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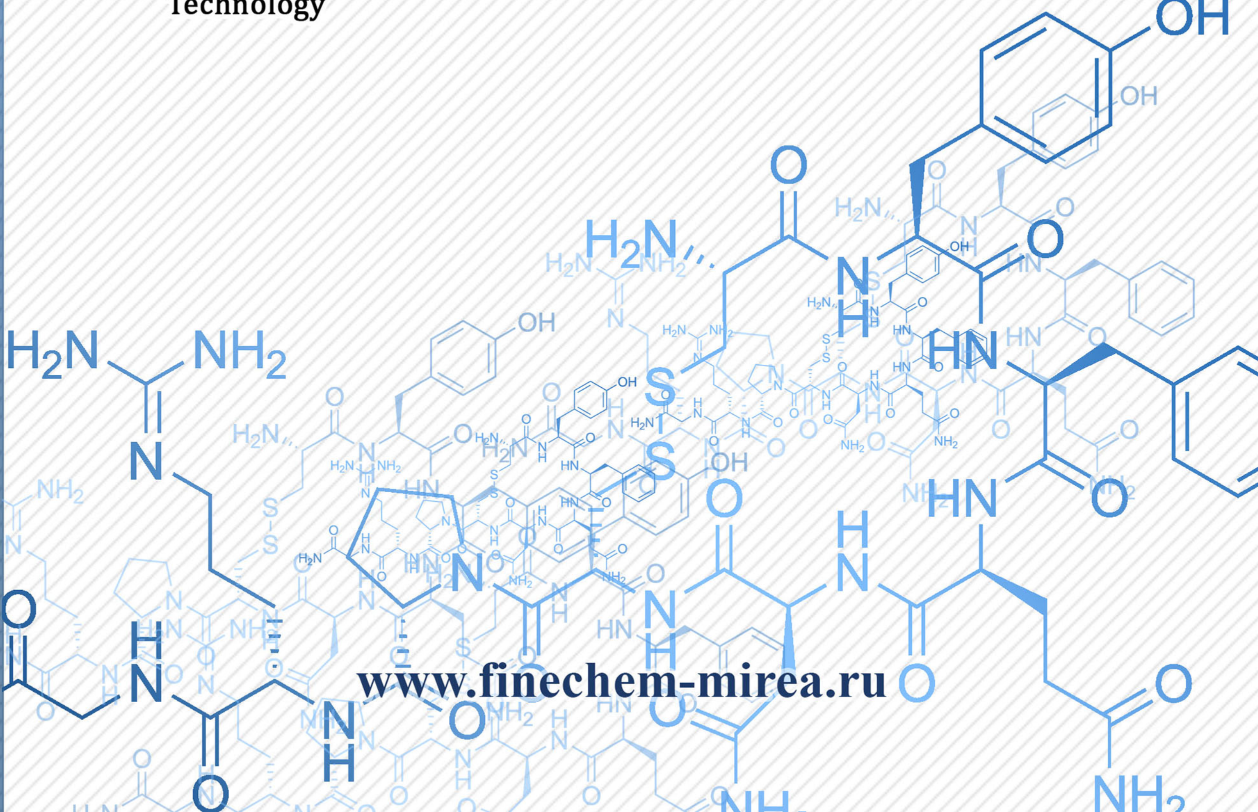
Fine Chemical Technologies

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



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frolkova_a@mirea.ru

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frolkova_a@mirea.ru

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E-mail: *seredina@mirea.ru*

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abisheva_z@mail.ru.

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https://orcid.org/0000-0002-0957-5594,
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kyuzhizhin@igic.ras.ru.

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Scopus Author ID 34770109800, ResearcherID I-5606-2016,
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ivanov_i@mirea.ru.

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http://orcid.org/0000-0002-0237-2313,
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Scopus Author ID 6602070468, ResearcherID R-1020-2016,
http://orcid.org/0000-0002-1764-0819,
president@isuct.ru.

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Belarusian State Technological University,
Minsk, Belarus.
Scopus Author ID 6602297257,
ela_krutko@mail.ru.

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Scopus Author ID 7006592304, ResearcherID G-5017-2017,
aiv@ibch.ru.

Aziz M. Muzafarov – Academician at the RAS,
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Scopus Author ID 6601954283, ResearcherID O-8453-2017,
http://orcid.org/0000-0002-4506-0694,
abisheva_z@mail.ru.

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

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kyuzhizhin@igic.ras.ru.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Scopus Author ID 7003604847,
andrzej.trochimczuk@pwr.edu.pl.

Цивадзе Аслан Юсупович – академик РАН, д.х.н., профессор, Институт физической химии и электрохимии им. А.Н. Фрумкина РАН, Москва, Российская Федерация.
Scopus Author ID 7004245066, ResearcherID G-7422-2014,
tsiv@phyche.ac.ru.

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RESEARCH ARTICLE

The reactivity of cinnamic acid derivatives as lignin precursors

Oleg K. Karimov[1,@], Galina Y. Kolchina[2], Galina A. Teptereva[1], Irina A. Chetvertneva[3], Eduard K. Karimov[1], Almaz R. Badretdinov[1]

[1]*Ufa State Petroleum Technological University, Ufa, 450062 Russia*
[2]*Bashkir State University, Sterlitamak Branch, Sterlitamak, 453103 Russia*
[3]*SBM Service Center of the Volga-Ural region, Moscow, 119330 Russia*
[@]*Corresponding author, e-mail: karimov.oleg@gmail.com*

