөлудің әр түрлі вариантарын қамтамасыз ететін құрама әдістер де кеңінен пайдалануда. Қазіргі кездегі химиялық және электрохимиялық әдістермен салыстырғанда, физика-химиялық және комбинирленген талдау әдістерінің кеңінен қолданылуы олардың неғұрлым

үлкен сезімталдығына және іріктілігіне байланысты. Жұмыста өсімдік шикізаттағы флавоноидтерді сандық анықтаудың жаңа әдістері және казіргі кезде қолданылатын әдістерді дамыту жөніндегі әдеби мәліметтер талданды және сарапталды. Жоғары нәтижелі сұйықтық хроматография, спектрофотометрия және хроматомасспектрометрия сияқты әдістерге ерекше назар бөлінді. Жоғары нәтижелі сұйықтық хроматография — өте тез және жақсы өндірілетін, зерттелетін заттың аз мөлшерін қажет ететін, сапалық және сандық талдауда, заттарды препараттық бөліп алуда қолданылатын әдіс. Өсімдік шикізаттағы биологиялық белсенді заттарды бақылаудың ең тиімді және нақты әдісі — хроматомасспектрометрия. Бұл әдіс бөгде және флавоноидтерге ұқсас қосылыстардың болуына тәуелсіз жеке флавоноидтарды идентификациялауға мүмкіндік береді. Көптеген зерттеулердің Еуропалық және Британ фармакопеясында көрсетілген флавоноидтардың сандық анықталу әдістеріне негізделгені анықталды.

Кілт сөздер: флавоноидтар, кверцетин, жоғары сапалы сұйық хроматография, спектрофотометрия, комплексометриялық титрлеу.

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О методах количественного определения флавоноидов в растительном сырье

Многочисленные исследования показывают, что препараты, созданные на основе флавоноидов, являются высокоэффективными противоопухолевыми средствами, обладают антиоксидантными свойствами, снижают риск заболеваний сердечно-сосудистой системы. В настоящее время для идентификации и количественного определения флавоноидов в лекарственных средствах широко используются физико-химические методы анализа, такие как спектрофотометрия, абсорбционная спектроскопия. Однако все большее распространение получают комбинированные методы, включающие различные варианты хроматографического разделения исследуемых компонентов. Широкое использование физико-химических и комбинированных методов анализа, в первую очередь, связано с тем, что эти методы обладают значительно большей чувствительностью и селективностью по сравнению с современными химическими и электрохимическими методами. В работе обобщены и проанализированы литературные данные по разработке новых, а также развитию и применению существующих методов количественного определения флавоноидов в растительном сырье. Особое внимание уделено таким методам анализа, как метод высокоэффективной жидкостной хроматографии (ВЭЖХ), спектрофотометрия и хроматомасспектрометрия. Метод ВЭЖХ является быстрым, хорошо воспроизводимым методом, который требует малого количества анализируемого вещества и используется для количественного, качественного анализа и препаративного выделения. Наиболее доступным и объективным методом контроля биологически активных соединений в растительном сырье является хроматомасспектрометрический метод анализа, позволяющий идентифицировать отдельные флавоноиды независимо от присутствия посторонних или родственных соединений. Установлено, что большинство исследований основаны на методиках количественного определения флавоноидов, изложенных в Европейской и Британской фармакопеях и широко применяемых для стандартизации многих видов сырья, содержащих флавоноиды.

Ключевые слова: флавоноиды, кверцетин, высокоэффективная жидкостная хроматография, спектрофотометрия, комплексометрическое титрование.

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БЕЙОРГАНИКАЛЫҚ ХИМИЯ
НЕОРГАНИЧЕСКАЯ ХИМИЯ
INORGANIC CHEMISTRY

UDC 541.11:546.244

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Thermochemistry of new holmium-calcium tellurite

The new double holmium-calcium tellurite was synthesized by the ceramic technology. The formation of the equilibrium composition of the compound was monitored by X-ray diffraction. Double tellurite of holmium $HoCaTeO_{4.5}$ has been synthesized according to the results of X-ray analysis. Calorimetric investigation of the heat capacity of the new double tellurite $HoCaTeO_{4.5}$ was carried out for the first time in the range of 298.15–673 K. Calibration of the device was carried out on the basis of determining the thermal conductivity of a heat meter. The calorimeter performance was checked by measuring the heat capacity of α-Al_2O_3. The experimental data and the specific molar heat capacities have been processed by methods of mathematical statistics. The dependence equation $C_p^0 \sim f(T)$ has been derived on the basis of experimental data. According $C_p^0 \sim f(T)$ and the calculated value of $S^0(298.15)$ of tellurite the temperature dependence of the thermodynamic functions $H^0(T)–H^0(298.15)$, $S^0(T)$ and $\Phi^{xx}(T)$ have been determined. Abnormal jumps have been observed on the dependence $C_p^0 \sim f(T)$ associated probably with the phase transitions of the second order. The thermodynamic characteristics of the new tellurite can serve as source materials for inclusion in fundamental data banks and reference books, used to predict the thermochemical constants of similar compounds.

Keywords: calorimetry, holmium-calcium tellurite, heat capacity, phase transitions, thermodynamic functions.

Almost all processes observed in nature are associated with the transformation of energy by the absorption or release of heat. Knowledge in this area allows to understand better the structure of molecules, thermal effects of physical processes or chemical reactions and many biological phenomena, to optimize production processes and, and taking into account entropy, to identify the conditions of chemical equilibria. Information about the values of thermal effects and the nature of their occurrence is one of the main in the practice of research and in the optimization or control of many industrial processes.

Compounds of tellurium, which include little-studied complex oxo-compounds, in particular, double tellurites of *s-f*-elements, raise some interest because of their semiconducting, piezoelectric and ferroelectric properties.

At the Department of inorganic and technical chemistry of the Karaganda State University named after academician Ye.A. Buketov systematic research on search and the development of scientific bases of directed synthesis of new oxo-compound of tellurium and selenium which have unique physical properties has been carried out [1, 2].

The aim of this work was to study the calorimetry of new tellurite $HoCaTeO_{4.5}$ in the temperature range of 298.15–673 K.

Double holmium-calcium tellurite with $HoCaTeO_{4.5}$ composition was synthesized by the ceramic technology from holmium (III) oxide, tellurium (IV) oxide, and calcium carbonate of «chemically pure» grade. In our previous work [3] the method of synthesis and radiographic characteristics of this compound were described. Formation of the equilibrium composition of the compound was monitored by the X-ray analysis. The powder X-ray diffraction pattern of each compound was indexed by means of homology. The correct-

ness of the indication is confirmed by the good agreement between the experimental and calculated values $10^4/d^2$ and the agreement between the X-ray and pycnometric densities.

The heat capacities of double holmium-calcium tellurite were studied via dynamic calorimetry on an commercial IT-S-400 calorimeter in the temperature range of 298.15–673 K. The calibration of an instrument was carried out on the basis of determination of thermal conductivity of the calorimeter K_t [4]. Several experiments with copper sample and an empty vial were carried out for this purpose. The thermal conductivity of the calorimeter was determined by the formula

$$K_T = C_{\text{cop. sample}} / (\overline{\tau}_{TM} - \overline{\tau}^0_T), \quad (1)$$

where $C_{\text{cop. sample}}$ — full heat capacity of the copper sample, J/(mol·K); $\overline{\tau}_{TM}$ — the average time delay in the calorimeter in experiments with a copper sample, s; $\overline{\tau}^0_T$ — the average value of the time delay in experiments with an empty ampoule, s.

Full heat capacity of the copper sample was calculated by the formula

$$C_{\text{cop.sample.}} = C_M \cdot m_{\text{sample}}, \quad (2)$$

where C_M — the tabular value of the specific heat capacity of copper, kJ/(kg·K); $m_{\text{sample.}}$ — the mass of the copper sample, kg.

The specific heat capacity of the test substance calculated by the formula

$$C_{sp.} = \frac{K_T}{m_0} \cdot (\tau_T - \tau^0_T), \quad (3)$$

where K_T — the thermal conductivity of the calorimeter; m_0 — the mass of the test substance, kg; τ_T — the time delay of the temperature in the calorimeter, s; τ^0_T — the time delay of the temperature of the calorimeter in experiments with an empty ampoule, s.

Then, values of the molar heat capacity were calculated from the values of specific heat by the formula

$$C_M = C_{sp.} \cdot M, \quad (4)$$

where $C_{sp.}$ — specific heat of a substance, J/(g·K); M — the molecular weight of substance, g/mol.

Five parallel experiments were carried out at each fixed temperature, the results of which were processed by methods of mathematical statistics [5]. For the average values of the specific heat capacities at each temperature the standard deviation δ [J/(g·K)] was calculated according to the formula

$$\overline{\delta} = \sqrt{\sum_{i=1}^{n} \frac{(c_i - \overline{c})^2}{n-1}}, \quad (5)$$

where n — the number of experiments; c_i — the measured specific heat capacity; $\overline{c}$ — the arithmetic mean of the values of the specific heat capacity.

Random component of error was calculated for average values of molar heat capacity

$$\dot{\Delta}, \% = \frac{\delta t_P}{\overline{c}} \cdot 100, \quad (6)$$

where $\dot{\Delta}$ — the random component of error; t_P — Student's ratio is equal to 2.78 for $n = 5$ at $p = 0.95$. The random component of the error ($\dot{\Delta}$) is expressed in J/(mol·K).

Operation of the calorimeter was tested by measuring the heat capacity of α-Al_2O_3. The resulting $C_p^0(298.15)$ for α-Al_2O_3 = 76.0 J/(mol·K) was in satisfactory agreement with the reference value (79.0 J/(mol·K) [6]. The results of the study of the heat capacity of the synthesized holmium-calcium tellurite are presented in the Table 1.

From the results given in the Table 1, it is seen that error components in measuring heat capacities on the IT-S-400 calorimeter does not exceed (±10 %) in the entire temperature range [7].

In studying the temperature dependences of the heat capacities of double holmium — calcium tellurite at 398 and 548 K, we observed abnormally peaks associated probably with second-order phase transitions (see Fig.). These transitions could be due to the redistribution of cations, with the change in the coefficient of thermal expansion and changes in the magnetic moment of the double tellurite synthesized.

Based on the experimental data (Table 1) with considering the temperatures of second-order transitions there has been derived the equation of temperature dependence for the compounds heat capacity C_p^0 [J/(mol K)]

$$C_p^0 = a + bT + cT^{-2}, \quad (7)$$

the coefficients of which are given in the Table 2. The error in the coefficients of dependences $C_p^0 \sim f(T)$ was determined using average values of random errors for the considered interval of temperatures.

Table 1

Experimental specific and molar heat capacities of $HoCaTeO_{4.5}$

T, K	$C_p \pm \bar{\delta}$, J/(g · K)	$C_p \pm \dot{\Delta}$, J/(mol · K)
298.15	0.7530 ± 0.0008	305 ± 0
323	0.8063 ± 0.0253	326 ± 10
348	0.8441 ± 0.0013	342 ± 1
373	0.9793 ± 0.0475	396 ± 19
398	1.0406 ± 0.0001	421 ± 0
423	0.5664 ± 0.0004	229 ± 0
448	0.6059 ± 0.0177	245 ± 7
473	0.6324 ± 0.0046	256 ± 2
498	0.6830 ± 0.0009	276 ± 0
523	0.7898 ± 0.0409	320 ± 17
548	0.8262 ± 0.0007	334 ± 0
573	0.6583 ± 0.0609	266 ± 25
598	0.6376 ± 0.0000	258 ± 0
623	0.5696 ± 0.0062	230 ± 3
648	0.5080 ± 0.0233	206 ± 9
673	0.5016 ± 0.0001	203 ± 0

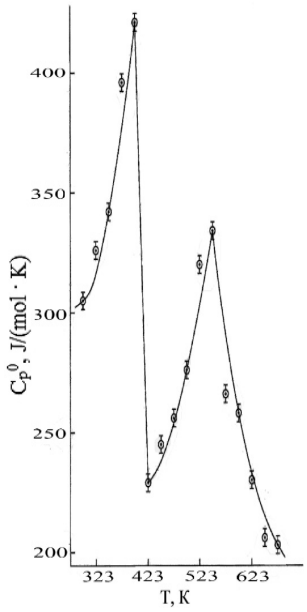

Figure. The temperature dependence of heat capacity of $HoCaTeO_{4.5}$

Table 2

Coefficients of equation (7) in the range of 298.15–673 K for holmium-calcium tellurite

Coefficients			ΔT, K
a	$b \cdot 10^{-3}$	$c \cdot 10^{5}$	
–(1089.9±33)	315.7±0.09	402.9±12	298.15–398
3475.3±104	–(767.4±0.23)	–	398–423
–(1171.2±35)	226.8±0.07	789.4±24	423–548
–(1405.2±42)	146.9±0.04	2806.7±84	548–673

Due to the fact that the technical characteristics of the device do not allow direct calculation of the standart entropy $S^0(298.15)$ of tellurites from the experimental data on $C_p^0 \sim f(T)$, it was estimated by means of Kumok's ion increments [8].

Based on known correlations using experimental data on $C_p^0 \sim f(T)$, and the estimated values of $S^0(298.15)$ the temperature dependences of thermodynamic functions were calculated. The thermodynamic functions $H^0(T)–H^0(298.15)$, $S^0(T)$ and $\Phi^{xx}(T)$ was calculated by the following formulas:

$$H^0(T) - H^0(298.15) = \int_{298.15}^{T} C_p^0 dT \; ; \tag{8}$$

$$S^0(T) = S^0(298.15) + \int_{298.15}^{T} \frac{C_p}{T} dT \; ; \tag{9}$$

$$\Phi^{xx}(T) = S^0(T) - \frac{H^0(T) - H^0(298.15)}{T} . \tag{10}$$

The results are presented in the Table 3.

Table 3

Thermodynamic properties of tellurite $HoCaTeO_{4.5}$ in the range of 298.15–673 K

T, K	$C_p^0(T) \pm \Delta$, J/(mol·K)	$S^0(T) \pm \Delta$, J/(mol·K)	$H^0(T) - H^0(298.15) \pm \Delta$, J/mol	$\Phi^{xx}(T) \pm \Delta$, J/(mol·K)
298.15	305 ± 0	188 ± 19	-	188 ± 19
323	316 ± 10	211 ± 21	7383 ± 464	189 ± 19
348	341 ± 1	234 ± 23	14967 ± 941	191 ± 19
373	377 ± 19	257 ± 26	23373 ± 1470	195 ± 19
398	421 ± 0	283 ± 28	33102 ± 2082	199 ± 20
423	229 ± 0	302 ± 30	41227 ± 2593	205 ± 20
448	238 ± 7	316 ± 32	47044 ± 2959	211 ± 21
473	254 ± 2	329 ± 33	53175 ± 3345	217 ± 22
498	276 ± 0	343 ± 34	59787 ± 3761	223 ± 22
523	303 ± 17	357 ± 36	67015 ± 4215	229 ± 23
548	334 ± 10	372 ± 37	74970 ± 4716	235 ± 23
573	291 ± 25	386 ± 39	82762 ± 5206	241 ± 24
598	258 ± 0	397 ± 40	89608 ± 5636	248 ± 25
623	233 ± 3	407 ± 41	95730 ± 6021	254 ± 25
648	215 ± 9	416 ± 42	101318 ± 6373	260 ± 26
673	203 ± 0	424 ± 42	106533 ± 6701	266 ± 27

For all values of heat capacity and enthalpy over the whole range of temperatures there were evaluated average random components of the error, and for the values of entropy and thermodynamic potential the accuracy of the calculation of entropy (±3 %) was included to the estimation of error.

Thus, for the first time the capacity of the new holmium-calcium tellurite in the range of 298.15–673 K has been investigated by the method of dynamic calorimetry. Equations of temperature dependence were derive and thermodynamic functions $C_p^0(T)$, $S^0(T)$, $H^0(T) - H^0(298.15)$ and $\Phi^{xx}(T)$ of the double tellurite synthesized were determined. λ-Like effects attributable to a second-order phase transition were detected on the curve of dependences $C_p^0 \sim f(T)$. The existence of a second-order phase transition indicates that this compound could have unique electrophysical properties. Thermodynamic characteristics of the new tellurite can serve as the starting materials for inclusion in basic data banks and references and can also be used for directed synthesis of new derivatives of chalcogens with desired properties.

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Гольмий-кальций жаңа теллуритінің термохимиясы

Керамикалық технологиямен жаңа гольмий-кальций қос теллуриті синтезделді. Қосылыстың тепетеңдік құрамының түзілуі рентгенфазалық талдау әдісімен бақыланды. Рентгенфазалық талдау нәтижесі бойынша $HoCaTeO_{4.5}$ гольмий қос теллуритінің синтезделгені анықталды. Алғаш рет 298,15–673 К аралығында жаңа $HoCaTeO_{4.5}$ қос теллуритінің жылу сыйымдылығы калориметрлік әдіспен зерттелді. Құрылғының градуирленуі жылу өлшеуіштің жылулық өткізгіштігін анықтау негізінде жүзеге асырылды. Калориметрдің жұмысы α-Al_2O_3-тің жылу сыйымдылығын өлшеумен тексерілді. Меншікті және мольдік жылу сыйымдылықтарының тәжірибелік мәліметтері математикалық статистика әдістерімен өңделді. Тәжірибелік мәліметтердің негізінде $C_p^0 \sim f(T)$ тәуелділік теңдеуі шығарылды. $C_p^0 \sim f(T)$ және теллуриттің есептелген $S^0(298.15)$ мәні бойынша $H^0(T) - H^0(298.15)$, $S^0(T)$ және $\Phi^{xx}(T)$ термодинамикалық функцияларының температуралық тәуелділіктері анықталды. $C_p^0 \sim f(T)$ тәуелділігінде, II текті ауысумен болуы мүмкін, күрт аномалды секірулер байқалды. Жаңа теллуриттің термодинамикалық сипаттамалары іргелі мәліметтер банкіне және анықтамаларға бастапқы материалдар болуы ықтимал, сол сияқты ұқсас қосылыстардың термохимиялық константаларын болжауда қолданылуы мүмкін.

Кілт сөздер: калориметрия, гольмий-кальций теллуриті, жылу сыйымдылығы, фазалық түрленулер, термодинамикалық функциялар.

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Термохимия нового теллурита гольмия-кальция

На основе керамической технологии синтезирован новый двойной теллурит гольмия-кальция. Образование равновесного состава соединения контролировали методом рентгенофазового анализа, по результатам которого было установлено, что синтезирован двойной теллурит гольмия $HoCaTeO_{4.5}$. Впервые в интервале 298,15–673 К проведено калориметрическое исследование теплоемкости нового двойного теллурита $HoCaTeO_{4.5}$. Градуировку прибора осуществляли на основании определения тепловой проводимости тепломера. Проверку работы калориметра проводили измерением теплоемкости α-Al_2O_3. Экспериментальные данные удельной и мольной теплоемкостей обработаны методами математической статистики. На основе экспериментальных данных выведено уравнение зависимости $C_p^0 \sim f(T)$. По $C_p^0 \sim f(T)$ и вычисленного значения $S^0(298,15)$ теллурита, определены температурные зависимости термодинамических функций $H^0(T) - H^0(298,15)$, $S^0(T)$ и $\Phi^{xx}(T)$. На зависимости $C_p^0 \sim f(T)$ наблюдаются аномальные скачки, связанные, вероятно, с фазовыми переходами II рода. Термодинамические характеристики нового теллурита могут служить исходной информацией для включения в фундаментальные банки данных и справочники, а также использованы для прогнозирования термохимических констант аналогичных соединений.

Ключевые слова: калориметрия, теллурит гольмия-кальция, теплоемкость, фазовые переходы, термодинамические функции.

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UDC 548.56:546.87:541.145

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Solvothermal synthesis of BiOCl nanoplates with excellent photocatalytic activity for dye degradation

A two-phased solvothermal method was employed to synthesize BiOCl nanoplates using $Bi(NO_3)_3 \cdot 5H_2O$, sodium oleate and KCl as the starting materials. The phases, morphology and optical property of the products were characterized by X-ray powder diffraction (XRD), transmission electron microscopy (TEM) and UV-vis diffuse reflectance spectroscopy (DRS). XRD and TEM images showed that the BiOCl nanoplates have a tetragonal phase with the lateral length of 50–100 nm. DRS exhibited that the obtained BiOCl samples have great absorption in the ultraviolet light range. Methyl orange (MO) and Rhodamine B (RhB) were used as the target degradation to assess the photocatalytic properties of the samples. Under UV irradiation, the degradation rate of MO and RhB was reached to 96.3 % and 97.7 % within 30 min. The results indicated that the BiOCl nanoplates have great potential applications in dye degradation.

Keywords: BiOCl nanoplates, two-phased solvothermal method, photocatalytic, dye degradation.

1 Introduction

Water is essential to human life, industrial and agricultural production of natural resources. During the last few decades, the dye using caused serious environmental pollution, especially water pollution. Textile industry is rated as one of the most polluting sector among the different human activities due to their high discharge volume and effluent composition [1]. Solving the dye wastewater problem has become a hot topic of concern in the world. To date, semiconductor photocatalysis has attracted increasing attention as a potential environmental technology for wastewater remediation [2]. Photocatalysis is one of the most promising methods for environmental protection. It is friendly to the environments and has a relatively low cost. Thus, heterogeneous photocatalysts with high activities have attracted considerable interest

Recently, bismuth-based photocatalysts have received tremendous attention due to its unique layered structure that helps the separation of photo-generated electron-hole pairs [3]. Among them BiOCl as one of the most important bismuth oxyhalides, the predicted energy gap value is 3.3 eV, belongs to the indirect band gap semiconductor characteristic. In indirect bandgap semiconductor material, composite of electron-hole pairs can be conducted only by electron emission or absorption, which reduces the combination probability of photo generated electrons and holes [4]. Therefore, indirect jumps the characteristic and open style laminated structure at the same time exists is advantageous to the electron-hole effective separation and the electric charge transfer, causes that BiOCl have the good photochemical catalysis activity and the stability [5]. It has been revealed that the photocatalytic properties of BiOCl are not only related with the morphology but also synthetic methods. Various BiOCl nanostructures including nanobelts [6], nanowires [7], nanofibers [8],

nanoplates [9] and 3D hierarchical nanostructures [10, 11] have been fabricated via different synthetic routes, such as hydro/solvothermal method [12, 13], ionothermal synthesis [14], template-assisted synthesis [15], microwave-assisted synthesis [16] and hydrolytic synthesis [17, 18]. The prepared samples in terms of performance need further improvement, and the synthesis conditions are relatively harsh. In recent years, lamellar structure BiOCl materials have attracted much attention [19, 20]. Owing to its unique electronic, magnetic, optical, and catalytic properties, which mainly arise from their large surface areas [21]. Therefore, exploring a facile method to prepare BiOCl nanoplates structure with excellent photocatalytic activity for dye degradation is still desired.

In this paper, a two-phased solvothermal method was employed to synthesis BiOCl nanoplates. The photocatalytic activities of the as-prepared samples were evaluated by degradation of MO and RhB under UV light irradiation. The as-prepared BiOCl sample showed excellent photocatalytic activity for the degradation of MO and RhB, which was prepared without the presence of CTAB or NaOH. The degradation rate of MO and RhB was approached to 96.3 % and 97.7 % within 30 min under the same conditions. It is expected that the present study could be great potential value in photocatalytic activities.