Objectives. *Cinnamic acid derivatives belong to a large class of phenolic compounds, which are widely distributed in plants and have high potential for use in the medical and industrial fields. They have various useful practical properties, e.g., antioxidant, anti-inflammatory, antiplatelet, and anti-melanogenic properties. Hydroxycinnamic acids are of particular interest as phenylpropanoids, which are the starting compounds of lignin. The aim of this work was to study the electronic structure and analyze the reactivity of the simplest representatives of phenylpropanoids formed during the biosynthesis of the coumaric (p-hydroxycinnamic), caffeic (3,4-dihydroxycinnamic), ferulic (3-methoxy-4-hydroxycinnamic), sinapic (3,5-dimethoxy-4-hydroxycinnamic), and 3,4-dimethoxycinnamic acids. These acids are the biogenetic precursors of most other phenolic compounds (coumarins, melanins, lignins, and flavonoids) and are found in almost all higher plants.*

Methods. *Calculations with full optimization of the geometric parameters were performed using the original Hartree–Fock theory and hybrid density functional method. All calculations were performed using the Firefly program.*

Results. *A comparative quantum chemical calculation of the geometric parameters of hydroxycinnamic acid molecules was conducted via two methods, and the values of the charges on atoms according to Mulliken were determined. It was found that with the addition of hydroxyl and methoxy substituents at the meta and para positions relative to the carboxyl fragment, the electron density shifts toward the benzene ring, and the symmetry of the molecule decreases. Additionally, in these structures, there is π,π-conjugation of the carboxyl fragment of the –CH=CHCOOH molecule with the aromatic ring, which significantly affects the geometric configuration of the molecule. The maximum positive charge is concentrated on the C_9 atom, while the maximum negative charge is on the oxygen atoms belonging to the methoxy substituents and the hydroxyl group, which confirms the role of oxygen atoms in the chemical transformations of acids.*

Conclusions. *Two different methods were used to calculate the geometric, electronic, and energy parameters and electrophilicity indices of the studied hydroxycinnamic acids in the gas phase. The obtained values were consistent (within the limits of error) with the experimental data as well as the results described in earlier works' calculations by other methods.*

Keywords: *oxy-cinnamic acids, coumaric acid, caffeic acid, sinapic acid, ferulic acid, dimethoxycinnamic acid.*

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Исследование реакционной способности производных коричной кислоты – предшественников лигнина

О.Х. Каримов[1,@], **Г.Ю. Колчина**[2], **Г.А. Тептерева**[1], **И.А. Четвертнева**[3], **Э.Х. Каримов**[1], **А.Р. Бадретдинов**[1]

[1]Уфимский государственный нефтяной технический университет, Уфа, 450062 Россия
[2]Стерлитамакский филиал Башкирского государственного университета, Стерлитамак, 453103 Россия
[3]ООО «Сервисный Центр СБМ» Волго-Уральского региона, Москва, 119330 Россия
[@]Автор для переписки, e-mail: karimov.oleg@gmail.com

Цели. *Производные коричной кислоты относятся к большому классу фенольных соединений, которые широко распространены в растительности и обладают высоким потенциалом для применения в медицине и промышленности. Они обладают различными практически полезными свойствами, например, антиоксидантными, противовоспалительными, антиагрегантными и антимеланогенными свойствами. Отдельный интерес представляют оксикоричные кислоты как фенилпропаноиды, являющиеся исходными соединениями лигнина. Целью данной работы является исследование электронной структуры и анализ реакционной способности простейших представителей фенилпропаноидов, образующихся в процессе биосинтеза: кумаровой (п-оксикоричной), кофейной (3,4-дигидроксикоричной), феруловой (3-метокси-4-гидроксикоричной), синаповой (3,5-диметокси-4-гидроксикоричной) и 3,4-диметоксикоричной кислот. Эти кислоты являются биогенетическими предшественниками большинства других фенольных соединений (кумаринов, меланинов, лигнина и флавоноидов) и встречаются практически во всех высших растениях.*

Методы. *В рамках ограниченного метода Хартри Фока и метода гибридного функционала плотности оптимизированы исследуемые молекулы. Все расчеты проводились с использованием программы Firefly.*

Результаты. *Проведен сравнительный квантово-химический расчет геометрических параметров молекул оксикоричных кислот двумя методами, приведены значения зарядов на атомах по Малликену. При введении гидроксильных и метоксильных заместителей в м- и п-положения относительно карбоксильного фрагмента происходит смещение электронной плотности в сторону бензольного кольца и, как следствие, понижение симметрии молекулы. Также в исследуемых структурах имеется π,π-сопряжение карбоксильного фрагмента молекулы –CH=CHCOOH с ароматическим кольцом, что существенно сказывается на геометрической конфигурации молекул. Максимальный положительный заряд сосредоточен на атоме C_9, а максимальный отрицательный – на атомах кислорода, относящихся к метоксильным заместителям и гидроксильной группе, что подтверждает роль кислородных атомов в химических превращениях кислот.*

Выводы. *В работе двумя различными методами были рассчитаны геометрические, электронные и энергетические параметры, а также индексы электрофильности исследуемых оксикоричных кислот в газовой фазе. Полученные величины согласуются в пределах погрешностей с экспериментальными данными, а также описываемыми в ранних работах при расчетах другими методами.*

Ключевые слова: *оксикоричные кислоты, кумаровая кислота, кофейная кислота, синаповая кислота, феруловая кислота, диметоксикоричная кислота.*

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Cinnamic acid derivatives (hydroxycinnamic acids) belong to a large class of phenolic compounds, which are widespread in vegetation and have high potential for use in medicine and industry. They are involved in the biosynthesis of lignins and flavonoids as well as interact with sugars, cell wall polysaccharides, acyclic and alicyclic acids, terpenes, amines, alkaloids, and several other substances.