2 Experimental

2.1 Preparation of photocatalyst

All of the reagents were analytical grade and were used as received. In a typical synthesis process, 2 mmol of $Bi(NO_3)_3 \cdot 5H_2O$ and 6 mmol of sodium oleate were put into 200 mL three-necked flask containing 15 mL of deionized water, 15 mL of ethanol and 30 mL of hexane. After stirred at room temperature for 1 h, the flask was moved into an oil bath and refluxed at a temperature of 70 ºC for 30 minutes. Finally 4 mmol of KCl was added for heating backflow with stirring for 1 h. After cooled down to room-temperature, the mixture was transferred into a 25 mL capacity Teflonlined stainless steel autoclave, and kept at 180 ºC for 12 h, and finally cooled to room temperature naturally. The product was washed with deionized water and ethanol for three times. The final products were then dried at room temperature for further characterization. This sample was denoted by BiOCl-1. For comparison, the BiOCl samples prepared by adding 6 mmol CTAB or NaOH with stirring of 30 min before the addition of KCl under the same conditions was denoted by BiOCl-2 and BiOCl-3, respectively. Another comparison sample was prepared by just refluxing for 2 h without the solvothermal treatment, which was denoted by BiOCl-4.

2.2 Characterization

The crystal structure of the samples was determined by X-ray diffraction (XRD, BRUKER D2 with Cu K_α radiation (λ = 1.54178 Å)). The microstructures of the samples were characterized by transmission electron microscopy (TEM, Hitachi H-600). The optical properties of the samples were tested by UV solid reaction instrument (Shimadzu UV-4802S PC).

2.3 Photocatalytic activity measurement

For photocatalytic measurement, take MO and RhB as the target degradation. 20 mg catalyst dissolved in 50 ml 10 mg/L MO and RhB solution respectively. Before the lighting, the suspensions were magnetically stirred in dark for 1 h in photochemical reaction apparatus (Xu Jiang machine plant in Nanjing XPA) to reach the adsorption-desorption equilibrium and then exposed to light from a 100 W Hg lamp. The suspension has been given time interval for liquid. Fetched suspensions was fed into a centrifuge tube, then placed the mixture in a centrifuge (Shanghai Anting Scientific Instrument Factory TCL-16C) in 10000 r/min centrifuged for 5 minutes to remove the catalysts. The suspensions were analyzed on a UV-vis spectrophotometer (Shimadzu UV-2550 PC) for testing analysis. The percentage of degradation is reported as C/C_0, where C is the concentration of the dyes for each irradiated time, and C_0 is the starting concentration.

3 Result and discussion

3.1 XRD and TEM

Figure 1 showed the XRD patterns of the as-prepared samples. All of the diffraction peaks can be tallied with the standard card peaks of BiOCl (JCPDS card no. 06–0249) except the weak reflection of $Bi_4O_5Cl_2$ in the sample BiOCl-3. The peaks were narrow and strong, indicating that the as-prepared samples had good crystallinity. The XRD pattern of BiOCl-4 revealed a small amount of $Bi_4O_5Cl_2$ impurity.

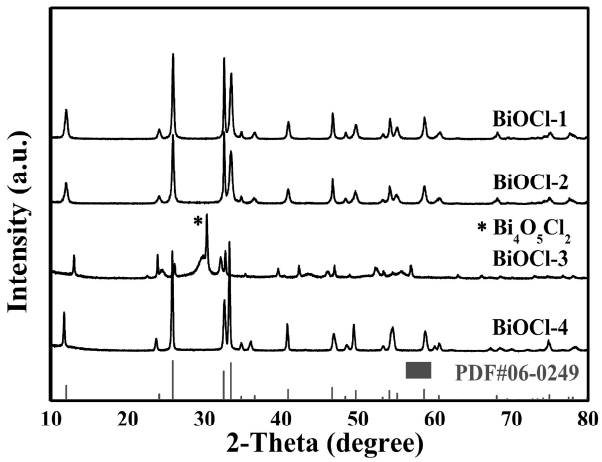
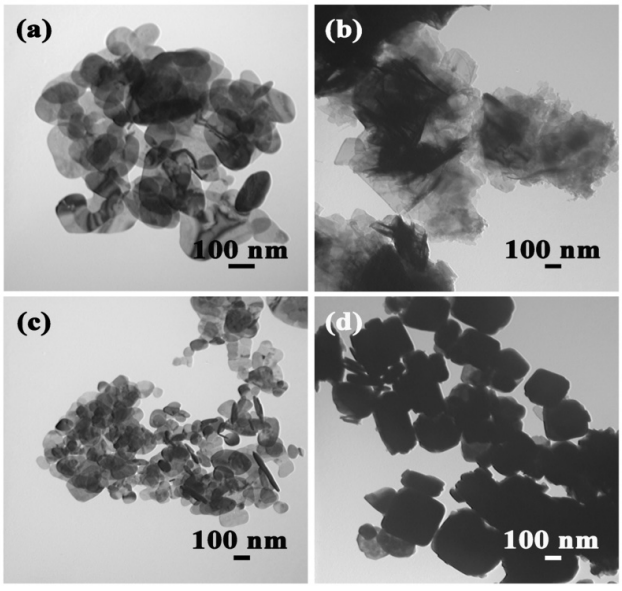


Figure 1. XRD patterns of BiOCl powder prepared at different conditions

Figure 2 showed the typical TEM images of the BiOCl samples. It is clearly observed that the samples consist of nearly regular sheets with a large distribution of 50–100 nm. As shown in Figure 2(*a*), BiOCl-1 has a clear sheet structure. This nanoplate dispersed well and there is no significant agglomeration. The sample BiOCl-2 shown in Figure 2(*b*), has larger sizes and serious agglomeration. Figure 2(*c*) showed BiOCl-3 nanoplate with a smaller size and obvious aggregation. BiOCl-4 (Fig. 2(*d*)) showed the morphology of the block structure. It can be concluded that BiOCl-1 has a more uniform particle size and better dispersion.



(*a*) — BiOCl-1; (*b*) — BiOCl-2; (*c*) — BiOCl-3; (*d*) — BiOCl-4

Figure 2. TEM images of BiOCl

Figure 3(*a*) showed the UV-vis diffuse reflectance spectra of the BiOCl samples. It can be seen that all the absorption peaks occurred at about 380 nm, which is consistent with the reported absorption edge of BiOCl [5]. Figure 3(*b*) is band gap of BiOCl samples, which was calculated by the following equation [22, 23].

$$\alpha h\upsilon = A(h\upsilon - Eg)^{n/2}, \quad (1)$$

Where α, υ, A and E_g represent the meaning of absorption coefficient, the frequency of the incident light, scaling factor and bandgap energy, respectively. Among them, the value of n depends on the type of semiconductor bandgap. The direct band gap semiconductor and indirect band gap semiconductor have different n value, and the value of n for indirect bandgap semiconductors is 4 [24, 25]. The band gap can be estimated by Tauc plot as shown in Figure 3(*b*). The band gaps of the as-prepared BiOCl samples were in the

range of 3.0 eV to 3.25 eV. Wherein, the band gap of BiOCl-1 was 3.25 eV. The BiOCl-1 sample exhibited wide ultraviolet absorption region and high light absorption, meaning that more electron-hole pairs can be produced under the UV irradiation, which would benefit its photocatalytic performance as shown below.

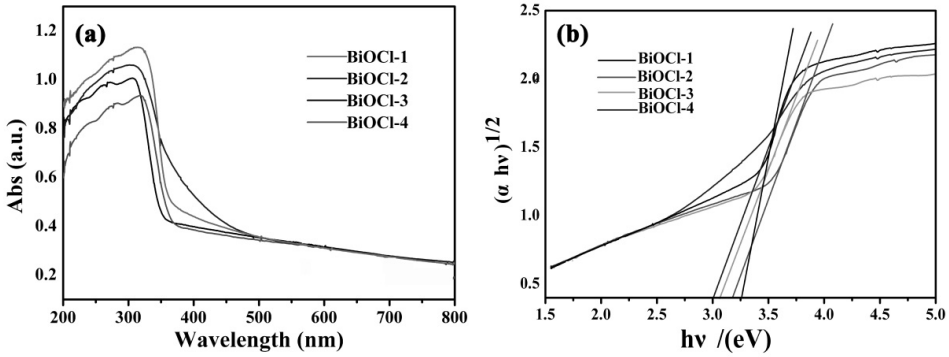


Figure 3. UV-vis diffuse reflectance spectra of BiOCl samples

3.2 Photocatalytic activity of BiOCl

The photocatalytic activities of as-synthesized BiOCl nano-plates have been evaluated by degradation of MO and RhB solution ultraviolet light irradiation. Figure 4 (*a–b*) shows the absorption spectra of MO and RhB solutions (10 mg/L) in the presence of BiOCl-1. The characteristic peak of MO at λ = 463.5 nm and RhB at λ = 663 nm weakened gradually along with the illumination time extension. When the illumination time was 30 min, the basic characteristic peaks were merely vanished. As a comparison, the photocatalytic activities of the other samples were checked under the same conditions. This indicated the as-prepared BiOCl has the excellent photochemical catalysis activity for both acid dyes and basic dyes. Figure 4(*c–d*) displayed the dye degeneration performance of BiOCl nanoplates prepared under different synthesis conditions. As showed in Figure 4(*c–d*), the dark adsorptions of MO and RhB were as low as 3 % and 9 %, respectively, showing almost no dye adsorption performance. When UV lamp was turned on, it was found that the sample of BiOCl-1 showed the highest catalytic activity among the samples and the degradation rate can reach to 96.3 % and 97.7 % within 30 min.

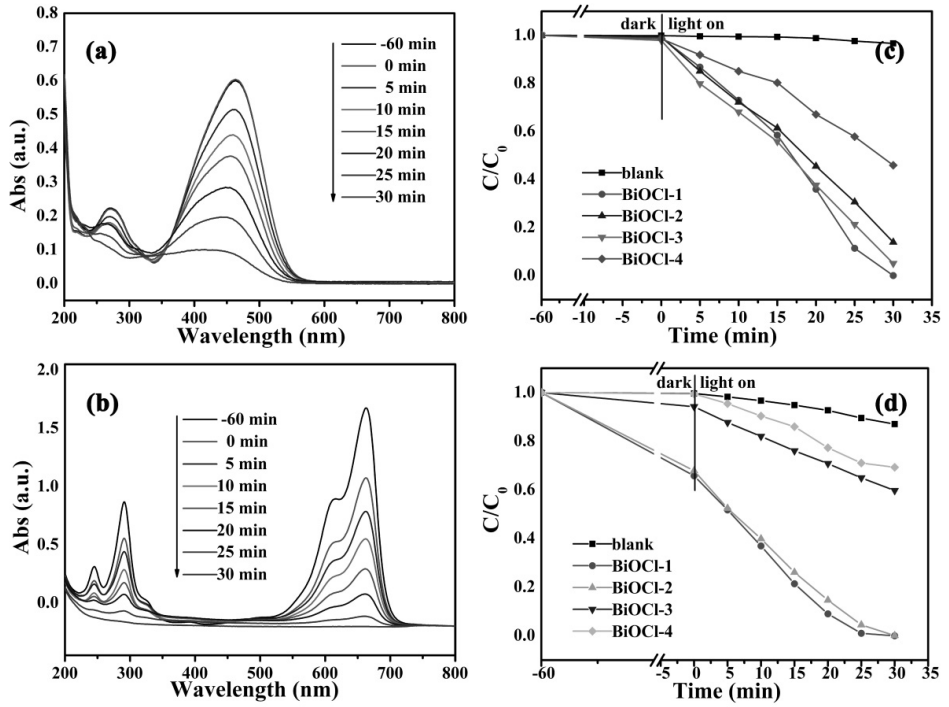


Figure 4. Spectral changes BiOCl-1 sample to ultraviolet MO and RhB solution absorption (*a–b*); BiOCl-1 sample for photocatalytic degradation of MO and RhB solution percentage (*c–d*)

4 Conclusions

In summary, the 2D sheet structure BiOCl nanoplates were synthesized through a two-phased solvothermal method. The lateral sizes of the nanoplates are in 50–100 nm range. The X-ray diffraction analysis indicates that the product is pure phase tetragonal BiOCl. The dye degradation experiment revealed its excellent catalytic performance for degradation of MO dye and RhB. The BiOCl nanoplates showed potential applications in the degradation of organic wastewater fields. This work provides a facile method for the synthesis of high photocatalytic activity BiOCl nanoplates.