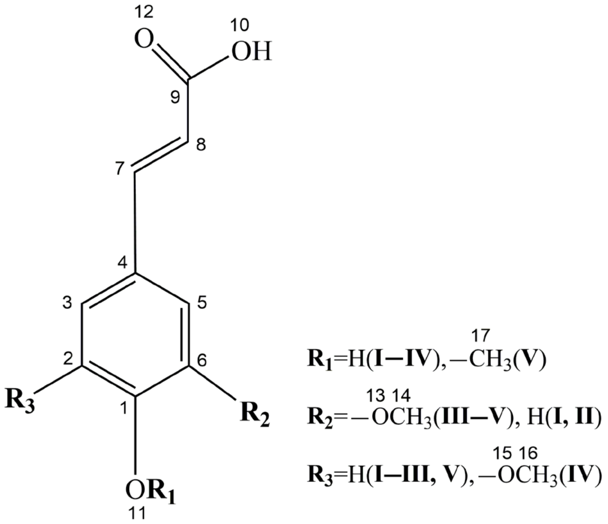
Various biological properties of oxy-cinnamic acids are known. For example, coumaric acid has antioxidant, anti-inflammatory, antiplatelet, and anti-melanogenic properties [1], while caffeic acid is a polar compound with a strong chelating ability toward metals as well as antioxidant activity [2, 3].

Oxy-cinnamic acids are of particular interest as phenylpropanoids, which are the starting compounds of lignin. In the course of biosynthesis, they are reduced to oxy-cinnamic alcohols [4], which serve as direct precursors of lignin.

Many reports have been devoted to the study of the structure and properties of lignin precursors. For example, in [5], the antioxidant properties of coumaric and sinapic acids are studied using quantum chemistry methods. Calculations within the framework of the density functional theory "Becke, 3-parameter, Lee–Yang–Parr" (B3LYP) in the 6-311+G(2d,2p) basis for compounds in a vacuum and an aqueous medium show that the OH group is responsible for the antioxidant properties. In another work [6], the structure of coumaric and caffeic acids is comparatively studied by physicochemical analysis methods and quantum chemical calculations. The results obtained, which are also calculated within the framework of the density functional theory B3LYP in the 6-311G basis set, are in good accordance with the experimentally obtained values.

Derivatives of cinnamic acid, i.e., *o*-coumaric, *m*-coumaric, caffeic, ferulic, and chlorogenic (caffeyl-3-quinic acid) acids [7], are studied using the limited Hartree–Fock method in the 6-311G(d) set. Hydroxycinnamic acid derivatives, in which the carboxyl group is separated from the aromatic ring by a vinyl bridge, are characterized by higher antioxidant activity than the corresponding benzoic acid derivatives.

The aim of this work is to study the electronic structure and analysis of the reactivity of the simplest representatives of phenylpropanoids formed during biosynthesis: coumaric (*p*-hydroxycinnamic) (I), caffeic (3,4-dihydroxycinnamic) (II), ferulic (3-methoxy-4-hydroxycinnamic) (III), sinapic (3,5-dimethoxy-4-hydroxycinnamic) (IV), and 3,4-dimethoxycinnamic acids (V) (see figure below). These acids are the biogenetic precursors of most other phenolic compounds (coumarins, melanins, lignins, and flavonoids) and are found in almost all higher plants.



Structural formulas of hydroxycinnamic acids.

MATERIALS AND METHODS

Calculations with complete geometric parameter optimization were performed using the restricted Hartree–Fock (RHF) theory and the hybrid density functional method B3LYP in the 6-311 (d,p) basis using the Firefly program[1], which is a version of the General Atomic and Molecular Electronic Structure System program (USA) [8] with new computational algorithms [9, 10].

RESULTS AND DISCUSSION

The geometric parameter calculations (Table 1) showed that the addition of hydroxyl and methoxyl substituents in the *meta* and *para* positions relative to the carboxyl fragment led to a shift in the electron density toward the benzene ring and, consequently, a decrease in the symmetry of the molecule. Additionally, in the studied structures, there was π,π-conjugation of the carboxyl fragment of the molecule –CH=CHCOOH with an aromatic ring, which significantly affected the geometric configuration of the molecule.

Considering the theory of valence bonds, the ∠CCO angles between bonds should be approximately 111°. The opening of ∠CCO (117.74°–124.96°) is associated with the introduction of methoxyl groups and, thus, the emergence of strong stress and increased reactivity (Table 1). The distortion of the bond angle $\angle C_7C_8C_9$ and

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[1] Granovsky A.A. Firefly version 7.1.G. URL: http://classic.chem.msu.su/gran/firefly/index.html (Accessed March 2, 2020).

its increase are associated with the influence of the carboxyl group.

Table 2 shows the values of the charges on atoms according to Mulliken as calculated by various methods. The obtained values show that the positive values were concentrated on the C_1 and C_9 atoms for all studied compounds. The positive charges of these atoms in the range from 0.227 (C_1) to 0.585 (C_9) were partially compensated by the sphere of negative charges on the oxygen atoms of the hydroxyl and carboxyl groups from –0.394 to –0.461.

The distribution of the point charges on atoms was such that the maximum positive charge was concentrated on the C_9 atom, while the maximum negative charge was on the oxygen atoms belonging to the methoxyl substituents (O_{11} – V, O_{13}, O_{15}) and the hydroxyl group (O_{11} – I–IV), which confirmed the role of oxygen atoms in the chemical transformations

Table 1. The values of the valence and dihedral angles of the acid molecules as calculated by the RHF/6-311(d,p) and B3LYP/6-311(d,p) methods

Angles	I		II		III		IV		V	
Calculation method	**RHF**	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**
$\angle O_{11}C_1C_2$	117.744	117.580	120.141	120.438	119.909	120.521	120.205	120.871	124.959	124.853
$\angle C_5C_4C_7$	123.346	123.277	122.761	122.761	122.915	122.500	122.559	122.528	122.998	123.012
$\angle C_7C_8C_9$	124.675	125.259	124.802	125.473	124.678	125.483	124.786	125.503	124.520	125.181
$\angle C_8C_9O_{10}$	117.582	117.471	117.639	117.542	117.577	117.539	117.649	117.571	117.491	117.410
$\angle O_{10}C_9C_8C_7$	−23.340	−21.822	−23.017	−20.897	−23.666	−20.348	−22.959	−20.480	−24.246	−22.315