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Бояғыштардың деградациясына арналған жоғары фотокаталитикалық белсенді BiOCl нанобөлшектерінің сольвотермалды синтезі

Екіфазалы сольвотермалды әдіс бойынша BiOCl наноқабықшаларын синтездеу үшін бастапқы материал ретінде $Bi(NO_3)_3 \cdot 5H_2O$, натрий олеаты және KCl қолданылды. Туындылардың фазасын, морфологиясын және оптикалық қасиеттерін сипаттау үшін рентгендік ұнтақтық дифракция (XRD), электрондық микроскопия (TEM), ультракүлгін спектр аймағында (DRS) диффузиялық шағылыстыру спектроскопия пайданылды. XRD және TEM суреттері BiOCl наноқабықшаларының латералды ұзындығы 50–100 нм, пішіні тетрагоналды екенін көрсетті. BiOCl алынған үлгілері ультракүлгін сәуле аймағында жоғары сіңіру қабілетімен сипатталатынын DRS көрсетті. Үлгілердің фотокаталитикалық қасиеттерін бағалау үшін метилоранж (МО) және родамин В (RhB) қолданылды. Ультракүлгін сәулесінде МО және RhB деградациялау жылдамдығы 96,3 % и 97,7 % дейін 30 мин аралығында жоғарлады. Қорытынды нәтижесі бояуды азайту барысында BiOCl нанобөлшектердің әлеуетті қолдану аймағы артатындығын көрсетті.

Кілт сөздер: BiOCl наноқабықшалар, екіфазалы сольвотермалды әдіс, фотокаталитикалық қасиеттер, құлдырау.

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Сольвотермальный синтез нанопластинок BiOCl с высокой фотокаталитической активностью для деградации красителей

Для синтеза нанопластинок BiOCl использовали двухфазный сольвотермальный метод с применением в качестве исходных материалов $Bi(NO_3)_3 \cdot 5H_2O$, олеата натрия и KCl. Фазы, морфология и оптические свойства продуктов характеризовались методами рентгеновской порошковой дифракции (XRD), просвечивающей электронной микроскопии (TEM) и спектроскопии диффузного отражения в УФ–видимой области спектра (DRS). Изображения XRD и TEM показали, что нанопластины BiOCl имеют тетрагональную фазу с латеральной длиной 50–100 нм. DRS показал, что полученные образцы BiOCl обладают большим поглощением в диапазоне ультрафиолетового света. Для оценки фотокаталитических свойств образцов для деградации использовали красители метиловый оранжевый (МО) и родамин В (RhB). При УФ-облучении скорость деградации МО и RhB достигала 96,3 % и 97,7 % в течение 30 мин. Результаты показали, что нанопластины BiOCl имеют большой потенциал для деградации красителей при их применении.

Ключевые слова: нанопластинки BiOCl, двухфазный сольвотермальный метод, фотокаталитические свойства, деградация.

UDC 58(075)

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The effect of the industrial zone on the chemical composition of some medicinal plants

Biological characteristics of medicinal plants is largely determined by the place of their growth. This article presents the results of a study the influence of the industrial zone on the vegetation, the study of the influence of anthropogenic factors on the chemical composition of medicinal plants — hawthorn, sea buckthorn, yarrow growing in different conditions. The impact of industrial natural geotechnical systems is considered by the influence of JSC SSGPO (Sokolov-Sarbai Mining Production Association) and the adjacent territory of Rudny city. Sokolov-Sarbai Mining Production Association develops deposits of iron ore by open pit and underground methods. Analysis was performed with fruit, which is harvested from the territory of the industrial mining zone, and with fruit which is harvested on the rural territory, located at a more remote distance from the industrial zone, and pharmacy samples (Shymkent city). Alkalimetric method used for determining the total acidity of all samples. Qualitative analysis of organic acids was carried out by a method of paper chromatography, where the acids are extracted with a mixture of ether and acetone. The quantitative content of vitamin C (ascorbic acid) was determined by iodometric method. The quantitative content of tannins was determined by a permanganat-metric method. To confirm the presence of the iron, aluminum, calcium ions in samples harvested in the industrial area was determined by the ash content.

Keywords: medicinal plants, phytochemicals, hawthorn (Crataégus), sea Buckthorn (Hippóphaë rhamnoídes), yarrow (Achilléa millefólium), qualitative analysis, quantitative analysis, environment.

Nowadays, the problem of environmental protection is one of the most urgent. Certain contradictions in the interaction between society and nature are inevitable. The human society solves many civilization progress problems at the expense of the nature. People in the production process borrow everything what they need from the natural environment. Humankind has declared itself as a force and the power of an influence on the surface shell of the planet and today is almost equal to the cumulative effects of all living organisms. Every year, tens of millions of hectares of agricultural lands, forests are being destroyed. Thousands of species of animals and plants have disappeared. By today, the mining industry, especially open-pit mining is one of the most dangerous affects, influences for the environment and greatly impacts on nature. This entails a change in the landscape, the chemical composition of native plants.

Despite the emergence in the Arsenal of therapeutic agents in modern medicine and many synthetic antibiotic substances, interest in medicinal plants has not disappeared. Many higher plants accumulate organic substances used in pharmacology [1]. Biological characteristic of medicinal plants is largely determined by the place of their growth. In the harvesting of medicinal plants for the treatment and prevention of various diseases, it is necessary not only to know the specific characteristics of their properties, but also to procure medicinal raw materials correctly. We need to choose ecologically safe areas, not in contact with industrial zones, highways, building objects.

This article presents the results of a study the influence of the industrial zone on the vegetation, the study of the influence of anthropogenic factors on the chemical composition of medicinal plants — hawthorn, sea buckthorn, yarrow growing in different conditions.

The impact of industrial natural geotechnical systems is considered by the influence of JSC SSGPO (Sokolov-Sarbai Mining Production Association) and the adjacent territory of Rudny city, Kazakhstan. In this area there is a tension ecological situation, which was formed as a result of intense activity of the mining complex. Sokolov-Sarbai Mining Production Association develops deposits of iron ore by open pit and underground methods.

The chemical composition of medicinal plants (hawthorn, sea buckthorn, yarrow) native to Kostanay area (North part of Kazakhstan) today has not been studied thoroughly. In this regard, we have conducted chemical research of these medicinal plants. Hawthorn, sea buckthorn, yarrow — plants that are found on the territory of the industrial zone. These organisms can be considered to be as indicator organisms. Bioindication is a very good evaluation of the environment by the reaction of living organisms.

In traditional national medicine, the fruits and flowers of hawthorn is used for diseases of the heart, dizziness, shortness of breath, insomnia, diseases of the gastrointestinal tract, in gynecology. Hawthorn containing remedies are used in functional disorders of cardiac activity, if angioneurosis, atrial fibrillation and paroxysmal tachycardia. Hawthorn fruit harvested at maturity from late September until the first frosts. The chemical composition of the hawthorn has been well studied, e.g. in [2, 3].

Sea buckthorn blooms in April – May, before leafing or simultaneously with it. The fruits ripen in August – September. In fruits of sea buckthorn contains vitamins: ascorbic acid, carotenoids, tocopherols, thiamin, riboflavin, sterols, fatty and organic acids and other compounds [4, 5].

Yarrow herb has multilateral pharmacological properties due to the presence in medicinal raw material of various biologically active compounds. The leaves of the plant contain the alkaloid ahillein, essential oil which includes chamazulene; esters, camphor, thujone, borneol, glycosides of luteolin, tannins, resins, amino acids, organic acids, carotene, vitamin K, ascorbic acid, bitter substances [6, 7].

The collected materials were dried in air in the shade, in a ventilated room. During the preliminary analysis of aerial parts and fruits have been studied using qualitative reactions for the presence of organic acids, vitamin C, tannins, flavonoids.

Analysis was performed with hawthorn fruit, which is harvested from the territory of the industrial mining zone, and with hawthorn fruit which is harvested on the rural territory, located at a more remote distance from the industrial zone; yarrow herb, collected similarly from the territory of the industrial zone and from the rural territory as well. Pharmaceutical samples were also investigated (Shymkent city).

The leaves of the selected plants were removed from the plants, then washed under running tap water to remove dust. The plant samples were dried for few days and the leaves were crushed into the powder and stored in polythene bags for use. The powder was put into a test tube. Distilled water was added to the powder to soak it and shaken well, the solution then was filtered. The filtered extract of the selected plant samples were taken and used for further phytochemical analysis. Alkalimetric method used for determining the total acidity of all samples — hawthorn, sea buckthorn, yarrow.

For the quantitative determination of organic acids, the extraction was carried out with distilled water and titrated with 0.1 N solution of alkali. At account, it is necessary to take into account the amount of alkali consumed in the titration, and the amendment to the titer. The calculation is carried out as follows

$$X = \frac{a \cdot T \cdot 200 \cdot 10}{H \cdot 20},$$

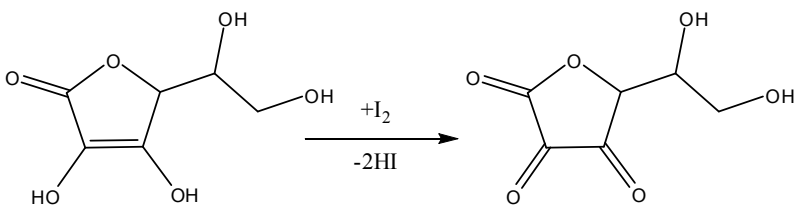
where a — amount of 0.1N NaOH, consumed in the titration, ml; T — the amendment to the alkali titer; 200 — the total volume of extract, ml; 20 — the volume of extract, spent for the titration, ml; H — weighed amount of substance, g; 10 — conversion into milli-equivalents of acids (1 ml of 0.1 N NaOH corresponds to 0.1 meq of acid); X — an amount of acids in plant sample, meq [2].

Qualitative analysis of organic acids was carried out by a method of paper chromatography, where the acids are extracted with a mixture of ether and acetone.

Analyzing the fruits of hawthorn, sea buckthorn, there has been determined the qualitative composition of the acid fractions by the method of ascending paper chromatography (R_f-value), with the use of special indicators of acids. As the mobile phase it was used the next mixture: *n*-butanol, formic acid, water. To prepare the mixture it was taken 250 ml of *n*-butanol, 25 ml of formic acid and 297 ml of water. All these solvents were transferred into a flask with a glass stopper, repeatedly shaken for several hours and allowed to settle during the day. After settling of mixture the top layer was used. (The upper layer of *n*-butanol, saturated with the formic acid).

The quantitative content of vitamin C (ascorbic acid) is determined by iodometric method in the fruits of hawthorn, sea buckthorn, and yarrow.