Table 2. The values of the charges on atoms according to Mulliken in the acid molecules as calculated by the RHF/6-311(d,p) and B3LYP/6-311(d,p) methods

Angles	I		II		III		IV		V	
Calculation method	**RHF**	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**
C_1	0.257	0.165	0.256	0.174	0.264	0.166	0.227	0.160	0.258	0.182
C_{ra}	0.133	–	0.141	–	0.143	–	0.110	–	0.133	–
C_2	−0.105	−0.086	−0.092	−0.085	−0.093	−0.087	0.226	0.137	−0.121	−0.013
C_3	−0.060	−0.061	−0.075	−0.061	−0.065	−0.054	−0.090	−0.049	−0.075	−0.065
C_4	−0.096	−0.088	−0.088	−0.096	−0.079	−0.099	−0.068	−0.090	−0.070	−0.076
C_5	−0.062	−0.047	−0.103	−0.052	−0.068	−0.071	−0.122	−0.068	−0.072	−0.032
C_6	−0.131	−0.120	0.219	0.121	0.174	0.151	0.284	0.176	0.216	0.124
C_7	−0.016	−0.047	−0.013	−0.046	−0.016	−0.042	−0.016	−0.043	−0.021	−0.050
C_8	−0.262	−0.213	−0.265	−0.218	−0.263	−0.222	−0.267	−0.220	−0.259	−0.211
C_9	0.583	0.377	0.584	0.378	0.583	0.378	0.585	0.379	0.582	0.377
m	0.314	–	0.321	–	0.318	–	0.308	–	0.300	–
O_{10}	−0.395	−0.306	−0.394	−0.306	−0.394	−0.306	−0.394	−0.306	−0.395	−0.307
O_{11}	−0.443	−0.349	−0.450	−0.347	−0.450	−0.345	−0.458	−0.355	−0.461	−0.344
O_{12}	−0.426	−0.316	−0.425	−0.318	−0.426	−0.319	−0.426	−0.319	−0.425	−0.316
O_{13}	–	–	−0.495	−0.406	−0.520	−0.405	−0.523	−0.411	−0.485	−0.363
O_{15}	–	–	–	–	–	–	−0.489	−0.367	–	–

of acids. The highest concentration of electron density was noted at the C_2 (V) = −0.121 atom due to the close arrangement of methoxyl groups in the *o*- and *m*- positions relative to it, which corresponded to the center of electrophilic attack in the aromatic ring.

Considering the C_1 atom bonded to phenolic hydroxyl, the local electrophilicity value *m* showed that these values decreased upon going to methoxy-substituted acids. Compounds IV and V were less electrophilic than phenol due to the influence of the methoxyl substituents located in the *o*-positions to phenolic hydroxyl. According to [11], the B3LYP hybrid density functional method underestimates ionization potentials, while the Hartree–Fock method provides values that are in good accordance with the experimental data.

Using the calculated data, the electrophilicity index values were also calculated (Table 3). Based on the calculated data, the global electrophilicity index ω for phenol was 0.244 eV [12]. All tested compounds were more electrophilic than phenol. This phenomenon was due to the electron-withdrawing effect of the –CH=CHCOOH and $–OCH_3$ groups located in the *p*-position to phenolic hydroxyl.

The ionization potential (IP) determines the reduction activity of a compound, i.e., its ability to easily donate an electron. Sinapic acid had the lowest IP value of the studied acids, confirming its high antioxidant properties [13]. The range of antioxidant activity in this case was as follows: sinapic acid > ferulic acid > caffeic acid ~ 3,4-dimethoxycinnamic acid > coumaric acid. The values in the table were in good accordance with the calculations in other works (e.g., the IP of coumaric acid in [6] was –6.4 eV and that of sinapic acid was –6.1 eV).

CONCLUSIONS

The optimization of the molecules of the cinnamic acid derivatives was performed via quantum chemistry methods, and the geometric, electronic, and energy characteristics of the studied molecules were calculated.

Based on the results, the reactivity series of the carbon and oxygen atoms of the studied molecules in electrophilic–nucleophilic reactions were built. For coumaric acid, two carbon atoms with reactivity $C_9 > C_1$ had a positive charge; in the series of atoms with negative charges, the reactivity was $C_8 > C_6 > C_4 > C_2 > C_3 > C_7 = C_5$ and $O_{11} > O_{12} > O_{10}$. For caffeic acid, three carbon atoms with reactivity $C_9 > C_1 > C_6$ had a positive charge; in

Table 3. The values of the acids' main energy characteristics as calculated by the RHF/6-311(d,p) and B3LYP/6-311(d,p) methods*

Calculation method	**I**		**II**		**III**		**IV**		**V**	
	RHF	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**	**RHF**	**B3LYP**
− IP, eV	8.559	6.424	8.445	6.252	8.498	6.148	8.341	6.106	8.416	6.254
− E_A, eV	−1.859	2.051	−1.752	2.081	−1.807	2.0122	−1.803	2.005	−1.898	1.979
η, eV	10.418	4.373	10.197	4.171	10.305	4.136	10.144	4.101	10.314	4.275
S, eV	0.096	0.229	0.098	0.240	0.097	0.242	0.099	0.244	0.097	0.234
E_{min}, $\times 10^{-3}$, eV	−15.515	−15.608	−17.553	−17.655	−18.615	−18.725	−21.715	−21.842	−19.677	−19.794
− μ, eV	3.350	4.238	3.347	4.167	3.346	4.080	3.269	4.056	3.259	4.117
ω, eV	0.539	2.053	0.549	2.081	0.543	2.013	0.527	2.005	0.515	1.982
Δω, eV	0.295	1.809	0.305	1.837	0.299	1.769	0.283	1.761	0.271	1.738

**Note*: IP – ionization potential; E_A – energy of electron affinity; η – index of absolute chemical hardness; *S* – index of absolute chemical softness; E_{min} – minimum energy of matter; μ – electronic chemical potential; ω – global electrophilicity index; $\Delta\omega = \omega - \omega_{PhOH}$.

the series of atoms with negative charges, the reactivity was $C_8 > C_{14} > C_4 > C_2 > C_5 > C_3 > C_7$ and $O_{13} > O_{11} > O_{12} > O_{10}$. For sinapic acid, the respective reactivities were $C_9 > C_6 > C_1 > C_2$ (atoms had a positive charge) and $C_8 > C_{14} > C_{16} > C_4 > C_5 > C_3 > C_7$ and $O_{13} > O_{15} > O_{11} > O_{12} > O_{10}$ (atoms had a negative charge). Finally, for 3,4-dimethoxycinnamic acid, the respective reactivities were $C_9 > C_1 > C_2$ (atoms had a positive charge) and $C_8 > C_{17} > C_{14} > C_4 > C_3 > C_7 > C_5 > C_2$ and $O_{13} > O_{11} > O_{12} > O_{10}$ (atoms had a negative charge).

The largest positive charge in all studied compounds was concentrated on the carbon atom of the carbonyl group, and the largest negative charge was on the oxygen atoms belonging to the methoxyl substituents and the hydroxyl group.

It was shown that large deformations of the bond angles $\angle O_{11}C_1C_2$ and $\angle C_7C_8C_9$ led to the emergence of strong stress, which in turn led to an increase in the reactivity of the oxy-cinnamic acid molecules.

Based on the physicochemical parameter calculations, the range of antioxidant activities of the considered compounds was compiled: sinapic acid > ferulic acid > caffeic acid ~ 3,4-dimethoxycinnamic acid > coumaric acid.

The authors declare no conflicts of interest.

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About the authors:

Oleg K. Karimov, Cand. of Sci. (Engineering), Associate Professor, Department of General Chemical Technology, Ufa State Petroleum Technological University (1, Kosmonavtov ul., Ufa, 450062, Russia). E-mail: karimov.oleg@gmail.com. https://orcid.org/0000-0002-0383-4268

Galina Y. Kolchina, Cand. of Sci. (Chemistry), Associate Professor, Department of Chemistry and Chemical Technology, Bashkir State University, Branch of the University in Sterlitamak (49, Lenina pr., Sterlitamak, 453103, Russia). E-mail: kolchina.gyu@mail.ru. https://orcid.org/0000-0003-2808-4827

Galina A. Teptereva, Dr. of Sci. (Engineering), Associate Professor, Department of General, Analytical and Applied Chemistry, Ufa State Petroleum Technological University (1, Kosmonavtov ul., Ufa, 450062, Russia). E-mail: teptereva.tga@yandex.ru. http://orcid.org/0000-0003-2328-6761

Irina A. Chetvertneva, Cand. of Sci. (Engineering), Head of the SBM Service Center LLC of the Volga-Ural region (5, Vavilova ul., Moscow, 119330, Russia). E-mail: chetvertneva@ufa.scsbm.ru. http://orcid.org/0000-0002-6798-0205

Eduard K. Karimov, Cand. of Sci. (Engineering), Associate Professor, Department of General Chemical Technology, Ufa State Petroleum Technological University (1, Kosmonavtov ul., Ufa, 450062, Russia). E-mail: karimov.edyard@gmail.com. http://orcid.org/0000-0002-4224-4586

Almaz R. Badretdinov, Postgraduate Student, Department of General Chemical Technology, Ufa State Petroleum Technological University (1, Kosmonavtov ul., Ufa, 450062, Russia). E-mail: almaz.badretdinov@list.ru. https://orcid.org/0000-0001-6529-882X

Об авторах:

Каримов Олег Хасанович, кандидат технических наук, доцент кафедры общей химической технологии, ФГБОУ ВО «Уфимский государственный нефтяной технический университет» (450062, Россия, Уфа, ул. Космонавтов, 1). E-mail: karimov.oleg@gmail.com. https://orcid.org/0000-0002-0383-4268

Колчина Галина Юрьевна, кандидат химических наук, доцент кафедры химии и химической технологии, Стерлитамакский филиал ФГБОУ ВО «Башкирский государственный университет» (453103, Россия, Стерлитамак, Пр. Ленина, 49). E-mail: kolchina.gyu@mail.ru. https://orcid.org/0000-0003-2808-4827

Тептерева Галина Алексеевна, доктор технических наук, доцент кафедры общей, аналитической и прикладной химии, ФГБОУ ВО «Уфимский государственный нефтяной технический университет» (450062, Россия, Уфа, ул. Космонавтов, 1). E-mail: teptereva.tga@yandex.ru. http://orcid.org/0000-0003-2328-6761

Четвертнева Ирина Амировна, кандидат технических наук, руководитель, ООО «Сервисный Центр СБМ» Волго-Уральского региона (119330, Россия, Москва, ул. Вавилова, 5). E-mail: chetvertneva@ufa.scsbm.ru. http://orcid.org/0000-0002-6798-0205

Каримов Эдуард Хасанович, кандидат технических наук, доцент кафедры общей химической технологии, ФГБОУ ВО «Уфимский государственный нефтяной технический университет» (450062, Россия, Уфа, ул. Космонавтов, 1). E-mail: karimov.edyard@gmail.com. http://orcid.org/0000-0002-4224-4586