Ascorbic acid is a strong reducing agent. During the titration iodine it is oxidized to form dehydroascorbic acid:



Ascorbic acid dehydroascorbic acid

In the calculation of vitamin C content in the product was used, the formula for determining the mass using the titer determined by the substance:

$$M = \frac{n \cdot E}{1000} \cdot V ,$$

where n — is the molar equivalent concentration of iodine; E — the molar mass of equivalent of ascorbic acid in grams equal to in this case, 88 grams; V — is the volume used for titration of iodine in ml.

For recalculating the content of vitamin C in 100 g of the product, you must use the formula:

$$X = \frac{M \cdot 1000}{2} .$$

According to literature data among biologically active substances of the samples it was observed a high content of tannins. This plant polyphenolic compounds of different molecular weight, is able to tan the skin. Qualitative tests for tannins: 1) gelatin; 2) with acetate of lead; 3) with salesonline alum (JACQUES). All these reactions give positive results indicating the presence of tannins in the samples.

The quantitative content of tannins was determined by a permanganat-metric method.

A portion of the crushed material, sifted through a sieve with a hole diameter of 3 mm, placed in a conical flask with a capacity of 100 ml, poured 50 ml of boiling water and heated in a water bath for 30 minutes with frequent stirring. Liquid stand up for a few minutes and carefully filtered through cotton wool into a volumetric flask with a capacity of 250 ml so that the particles of the raw materials do not fall on the cotton wool. Raw materials in the flask repeatedly extracted with boiling water, as described above, the liquid filtered into the same volumetric flask. The extraction is repeated several times until a negative reaction for tannins (sample with a solution of alum gentoomaniac). The liquid in a volumetric flask is cooled, and the volume of extraction was adjusted to the mark with water. 25 ml of the resulting liquid placed in a conical flask with a capacity of 1 l, add 750 ml of water and 25 ml of indigenously and titrated with constant stirring 0.1 n potassium permanganate until a golden yellow colouring.

1 ml of 0.1 n potassium permanganate solution corresponds to 0,004157 g of tannins in terms of tannin. In parallel, perform a trial experiment, titrating 25 ml of indigenously in 750 ml of water [2]. The percentage content of tannins is determined by the formula:

$$X = \frac{(V_1 - V_2) KDV \cdot 100 \cdot 100}{mV_3 (100 - \omega)} ,$$

where V_1 — volume of 0.1 $KMnO_4$, used for titration, ml; V_2 — the volume of 0.1 $KMnO_4$ spent on control experience, ml; K — correction for the titer (for oxalic acid); D — coefficient for tannin for hydrolyzable tannins equals 0.004157, for condensed — 0.00582; V — is the total volume of extract, ml; m — is the mass of a sample of raw material, g; V_3 — volume of extract taken for titration, ml; ω — the loss in weight of raw material on drying, %.

To confirm the presence of the metals Fe, Mn in samples harvested in the industrial area was determined by the ash content of yarrow. Ash substances of vegetable raw materials is called the residue of inorganic substances generated after combustion of materials and subsequent calcination of the residue to constant mass. Plants ash (total ash) consists of a mixture of various inorganic substances in the plant and mineral contaminants that can get into the raw material at harvest and drying.

Ash often contains the following elements: K, Na, Mg, Ca, Fe, Si, P less often and in smaller amounts Cu, Mn, Al, etc.

Results and discussion

In order to identify organic acids, as an indicator solution was used Bromphenol blue solution (pH of 6.7). Organic acids are painted in bright yellow on a cyan background [2]. Results are presented in Table 1.

Table 1

Total acidity, quantitative content of vitamin C and quantitative content of tannins of the analyzed samples

Acids	Hawthorn		Buckthorn		Yarrow	
	Industrial zone	Rural zone	Industrial zone	Rural zone	Industrial zone	Rural zone
Organic acids, meq	19.2	32.0	19.3	34.7	3.4	6.0
Vitamin c, mg/100 g	14.0	26.4	450.0	700.0	140.0	240.0
Tannins, %	4.52	4.94	1.05	2.26	2.33	3.63

During the determination of the total acidity, there was determined that the least content of free acids are in the raw material gathered from the territory of the industrial zone. This was probably due to the high content of metal ions in the soil of the factory. These differences in the content of organic acids, we assume, are related to the fact that free acids can form poorly soluble salts with metal ions, and this is reflected in the decrease in the content of free acids in the samples taken closer to the industrial area.

Table 1 also shows that the amount of vitamin C in raw material harvested in the countryside, higher in comparison with samples collected near the industrial zone. This can be explained by the redox properties of ascorbic acid in the presence of iron ions (Fe^{2+}, Fe^{3+}) [2]. *L* — ascorbic acid is oxidized by ions of Fe^{3+}, respectively, this leads to a reduction in the concentration of vitamin C in samples of the industrial zone. On the other hand, the increase in humidity also contributes to the accumulation of vitamin C [3].

From these data we can conclude that the percentage content of tannins in the samples (Table 1) taken from the territory of the industrial zone is reduced. This is due to the ability of metal ions to reduce the content of tannins by precipitation. On the other hand, the increase in the content of tannins in the samples procured from rural areas can be explained by the hydrolysis of glycosides, phenolic compounds as tannins are derivatives of phenolic compounds. This can occur due to frequent watering.

The qualitative composition of organic acids hawthorn fruit and sea buckthorn varies (Table 2). In the fruit of a hawthorn collected from the industrial area, there are ascorbic acid, malic, citric, succinic. Whereas in the fruit of hawthorn, collected from rural areas, the presence of only ascorbic acid and citric acid. In fruits of sea buckthorn collected from the industrial area, there are ascorbic, malic, succinic acid. Suburban sea buckthorn contains only ascorbic acid and citric acid. These differences can be explained by processes occurring in the citric acid cycle (the Krebs cycle), as the acid composition in the fruits depends on the stages of the cycle.

Table 2

Qualitative composition of the acid fractions in the fruit of hawthorn, buckthorn

Acids	R_f	Hawthorn		Buckthorn	
		Industrial zone	Rural zone	Industrial zone	Rural zone
Ascorbic acid	0.28	+	+	+	+
Tartaric acid	0.42	–	–	–	–
Malic acid	0.58	+	–	+	–
Citric acid	0.60	+	+	–	+
Succinic acid	0.82	+	–	+	–

The ash content in the sample with industrial zones is higher than in the pharmacy specimen (Table 3). This confirms the assumption that the yarrow from the territory of industrial zones accumulate metals that can form compounds with organic acids. This is also confirmed by the solubility of ash in water; completely soluble only ash pharmacy sample, since it contains no heavy metals. Ash samples collected from industrial areas, partly dissolved in acetic acid and completely in concentrated nitric acid when heated, which indicates the contents in the grass of the insoluble carbonates and sulfates of elements such as iron, aluminum and calcium.

Table 3

Inorganic analysis of the yarrow pharmacy specimen

Mineral components of ash	Industrial zone	Drugstore samples
Ash	11.62	4.98
Cl^-	+	+
CO_3^{2-}	+	+
Fe^{3+}	+	–
Al^{3+}	+	–
Ca^{2+}	–	–

Conclusion

Thus, it was studied the influence of industrial natural geotechnical systems on the content of biologically active substances, of medicinal plants, growing near the Sokolov-Sarbai mining production association factory. The results of the analysis show that the least content of free acids, vitamin C and tannins are in the raw material collected from the territory of the industrial zone. It can be explained by the accumulation of harmful and polluting substances by plant organisms.

The assumption, that plants are collected from the territory of the industrial zones accumulate metals, is confirmed by the fact that the ash content in the specimen from industrial zones is higher than in the pharmacy specimen.

It is clearly traced that plants growing on the territory of the Sokolov-Sarbai mining production association factory, which is the zone of emissions of iron-containing waste, also contain an excessive amount of iron.

One of the important conclusions, that should be noted, is the fact that when harvesting medicinal plants, it is necessary to choose the right areas where it is possible to collect medicinal raw materials. For this, it is necessary to choose environmentally clean areas, free of the industrial pollutions, and do not contact industrial enterprises, motorways, mining enrichment plants.

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Дәрілік өсімдіктердің химиялық құрамына өндіріс орындарының әсері

Дәрілік өсімдіктердің биологиялық сипаттамасы негізінен олардың өсу ортасына тәуелді. Мақалада долана, шырғанақ, мыңжапырақ сияқты дәрілік өсімдіктердің химиялық құрамына өндіріс орындарының және антропологиялық факторлардың әсерін зерттеу жұмыстарының нәтижелері берілген. Өндірістік гео-техникалық жүйенің әсері Соколов-Сарыбай тау-кен өндірістік бірлестігінің (ОАО «ССГПО» – «ССТКӨБ» ААҚ) және соған жақын орналасқан Рудный қаласының маңайынан дайындалған дәрілік өсімдіктердің химиялық құрамын зерттеу нәтижесінде тұжырымдалған. Соколов-Сарыбай тау-кен өндірістік бірлестігі ашық және жабық тәсілмен темір кендерін өндіреді. Зерттеу үшін долана мен шырғанақтың жемістері және мыңжапырықтың жер беті бөлігі өндіріс орындарына жақын жерлерден, ал салыстыру үшін өндіріс аймағынан алыс орналасқан саяжайлардан дайындалды. Барлық сынамалардың жалпы қышқылдылығы алкалиметриялық әдіспен анықталды. Органикалық қышқылдардың сапалық құрамы қағаз бетіндегі хроматография әдісімен эфир мен ацетонның қоспасымен экстракция нәтижесінде жүргізілді. С дәруменінің мөлшері иодометриялық әдіспен (аскорбин қышқылы), танниндердің мөлшері перманганатометрия әдісімен анықталды. Өндіріс аумағынан жиналған сынамалардың құрамында темір, алюминий иондарының барлығын дәлелдеу үшін сынамалардың күліне сапалық талдау әдістеріндегі арнайы реакциялар қолданылды.

Кілт сөздер: дәрілік өсімдіктер, фитохимия, долана, шырғанақ, мыңжапырақ, сапалық талдау, сандық талдау, экология.

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Влияние промышленной зоны на химический состав лекарственных растений

Биологические характеристики лекарственных растений в значительной степени определяются местом их произрастания. В статье представлены результаты изучения влияния промышленной зоны на растительный покров, влияния антропогенных факторов на химический состав лекарственных растений — боярышника, облепихи крушиновидной, тысячелистника обыкновенного, произрастающих в различных условиях. Влияние промышленной природной геотехнической системы рассмотрено на примере ОАО «ССГПО» (Соколовско-Сарбайское горно-производственное объединение) и прилегающей территории города Рудного. Соколовско-Сарбайским горно-производственным объединением разрабатываются месторождения железных руд открытым и подземным способами. Для анализа использовались плоды боярышника и облепихи, которые заготавливали с территории промышленной зоны, и для сравнения собирали плоды на территории дач, находившихся на более отдаленном расстоянии от промышленной зоны; трава тысячелистника, собранная аналогично с территории промышленной зоны и с территории дач. Для определения общей кислотности всех образцов использовался алкалиметрический метод. Качественное определение органических кислот проводили методом бумажной хроматографии, для этого кислоты экстрагировали смесью эфира и ацетона. Количественное содержание витамина С (аскорбиновой кислоты) определяли йодометрическим методом. Количественное содержание танинов определяли методом перманганатометрии. Для подтверждения присутствия ионов металлов железа, алюминия, кальция в образцах, собранных в промышленной зоне, определяли зольность тысячелистника.

Ключевые слова: лекарственные растения, фитохимия, боярышник, облепиха крушиновидная, тысячелистник обыкновенный, качественный анализ, количественный анализ, экология.

UDC 662.74:552.57

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Kinetics and thermodynamics of the process of hydrodesulfurization of Shubarkol coal hydrogenate

When processing coals and oils containing sulfur compounds, the resulting fuel components do not meet the requirements of the State standards for sulfur content. Sulfur affects negatively the quality of the target product and makes processing difficult, therefore hydrodesulfurization of coal hydrogenates and oils is an important stage before further processing. Sulfur compounds are very harmful impurities for liquid products (hydrocarbons). They are toxic, give an unpleasant smell to liquid products, affect detrimentally the antiknock properties of gasolines, promote resin formation in internal combustion engines and, most importantly, cause corrosion of metals. Therefore, the presence of these substances is extremely undesirable and unacceptable. There has been researched the process of hydrodesulphurization of hydrogenates of the coal from Shubarkol Deposit in the presence of catalyst of pyrite and natural zeolite. Using the method of equilibrium-and-kinetic analysis there have been calculated the rates of the process of hydrodesulphurization of liquid products and Gibbs energy that are necessary for improvement of process-dependent parameters of hydrofining of liquid products of hydrogenation. It is indicated that the optimum time of the process of hydrodesulphurization is 15–25 minutes. The content of sulfur in the fraction under 200 ºC is 0.043 per cent and in the fraction of 200–300 ºC is 0.065 per cent and that indicates a high degree of hydrofining of hydrogenate in the presence of the above catalyst. A high value of ΔG (in absolute value) indicates a high thermodynamic probability of hydrodesulfurization process in the given temperature range. These data are necessary for the development of recommendations for determining the optimal conditions for the process.

Keywords: hydrodesulfurization, hydrogenizat, kinetic analysis equilibrium.

Introduction

The Republic of Kazakhstan possesses enormous reserves of energy resources. In our country there are deposits of high-viscosity index oil (heavy oil) and coal that can be the sources for production of synthetic motor fuel and boiler fuel. In recent years there have considerably decreased the volumes of oil extraction and there is expected the deceleration in increase of the developed reserves of fossil fuels comparing with the rates of extraction. Extraction of oil in distant and hard-to-reach regions becomes so expensive that the production of synthetic oil out of coal in many cases is considered to be a competitive process as compared with the oil extraction. Therefore there arises a practical importance of producing fuel and chemical products out of coal and heavy oils that can be considered as one of the prospective lines in the energy sector and petrochemical industry of the nearest future. The process of direct hydrogenation of coal, heavy oils, petroleum bitumens and the products of coal liquefaction is one of the effective methods.

However, it should be noted that the fuel components produced as result of processing coals and oils that contain sulphur compounds do not meet the requirements of the State Standards as to sulphur content. Sulphur negatively affects the quality of the target product and complicates the processing, therefore hydrodesulphurization of coal hydrogenates and oils is a very important stage prior their further processing.

As is known, sulphur compounds are a very detrimental admixture for liquid products (hydrocarbons). They are toxic, impart an unpleasant odor to the liquid products, detrimentally effect the antiknock qualities of benzines, conduce to tar formation in internal-combustion engines and, what is most important, lead to corrosion of metals. Therefore the presence of these substances is extremely undesirable and inadmissible. The issues of refining sulphur oil-products by the method of hydrogenation without a considerable decomposition of hydrocarbons have been considered by many researchers. In the direction there worked B.L. Moldavsky, V.N. Pokorsky, K.P. Lavrovsky and P.V. Puchkov, A.V. Agafonov, et al. Most of their works are devoted to refining oil-products that are light as to their fraction content with the purpose of producing benzene and tractor kerosenes.

Previously there were conducted researches of hydrodesulfurization ability of Y-type zeolite that contained various admixtures. It was defined that zeolite catalysts that contain cobalt, nickel and rare-earth forms of Y-type zeolite possess a high hydrodesulfurization ability [1].

For hydrofining of oil-products there are mostly used aluminum-nickel-molybdenum (ANM) catalysts. However, zeolite-containing ANM catalysts are becoming more wide-spread; they are notable for a high activity in the processes of hydrofining [2–5]. Introduction of Y-zeolite into ANM-composition, besides the increase in activity of the catalyst, increased the efficiency of raw-materials plants (by 10–15 per cent), reduced the temperature of hydrofining (by 288–293 K) and extended the cycle length and general service period of catalysts. However, the role of zeolite in improvement of catalytic, operational and regeneration qualities of the catalysts of hydrofining is still not explored enough [4].

Therefore the aim of this work is to define kinetic and thermodynamic parameters of the process of hydrodesulphurization of the coal hydrogenate in the presence of the catalyst of pyrite and natural zeolite with the usage of equilibrium-and-kinetic analysis (EKA) method.

Experimental part

In the course of the work there was performed the definition of kinetic and thermodynamic parameters of the process of hydrodesulphurization with the usage of EKA method that has been worked out by Professor V.P. Malyshev [5].

The object of the research was hydrogenate of the coal from Shubarkol Deposit with the following physical and chemical characteristics (mass per cent): A — 2.8–3.7; S — 0.4–0.49; V — 45.0–45.8; C — 76.99; H — 5.35.

As the catalyst of the process of hydrodesulphurization of hydrogenate of Shubarkol coal there was used a mixture of pyrite and natural zeolite (60 per cent of pyrite and 40 per cent of zeolite).

The experiments on hydrodesulphurization of liquid products (hydrogenate) were performed in the rotary autoclave (with the volume of 0.02 l). The autoclave was loaded with hydrogenate, then there was added a calculated amount of catalyst (5 per cent of hydrogenate). The autoclave was closed, blown through with hydrogen and excessive (initial) pressure of hydrogen (2 MPa) was created. The mixture was heated up to the necessary temperature with the rate of 278 K per min. and kept for the defined period of time under the temperature of 703 K. After cooling of the autoclave up to the ambient temperature the resulted liquid products were separated and there was performed distillation in accordance with the State Standard 2177–48 [6]. In the resulted fractions of hydrogenate there was defined the sulphur content according to the State Standard 1437–75 [7].

Results and discussions

The research of kinetics and thermodynamics of the process of hydrodesulphurization is necessary for improvement of the process-dependent parameters of hydrofining of the liquid products of hydrogenation. However at the same time there appear a number of methodological difficulties: first, it is practically impossible to identify a great number of individual compounds — the products of transformation of the organic mass of coal — therefore in practice they have to be grouped in accordance with some conventional physical and chemical qualities; second, the kinetics of the process in this case is formal and interpretation of its parameters from the point of view of the structural peculiarities of the source coal is quite a difficult task; third, for one and the same process different authors offer different kinetic models, the parameters of which are defined in complicated calculations, it makes them incomparable and non-general, and that complicates the performance of analysis of a model.

Taking into consideration the bibliographical data on kinetics of hydrodesulphurization there can be suggested the following scheme of hydrodesulphurization of the liquid products (hydrogenate) under moderate pressure of the hydrogen (Fig. 1).

The kinetic scheme of the process of hydrodesulphurization. According to the scheme indicated on the Figure 1 there is the following system of differential equations:

$$\frac{d[C_1]}{d\tau} = -\left(k_1 + k_2 - k_3\right)C_1 + k_4 C_3;$$

$$\frac{d[C_2]}{d\tau} = k_1 C_1 + k_5 C_3;$$

$$\frac{d[C_3]}{d\tau} = k_2 C_1 - k_5 C_3;$$

$$\frac{d[C_4]}{d\tau} = k_3 C_1 - k_6 C_4 - k_7 C_4,$$

where $k_z = k_1 + k_2 + k_3 + k_4 + k_5 + k_6 + k_7$; C_1, C_2, C_3, C_4 are the mass fractions of the respective components ($C_1 + C_2 + C_3 + C_4 = 1$).

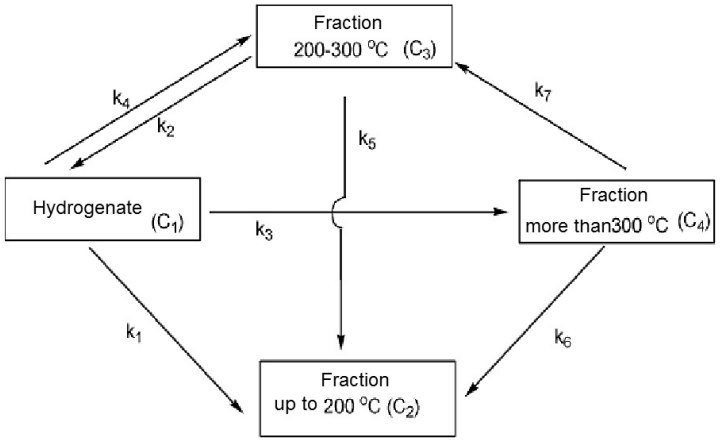

Figure 1. Kinetic scheme of the process of hydrodesulphurization of hydrogenate

The calculation of the system of equations was performed on PC IBM 486D4x0 with the usage of the special «Search» program [8–10]. The designed program makes it possible to calculate the kinetic dependences under the defined initial conditions and realize automated selection with the usage of the method of gradient of optimum values of constants of k_1–k_7 rates. Optimization of the constants of rates was realized provides there was a minimum of deviation squares between the experimental and calculated values of the mass fractions of the products of hydrodesulfurization. The constants of rate of hydrodesulphurization are $k_1 = 1.235$, $k_2 = 1.134$, $k_3 = 0.752$, $k_4 = 0.453$, $k_5 = 0.578$, $k_6 = 0.183$, $k_7 = 0.457$. Basing on analysis of the results of the rate constants there can be drawn the conclusion that the influence of the constants on the output of the products of the process of hydrodesulphurization is ambiguous. Thus, the output of the fraction under 200 ºC is mainly determined by the value of k_1 rate constant. The output of the fraction of 200–300 ºC decreases with the growth of the temperature and is mainly determined by the rate of reaction k_2. The constant of the rate of reverse reaction k_4 decreases with the growth of temperature.

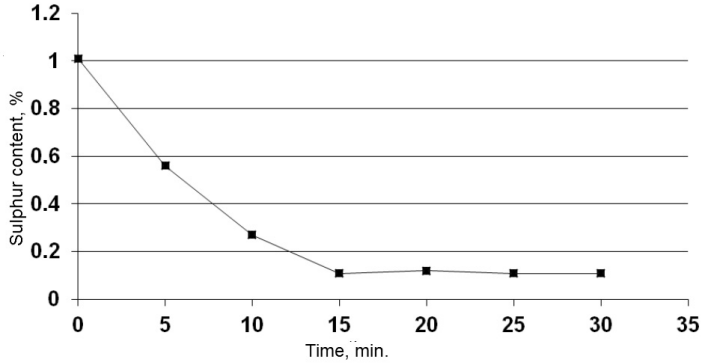

Figure 2. Kinetic data of the process of hydrodesulphurization of hydrogenate

On Figure 2 there is indicated the dependence of the sulphur content in hydrogenate on the time of the process of hydrodesulphurization. The analysis of the kinetic data of the process of hydrodesulphurization indicates that the optimal time of the process is 15–25 minutes, since there is observed the maximal output of the abovementioned fractions. The mentioned fractions contain sulphur in the following amounts:

Fraction under 200 ºC — 0.043 per cent (State Standard — 0.02–0.1 per cent);

Fraction of 200–300 ºC — 0.065 per cent (State Standard — 0.2–1.0 per cent);

The content of sulphur in the initial hydrogenate produced from the coal from Shubarkol Deposit amounts to 1.01 per cent.

Basing on the experimental data of the research of the process of hydrodesulphurization of hydrogenate there was calculated the Gibbs energy (ΔG) using the formula:

$$G = -RT \ln K_P;$$

$$K_P = k_2 / k_4;$$

$$\ln K_P = 2.5033;\ K_P = 0.918;$$

$$\Delta G = -5365.5.$$

The high value of (G (in absolute magnitude) indicates a high thermodynamic probability of performance of the process of hydrodesulphurization in this temperature range.