Бадретдинов Алмаз Рафисович, магистрант, ФГБОУ ВО «Уфимский государственный нефтяной технический университет» (450062, Россия, Уфа, ул. Космонавтов, 1). E-mail: almaz.badretdinov@list.ru. https://orcid.org/0000-0001-6529-882X

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THEORETICAL BASES OF CHEMICAL TECHNOLOGY

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RESEARCH ARTICLE

Energy saving in the extractive distillation of isobutyl alcohol–isobutyl acetate with *n*-butyl propionate

Pavel S. Klauzner[@], Danila G. Rudakov, Elena A. Anokhina, Andrey V. Timoshenko

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

Objectives. *Determination of the effectiveness of using various types of heat pumps in the extractive distillation of an isobutyl alcohol–isobutyl acetate mixture with n-butyl propionate as the entrainer.*
Methods. *As the main research method, mathematical modeling was performed using the Aspen Plus V. 9 software package. As a model for describing the vapor–liquid equilibrium, the local composition equation-based UNIQUAC model was employed, and the Redlich–Kwong model was adopted to examine the non-ideal vapor phase. When modeling the conventional scheme of extractive distillation, parametric optimization was carried out according to the criterion of total energy costs in the reboilers of the columns. For economical evaluation, Aspen Process Economic Analyzer V10.1 tools were employed.*
Results. *In comparison with the conventional extractive distillation scheme, three variants of schemes with vapor-recompression heat pumps were considered: with a heat pump placed on an extractive distillation column, on an extractive agent regeneration column, and with two heat pumps placed on both columns of the scheme. A scheme with an internal heat pump was also proposed, in which the heat pump compressor is located between sections of the extractive column that operate at different pressures: 506.6 kPa in the top sections and 101.3 in the bottom section. An economic analysis was conducted for all the considered schemes to calculate the total annual costs. It was shown that schemes with vapor-recompression heat pumps can significantly reduce the energy costs of extractive distillation by up to 39.6%; however, a significant reduction in the total annual costs is achieved only with sufficiently long operation periods of the plants. The reduction in the energy costs in the scheme with an internal heat pump was 44%, and the total annual costs were in the range of 20.2–30.1%, depending on the operating time of the plant.*
Conclusions. *It was shown that using heat pumps in the extractive distillation of the mixture of isobutyl alcohol–isobutyl acetate with n-butyl propionate as the entrainer can significantly reduce energy costs. The scheme with an internal heat pump is the most economical of all the considered schemes.*

Keywords: *extractive distillation, heat pump, energy saving.*

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Энергосбережение в экстрактивной ректификации смеси изобутиловый спирт–изобутилацетат с бутилпропионатом

П.С. Клаузнер@, Д.Г. Рудаков, Е.А. Анохина, А.В. Тимошенко

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

Цели. *Определение эффективности применения тепловых насосов различного типа в экстрактивной ректификации смеси изобутиловый спирт–изобутилацетат с н-бутилпропионатом в качестве разделяющего агента.*
Методы. *Основной метод исследования – математическое моделирование в программном комплексе Aspen Plus V. 9. В качестве модели описания парожидкостного равновесия применялась основанная на уравнении локальных составов модель UNIQUAC, для учета неидеальности паровой фазы – модель Редлиха–Квонга. При моделировании традиционной схемы экстрактивной ректификации производилась параметрическая оптимизация по критерию суммарных энергетических затрат в кипятильниках колонн. Для экономической оценки применялись инструменты Aspen Process Economic Analyzer V10.1.*
Результаты. *В сравнении с традиционной схемой экстрактивной ректификации рассмотрено три варианта схемы с применением тепловых насосов открытого типа – с размещением теплового насоса на колонне экстрактивной ректификации, на колонне регенерации разделяющего агента и с размещением двух тепловых насосов на обоих колоннах схемы. Также предложена схема с внутренним тепловым насосом, в которой компрессор теплового насоса расположен между секциями экстрактивной колонны, которые работают при различных давлениях – 506.6 кПа в укрепляющей и экстрактивной секциях и 101.3 в отгонной. Была произведена экономическая оценка всех рассмотренных схем и вычисление полных приведенных затрат. Показано, что применение схем с тепловыми насосами открытого типа позволяет значительно, вплоть до 39.6%, снизить энергетические затраты на экстрактивную ректификацию, однако значительное снижение полных приведенных затрат достигается только при достаточно большом сроке функционирования установок. Снижение энергетических затрат в схеме с внутренним тепловым насосом составило 44%, а полных приведенных затрат – 20.2–30.1% в зависимости от времени функционирования установки.*
Выводы. *Показано, что применение тепловых насосов в процессе экстрактивной ректификации смеси изобутиловый спирт–изобутилацетат с бутилпропионатом в качестве разделяющего агента позволяет значительно снизить энергетические затраты. Наиболее экономичной из рассмотренных является схема с применением внутреннего теплового насоса.*

Ключевые слова: *экстрактивная ректификация, тепловой насос, энергосбережение.*

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INTRODUCTION[1]

Distillation is one of the main industrial processes for purifying and separating mixtures of different chemical components, and it is characterized by high specific energy costs [1]. This process consumes a significant amount of energy due to its low thermodynamic efficiency; consequently, researchers are constantly searching for strategies to reduce energy consumption. Currently, the main strategies for improving individual processes and technological schemes include internal [2] and external heat integration [3], as well as the use of heat pumps [4, 5].