Conclusion

Thus, there is given the scheme of hydrodesulphurization of liquid products (hydrogenate), there are researched the kinetics and thermodynamics of the process of hydrodesulphurization in the presence of the catalyst of pyrite and natural zeolite. The calculated Gibbs energy in absolute magnitude indicates a high probability of the performance of the process of hydrodesulphurization. These data are necessary for improvement of the parameters of the process of hydrofining of the liquid products.

It is defined that the optimal time of the process of hydrodesulphurization is 15–25 minutes. The indicated fractions contain sulphur in the following amounts: fraction under 200 ºC — 0.043 per cent, and fraction of 200–300 ºC — 0.065 per cent.

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Шұбаркөл көмір гидрогенизатының гидросульфирлеу үрдісінің термодинамикасы мен кинетикасы

Көмір мен мұнайды қайта өңдеу кезіндегі отын компонентерінің құрамындағы күкірт қосылыстары МЖСТ-нің күкірт құрамы бойынша талаптарды қанағаттандырмайды. Күкірт соңғы өнімнің сапасына кері әсерін тигізіп қайта өңдеуді қиындатады, сондықтан мұнай, көмір гидрогенизаттарын гидросульфирлеу маңызды болып табылады. Сұйық өнімдер (көмірсутектер) үшін күкіртті қосылыстар өте зиянды қоспа екені белгілі. Олар уытты, сұйық өнімдерге жағымсыз иіс береді, бензиннің антидетонационды қасиетіне кері әсерін тигізеді, металдардың коррозияға ұшырауын тудырады және ішкі жану қозғалтқыштың шайыр түзуіне септігін тигізеді. Сол себепті осы заттардың болуын тудыртпау қажет. Шұбаркөл кенорын көмірінен табиғи цеолит пен пирит катализаторының қатысуымен гидрогенизаттың гидросульфирлеу үрдісі зерттелді. Гидрогенизацияның сұйық өнімдерінің гидротазалағыш технологиялық сипаттамаларын жақсартуға болады, Гиббс энергиясы мен сұйық өнімдердің гидросульфирлеу үрдісінің жылдамдық константалары кинетикалық тепе-

теңдік тәсілмен есептелді. Гидросульфирлеу үрдісінің тиімді уақыты 15–25 мин екендігі көрсетілді. 200 ºС-дейінгі фракцияның құрамында күкірт мөлшері — 0,043 %, ал 200–300 ºС аралығында — 0,065 %, бұл жоғарыда келтірілген катализатор қатысында гидрогенизатты гидротазалау дәрежесінің жоғары екендігін көрсетті. Δ*G*-дің жоғарғы мәні осы температуралық аралықта гидросульфирлеу үрдісінің термодинамикалық жүру мүмкіндігінің жоғары екендігін дәлелдеді. Бұл мәліметтер үрдісті жүргізудің ең қолайлы жағдайын анықтау бойынша ұсыныстар жасауға қажет.

Кілт сөздер: гидродесульфуризациялау, гидрогенизат, кинетикалық талдау тепе-теңдігі.

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Кинетика и термодинамика процесса гидрообессеривания гидрогенизата шубаркольского угля

При переработке углей, нефтей, содержащих соединения серы, получаемые топливные компоненты не удовлетворяют требованиям ГОСТов по содержанию серы. Сера отрицательно влияет на качество целевого продукта и затрудняет переработку, поэтому гидрообессеривание угольных гидрогенизатов, нефтей — важный этап перед их дальнейшей переработкой. Для жидких продуктов (углеводородов) сернистые соединения являются очень вредной примесью. Они токсичны, придают жидким продуктам неприятный запах, вредно отражаются на антидетонационных свойствах бензинов, способствуют смолообразованию в двигателях внутреннего сгорания и, главное, вызывают коррозию металлов. Поэтому присутствие этих веществ крайне нежелательно и недопустимо. Исследован процесс гидрообессеривания гидрогенизата из угля Шубаркольскоко месторождения в присутствии катализатора пирита и природного цеолита. Методом равновесно-кинетического анализа рассчитаны константы скорости процесса гидрообессеривания жидких продуктов и энергия Гиббса, которые необходимы для улучшения технологических параметров гидроочистки жидких продуктов гидрогенизации. Показано, что оптимальное время процесса гидрообессеривания 15–25 мин. Содержание серы во фракции до 200 ºС — 0,043 %, а во фракции 200–300 ºС — 0,065 %, что свидетельствует о высокой степени гидроочистки гидрогенизата в присутствии указанного выше катализатора. Высокое значение Δ*G* (по абсолютной величине) говорит о высокой термодинамической вероятности протекания процесса гидрообессеривания в данном температурном интервале. Эти данные необходимы для разработки рекомендаций по определению оптимальных условий проведения процесса.

Ключевые слова: гидродесульфуризация, гидрогенизация, равновесие кинетического анализа.

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UDC 533.601

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Investigation of the influence of electrohydroimpulse technology on physico-chemical characteristics of oil sludges

The article is devoted to the investigation of the influence of electrohydropulse processing of Zhana-Ozen oil sludge using the method of probabilistic-deterministic planning of the experiment, in which the mutual influence of various factors is taken into account. It has been established that the dominant factors that influence the decrease in the kinematic viscosity, the increase in the yield of light and middle fractions up to 300^0C from the Zhana-Ozen oil sludge in the process of destruction of the heavy part of the organic mass of oil are inter-electrode distance, processing time and discharge voltage.

Keywords: electrohydropulse technology, oil sludge, kinematic viscosity, interelectrode distance, voltage.

Modern methods of processing, utilization of oil sludge and oil-bearing technogenic raw materials are not technologically and energy-intensive and require significant capital investments, so the volumes of utilization are lagging behind the volumes of their formation and new ones are added to the accumulated volumes. The level of soil contamination with oil products and oil sludge has now approached 10 million cubic meters. In addition, the land area contaminated or damaged as a result of various accidents at gas and oil pipelines, plants and other facilities is constantly growing [1].

The choice of the method for processing and neutralizing oil sludge depends mainly on the amount of petroleum products contained in them and in each specific case a differentiated approach, taking into account both environmental and economic indicators, is required.

There are various ways of processing oil-containing technogenic raw materials:

– thermal-combustion in open barns, furnaces of various types, production of bituminous residues;
– biological-microbiological degradation in soil directly in storage areas, biothermal decomposition;
– physical — burial in special repositories, separation in the centrifugal field, vacuum filtration and filtration under pressure;
– physico-chemical — the use of specially selected reagents that change physico-chemical properties, followed by treatment on special equipment;
– chemical — extraction with the help of solvents, solidification with the use of mineral (cement, liquid glass, clay) and organic (epoxy and polystyrene resins, polyurethanes, etc.) additives [2].

Data on the accumulation of oil sludge in Kazakhstan show that their processing does not cover the volume of annual formation. Thus, it is necessary not only to find processing technologies, but also to recommend and adapt special technology from many existing ones to each specific type of waste. The choice is further complicated by the fact that many technologies can be applied to individual types of waste, but none of them meets the universality requirement and cannot be applied to all types of wastes.

In this regard, the use of the phenomenon of electrohydropulse treatment in the processing of oil sludges is of great practical interest [3].

One of the types of complex extreme impact is the effect of electrohydraulic discharge, which combines the simultaneous impact on the substance of strong mechanical compression, powerful ultrasound, hard x-ray, ultraviolet and infrared radiation. The electromagnetic fields produced during the discharge also exert a strong influence both on the discharge itself and on the ionic processes occurring in the surrounding liquid. Under their influence, various physical changes and chemical reactions occur in the material being processed. It has been established that the following factors such as discharge voltage, processing time, capacitor bank capacity, interelectrode distance of the processing cell, and effect of the hydrogen donor influence the change in the kinematic viscosity and the yield of the light and middle fractions from the oil sludge.

We investigated the effect of the duration of the electrohydropulse treatment, the interelectrode distance in the stand unit cell, the capacitance of the capacitor bank and the impulse voltage in the bench set-up to

reduce the kinematic viscosity of the oil and increase the yield of light and middle fractions from the oil sludge. The object of investigation is the oil sludge of Zhana-Ozen of the Mangystau region.

We carried out laboratory studies using the method of probabilistic-deterministic planning of the experiment, in which the mutual influence of various factors is taken into account, to determine the optimal conditions and create a mathematical model of the Zhana-Ozen oil sludge treatment process with the help ofelectrohydropulse action [4].

The program of probabilistic-deterministic planning of the experiment was created by the order of Doctor of Technical Sciences, Professor S.V. Belyaev (ChMI named after Abishev of MES RK). The author of the program is Ph.D., Associate Professor V.N. Fomin The ExprDraw and ExprMake modules developed by Anton Grigoriev [4–7] are used to display mathematical formulas.

The investigated factors and their levels are presented in Table 1.

Table 1

Factors studied and their levels

Factors	1	2	3	4	5
X_1 — processing time, min	1	2	3	4	1
X_2 — capacitor bank capacity, uF	0.1	0.25	0.5	0.75	0.1
X_3 — interelectrode distance, mm	6	7	8	9	6
X_4 — volume of catalyst added, g	2.17	4.34	6.51	8.68	2.17
X_5 — volume of added donor (alcohol), ml	10	20	30	40	10

Since the dependence of the yield of liquid products from high-viscosity oil on the above factors is nonlinear, the method of mathematical design of an experiment based on nonlinear multiple correlation was used. Variable factors were varied at 5 levels. The experimental design matrix is shown in Table 2. Each row of the matrix corresponds to the experimental conditions, and the structure of the matrix is such that, in all experiments, the level of any factor occurs once with each level of all factors.

Table 2

Experimental design matrix

	#exp.	X_1, min	X_2, uF	X_3, mm	X_4, g	X_5, ml	$Y_{1\,exp.}$, mm^2/s	$Y_{1\,theor.}$, mm^2/s	$Y_{2\,exp.}$, %	$Y_{2\,theor.}$, %
I	1	1	0.1	6	2.17	10	6.49	6.4753	16.75	19.3513
	2	1	0.25	7	4.34	20	6.53	6.3652	35.43	27.5111
	3	1	0.5	8	6.51	30	5.71	5.8326	34.07	28.1789
	4	1	0.75	9	8.68	40	5.32	5.2757	23.51	25.8662
II	5	2	0.1	7	6.51	40	5.36	5.6627	18.35	21.9999
	6	2	0.25	6	8.68	30	5.96	6.0648	44.92	27.0224
	7	2	0.5	9	2.17	20	5.72	5.553	20.79	22.2943
	8	2	0.75	8	4.34	10	5.12	4.8923	24.08	21.8885
III	9	3	0.1	8	8.68	20	6.22	5.9686	28.21	29.6722
	10	3	0.25	9	6.51	10	4.67	5.2587	40.54	23.9503
	11	3	0.5	6	4.34	40	5.91	5.3391	19.78	26.6007
	12	3	0.75	7	2.17	30	5.01	5.2556	19.98	27.2807
IV	13	4	0.1	9	4.34	30	6.23	5.9072	22.9	33.4732
	14	4	0.25	8	2.17	40	5.08	5.2635	52.35	28.1584
	15	4	0.5	7	8.68	10	5.4	5.1711	25.36	33.5923
	16	4	0.75	6	6.51	20	5.36	5.7338	47.99	39.8488

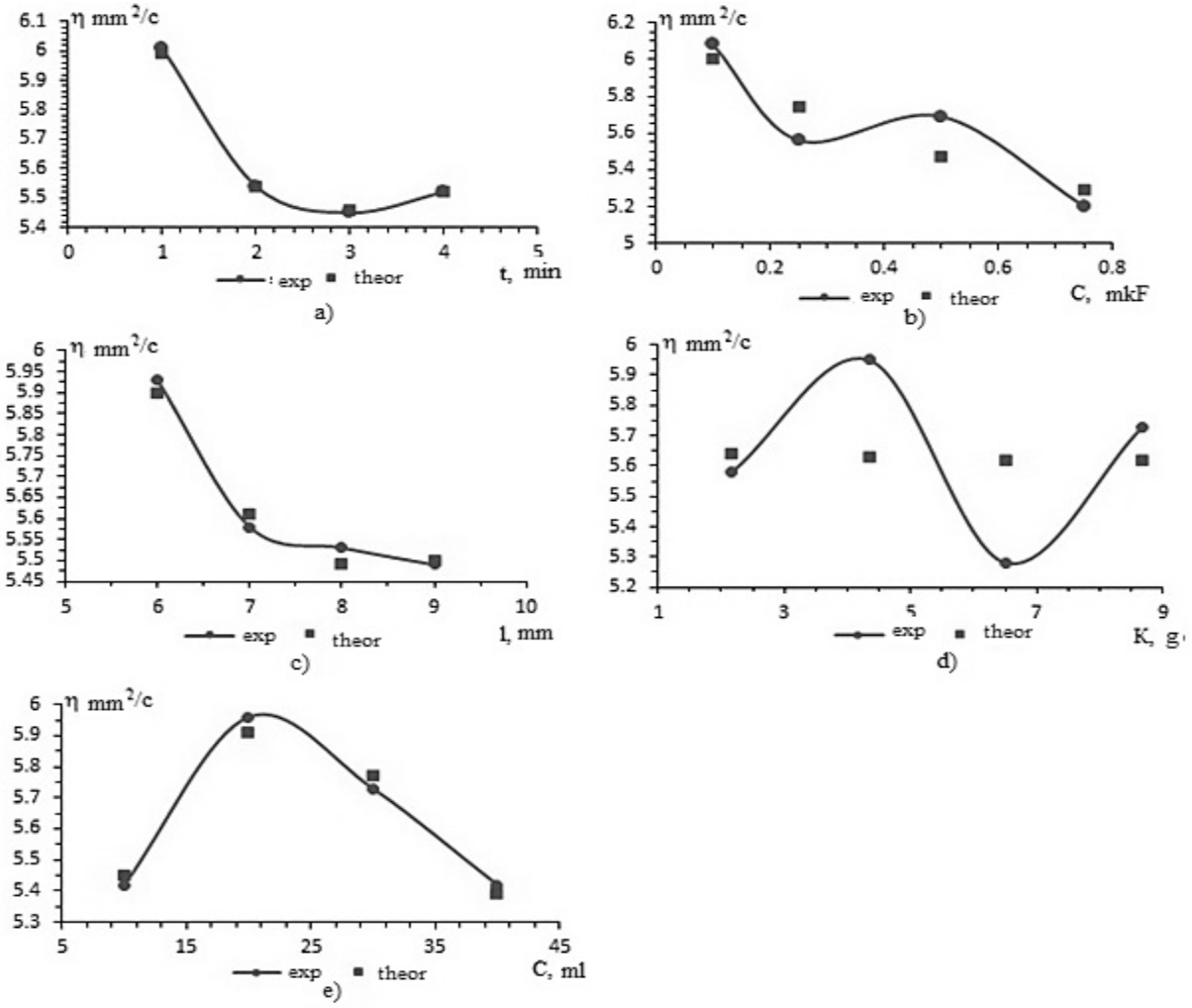
The $Y_{1\,exp.}$ and $Y_{2\,exp.}$ columns show the results of all the experiments to determine the kinematic viscosity of the Zhana-Ozen oil sludge, which was pretreated with an electrohydropulse effect (EHE). $Y_{1\,exp.}$ is the yield of the fraction up to 300 ºC from the oil sludge, $Y_{2\,exp.}$ is the calculated kinematic viscosity of the fraction up to 300 ºC, and $Y_{1\,theor.}$ and $Y_{2\,theor.}$ are calculated values of the yield of light and middle fractions up to 300 ºC on the basis of the generalized equation of Protod'yakonov-Malyshev. The matrix for planning the experiment for the preliminary treatment of oil sludge by means of electrohydropulse action is given in Table 2.

If the interval of the change of functions does not go beyond the permissible spread or confidence interval, then the functions are significant. Therefore, each function was checked for significance using the nonlinear multiple correlation coefficient (1) R and the significance t_R (2) of this coefficient:

$$R = \sqrt{1 - \frac{(N-1)\sum_{1}^{N}\left(Y_{\text{exp.}} - Y_{\text{theor.}}\right)^2}{(N-K-1)\sum_{1}^{N}\left(Y_{\text{exp.}} - Y_{\text{mean}}\right)}} > 0.66\,; \quad (1)$$

$$t_R = \frac{R\sqrt{n-k-1}}{1-R^2} \rangle 2\,, \quad (2)$$

where R — is the coefficient of multiple correlation; N — is the number of points described; K — is the number of active factors; $Y_{\text{exp.}}$ — is the experimental result; $Y_{\text{theor.}}$ — is the theoretical result; Y_{mean} — is the mean experimental value (see Fig.).



X_1 — on processing time; X_2 — on condenser battery capacity; X_3 — on interelectrode distance; X_4 — on consumption of added catalyst; X_5 — from the flow rate of the added hydrogen donor (alcohol)

Figure. Particular dependences of decrease in kinematic viscosity of light and middle fractions up to 300 ºC

The least squares method was used for the mathematical description of the graphical dependence on various factors. The values of the partial functions and the calculated values of the partial functions of the change in the kinematic viscosity and the yield of the fraction up to 300 ºC respectively for each factor are given in Tables 3–6.

Table 3

Theoretical and experimental values of particular functions for kinematic viscosity

Function		Levels				Mean
		1	2	3	4	
$Y_1 = 5.562e^{0.07791X_1}X_1^{-0.2306}$	theor.	5.99	5.54	5.46	5.52	5.62
	exp.	6.01	5.54	5.45	5.52	5.63
$Y_2 = 5.519e^{-0.07282X_2}X_2^{-0.04089}$	theor.	6.00	5.74	5.47	5.29	5.62
	exp.	6.08	5.56	5.69	5.20	5.63
$Y_3 = 29.69e^{0.1777X_3}X_3^{-1.495}$	theor.	5.90	5.61	5.49	5.5	5.63
	exp.	5.93	5.58	5.53	5.49	5.63
$Y_4 = 5.619 + \frac{0.05041}{X_4}$	theor.	5.64	5.63	5.62	5.62	5.63
	exp.	5.58	5.95	5.28	5.73	5.63
$Y_5 = 2.695e^{-0.01783X_5}X_5^{0.3816}$	theor.	5.45	5.91	5.78	5.39	5.63
	exp.	5.42	5.96	5.73	5.42	5.63

Table 4

Theoretical and experimental values of the partial functions of fractions yield up to 300 ºC

Function		Levels				Mean
		1	2	3	4	
$Y_1 = 18.2e^{0.4228X_1}X_1^{-0.7264}$	theor.	25.23	23.30	26.88	33.77	27.29
	exp.	27.44	27.04	27.13	37.15	29.69
$Y_2 = \frac{1}{0.0381 - 0.005184X_2}$	theor.	26.12	26.66	27.67	28.72	27.29
	exp.	21.55	43.31	25	28.89	29.69
$Y_3 = \frac{1}{0.02893 + 0.000717X_3}$	theor.	28.21	27.6	26.97	26.4	27.29
	exp.	32.36	24.78	34.68	26.94	29.69
$Y_4 = 33.13 - \frac{14.35}{X_4}$	theor.	24.27	27.37	28.49	29.04	27.29
	exp.	27.47	25.55	35.24	30.5	29.69
$Y_5 = 6.814e^{-0.03246X_5}X_5^{0.7362}$	theor.	24.7	29.83	28.99	28.66	27.29
	exp.	26.68	33.11	30.47	28.5	29.69

Table 5

Coefficient of correlation *R* for particular functions and its significance t_R

Function	*R*	t_R	Significance of the function
Y_1	1.00	1.10 < 2	Significant
Y_2	0.82	3.52 > 2	Significant
Y_3	0.98	32.23 > 2	Significant
Y_4	0.58	1.22 < 2	Significant
Y_5	0.98	39.6 > 2	Not significant

Table 6

Coefficient of correlation *R* for particular functions at light fractions output up to 300 ºC and its significance t_R

Function	*R*	t_R	Significance of the function
Y_1	0.92	8.89 > 2	Significant
Y_2	0.62	1.42 < 2	Significant
Y_3	0.57	1.19 < 2	Not significant
Y_4	0.28	0.43 < 2	Not significant
Y_5	0.94	11.06 > 2	Significant

As a function of the response of the influence of the electrohydropulse action, we adopted the decrease in the kinematic viscosity of the hydrogenate and the yield of the fraction up to 300 ºC. The mathematical model of the process of treatment of heavy oil by means of electrohydropulse action is based on the Protod'yakonov-Malyshev formula.

The experiment performed under these conditions gives a good agreement with the theoretically calculated value of the decrease in the kinematic viscosity of hydrogenate and the yield of the fraction up to 300 ºC from the treated oil hydrogenate.

Thus, we found that the dominant factors affecting the decrease in the kinematic viscosity, the increase in the yield of light and middle fractions up to 300 ºC from the Zhana-Ozen oil sludge in the process of destruction of the heavy part of the organic mass of oil are: interelectrode distance, processing time and discharge voltage. The optimal conditions for carrying out the process of destruction of the Zhana-Ozen oil sludge by means of electrohydropulse treatment are: X_1 — treatment time 4–8 minutes; X_2 — capacitor bank capacitance, C — 0.1 μF; X_3 — interelectrode distance, L — 4–8 mm; X_4 — quantity of added donor (catalyst) — 6.51 g; X_5 — the amount of added alcohol — 10–30 ml per kg of raw material.

The results obtained on the study of the group and individual composition of hydrogenates from the Zhana-Ozen oil sludge allow us to state that electrohydropulse treatment not only increases the destruction reaction rate of the heavy portion of the Zhana-Ozen oil sludge in the presence of catalytic additives, but also catalyzes the hydrogenation and hydrogenolysis reactions in parallel.

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Мұнай шайырының физика-химиялық қасиеттеріне электргидроимпульсті технологияның әсерін зерттеу

Мақала түрлі факторлардың ықпалы ескерелетін тәжірибені ықтималды-детерминді жоспарлау әдісін қолдану арқылы Жаңа Өзен мұнай шайырының физика-химиялық сипаттамасына электргидроимпульсті өңдеудің әсерін зерттеуге арналған. Мұнайдың ауыр органикалық массасының деструкциясы үрдісі барысында Жаңа Өзен мұнай шайырының 300 ºС температураға дейінгі жеңіл және орта фракциялардың шығымын арттыратын және кинетикалық тұтқырлықты төмендетуге әсер ететін негізгі факторлар анықталды, олар: электродаралық қашықтық, өңдеу ұзақтығы және разрядты кернеу.

Кілт сөздер: электргидроимпульсті технология, мұнай шайыры, кинематикалық тұтқырлық, электродаралық қашықтық, кернеу.

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Исследование влияния электрогидроимпульсной технологии на физико-химические характеристики нефтяных шламов

Статья посвящена исследованию влияния электрогидроимпульсной обработки на физико-химические характеристики нефтяного шлама Жана Озен с использованием метода вероятностно-детерминированного планирования эксперимента, в котором учитывается взаимное влияние различных факторов. Установлено, что доминирующими факторами, влияющими на уменьшение величины кинематической вязкости и увеличение выхода легкой и средней фракций до 300 ºС из нефтешлама Жана Озен в процессе деструкции тяжелой части органической массы нефти, являются межэлектродное расстояние, продолжительность обработки и разрядное напряжение.

Ключевые слова: электрогидроимпульсная технология, нефтяной шлам, кинематическая вязкость, межэлектродное расстояние, напряжение.

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