Extractive distillation (ED), a process based on the application of a special additional entrainer that changes (increases, circulates) the relative volatility of the components of the initial mixture, is used for the separation of azeotrope mixtures and mixtures of components with relative volatility close to one. In the chemical industry, it is used to isolate benzene from pyrolysis and reforming fractions [6], as well as butadiene and isoprene from the pyrolysis and dehydrogenation products of C_4–C_5 fractions [7]. Even though ED, in some cases, is characterized by significantly lower energy consumption than that of azeotropic distillation [8, 9] and that the separation method is based on pressure variation [10–13], reducing the energy costs associated with its operation is an urgent task due to the multi-tonnage technologies of basic organic and petrochemical syntheses, for which it is mainly used [14]. The aforementioned approaches for improving conventional distillation have been employed to improve the ED process. A significant difference is that the use of external heat pumps for conventional distillation is already widespread, e.g., the technology for the distillation of propane–propylene fraction, while the incorporation of this approach in ED is still at the beginning stages [15].

The purpose of this work is to study the methods of applying heat pumps of various types to increase the energy efficiency of ED.

The technological schemes of the ED of an azeotropic mixture of isobutyl alcohol (IBA)–isobutyl acetate (IBAC) with *n*-butylpropionate (BP) as an entrainer were selected as the object of research. Since the mathematical modeling of chemical and technological processes is a powerful modern method for developing new technologies and improving traditional approaches [16], the Aspen Plus software package version 9.0 was used to solve the problem of increasing the separation efficiency of the above mixture.

Modeling of the conventional ED scheme

To simulate the vapor–liquid equilibrium, the UNIQUAC model was adopted, the parameters of which are shown in Table 1. We used both the binary interaction parameters built-in Aspen Plus for the IBA–IBAC system, which provide a more accurate description of the vapor–liquid equilibrium compared to [11], and the data [11] for the IBA–entrainer and IBAC–entrainer systems, since there are no built-in parameters for them. The average relative errors for each binary pair, when described by parameters from different sources, are shown in Table 2. To account for the imperfection of the vapor phase, the Redlich–Kwong equation of state was used.

To separate the mixture under consideration, both a conventional ED system with a heavy-boiling entrainer (Fig. 1) and systems using external and internal vapor-recompression heat pumps can be used. Since the ED of a binary mixture is conducted using a two-column system, heat pumps can be used separately for each of the columns or simultaneously for the two columns.

For all variants of the schemes, we considered the separation of the initial IBA–IBAC mixture with

Table 1. Binary coefficients of the UNIQUAC model

Component	Source			
	Liter.	DB	Liter.	Liter.
Component i	IBA	IBA	IBA	IBAC
Component j	IBAC	IBAC	BP	BP
a_{ij}	0.26671	0	0	0
a_{ji}	0.22675	0	0	0
b_{ij}	−58.459	1.3501	−17.787	−65.929
b_{ji}	−182.110	−45.3251	−24.770	64.567

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[1] See the list of abbreviations at the end of the article for the introduced designations.

Table 2. Relative errors of the vapor–liquid equilibrium (VLE) modeling

Source	Component i	Component j	ΔY^R, %	ΔT^R, %
Liter.	IBA	IBA	1.58	0.44
DB	IBA	IBA	1.37	0.36
Liter.	IBA	BP	1.82	0.11
Liter.	IBAC	BP	1.88	0.26

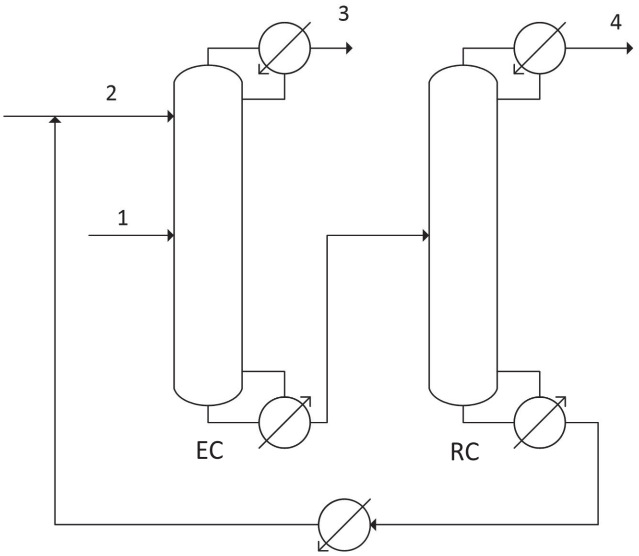


Fig. 1. Conventional scheme of the ED of mixture IBA–IBAC with BP as the entrainer. EC is the ED column, and RC is the entrainer regeneration column. (1) Feed, (2) entrainer, (3) IBA, (4) IBAC.

a concentration of 41 wt % isobutyl alcohol, a feed rate of 1500 kg/h, a temperature of 100°C, and a pressure of 108 kPa. The concentrations of IBA and IBAC in the product streams were maintained constant and equal to 99.5 mass %.

For the conventional ED (Fig. 1), the optimal operating parameters were selected according to the algorithm proposed in [17].

The pressure at the top of the columns was fixed at 101.3 kPa, and theoretical plates (TPs) with a pressure drop of 0.1013 kPa across the plates were considered. Calculations were performed in the design and verification version with the fixed quality of product flows. During the optimization process, the total number of plates in both columns, feed plates in the EC and RC columns, feed plate of the entrainer in the EC column, flow rate of the entrainer, and temperature of the entrainer were determined. The optimization criterion was the total heat duty on the reboilers Q_{total}. For optimization, we used the built-in tools of the Aspen Plus software package, such as the NQ curve, Sensitivity Analysis, and SQP optimization. The optimization procedure included several stages.

At the first stage, the total number of TPs in the columns was determined using the NQ curve tool with a fixed flow rate of the entrainer equal to 3000 kg/h: 66 and 48 in the EC and RC, respectively.

Further, the dependence of the operating parameters of the EC on the temperature of the entrainer feeding into it was studied. The data are shown in Table 3.

Table 3 shows that the energy consumption in the EC reboiler is almost independent on the entrainer supply temperature. The reflux ratio and steam flow in the upper part of the column increase by about 1.15 times when the $T_{\text{entrainer}}$ is increased from 110 to 146°C. As noted by M.K. Zakharov [20], an increase in the reflux ratio results in an increase in the internal energy savings during distillation, and an increase in the steam flow causes an increase in the efficiency of the heat pump application. Considering the above, we selected the entrainer supply temperature in the EC, equal to 146°C. In addition, the entrainer supply at this temperature allows you not to complicate the system with additional heat exchange on the recycling line of the separating agent.

Table 3. Dependence of the EC parameters on the entrainer temperature

T_S, °C	N_S/N_F	R	Q_{cond}, kW	Q_{reb}, kW
110	13/52	4.58	−533.7	611.7
120	13/52	4.78	−552.4	611.6
130	13/52	4.97	−571.2	610.9
140	13/52	5.17	−590.4	610.8
146	13/52	5.29	−601.4	610.6

To determine the limits of variation in the flow of entrainer, the minimum required amount of the entrainer, at which it is still possible to obtain products of a given quality for different positions of the NF and NS feed plates, is determined. The optimal entrainer feed rate at which the $Q_{\text{reb}}^{\text{EC}}$ reaches the minimum value is determined. The results are presented in Table 4.

Based on these results, 2450 kg/h and 3300 kg/h were selected as the limits of variation of the entrainer feed rate for the subsequent optimization procedure of the two-column ED scheme. Further, within the established limits of variation of the entrainer feed rate, it is shown, by computational experiments, that this parameter does not affect the optimal position of the feed plate in the RC. The results are presented in Table 5.

The minimum energy consumption is observed when the feed flow to the RC is located on the 22nd TP. In the future, when determining the optimal parameters of the ED scheme as a whole, this feed plate should be fixed in the regeneration column.

Using the Sensitivity Analysis and SQP Optimization tools simultaneously, the optimal position of the feed plates and the entrainer in the EC and the optimal flow rate of the entrainer for the two-column ED complex were determined. In this case, the Sensitivity Analysis tool varied the positions of the feed plates and the entrainer, and using SQP for each fixed position NS/NF, the optimal flow of the entrainer was selected, at which value the total duty on the column boilers ($Q_{\text{total}} = Q_{\text{reb}}^{\text{EC}} + Q_{\text{reb}}^{\text{RC}}$) reaches the minimum value. The results are presented in Table 6.

The final operating parameters of the conventional ED scheme are presented in Table 7. The optimal amount of the entrainer supplied is 2671 kg/h, and the entrainer temperature is 146°C.

Modeling schemes with vapor-recompression heat pumps

Plesu *et al.* [18] proposed a method for the preliminary assessment of the feasibility of using heat pumps in distillation based on the efficiency coefficient (C_{ef})

$$C_{\text{ef}} = \frac{Q_{\text{reb}}}{A} = \frac{T_{\text{reb}}}{\left(T_{\text{reb}} - T_{\text{cond}}\right)}\ , \quad (1)$$

Table 4. The minimal and optimal (for EC) entrainer rate depending on the position of N_S/N_F

N_S/N_F	$S_{\min}$, kg/h	S_{opt}, kg/h	Q_{reb} at $S_{\min}$, kW	Q_{reb} at S_{opt}, kW
12/51	2390	3000	721.2	603.3
12/52	2360	3050	710.3	601.3
12/53	2340	3100	715.2	604.6
13/51	2400	3050	738.1	603.2
13/52	2370	3100	708.5	605.5
13/53	2350	3150	721.1	608.9
14/51	2450	3200	730.9	605.7
14/52	2420	3250	702.2	607.3
14/53	2400	3300	725.5	610.5

Table 5. The optimal feed stage in the entrainer regeneration column at various entrainer amounts

S, kg/h	N_F	Q_{reb}, kW	Q_{cond}, kW	*R*
2450	22	358.9	−354.5	3.6
2600	22	378	−373.5	3.9
2800	22	397.7	−393.1	4.1
3000	22	417.4	−412.8	4.4
3300	22	437.2	−432.5	4.6

Table 6. Determination of the optimal operation parameters of the conventional ED scheme

N_S	N_F	*S*, kg/h	Q_{reb}^{EC}, kW	Q_{cond}^{EC}, kW	R^{EC}	Q_{reb}^{RC}, kW	Q_{cond}^{RC}, kW	R^{RC}	Q_{total}, kW
12	51	2732	630.8	−623.5	5.52	391.1	−386.5	4.04	1021.9
	52	2733	628.8	−621.5	5.50	391.0	−386.5	4.04	1019.8
	53	2635	635.3	−627.9	5.57	381.5	−377.0	3.91	1016.8
	54	2638	639.1	−631.8	5.61	382.0	−377.5	3.92	1021.2
13	51	2747	623.8	−616.5	5.45	392.6	−388.0	4.06	1016.3
	52	2747	620.5	−613.3	5.41	392.2	−387.7	4.05	1012.8
	53	2671	627.3	−620.0	5.48	385.2	−380.7	3.96	1012.5
	54	2672	632.3	−625.0	5.54	385.4	−380.9	3.96	1017.7
14	51	2842	618.8	−611.6	5.40	401.5	−396.9	4.17	1020.3
	52	2690	628.6	−621.4	5.50	386.6	−382.0	3.98	1015.2
	53	2657	632.3	−625.0	5.54	383.4	−378.9	3.94	1015.7
	54	2643	639.1	−631.8	5.61	381.9	−377.4	3.92	1021.0

Table 7. Optimal operating parameters of the conventional ED scheme

Columns	EC	RC
N_{total}	66	48
N_F	53	22
N_S	13	–
Q_{reb}, kW	618.2	394.3
Q_{cond}, kW	−515.2	−389.8
R	5.39	4.08
T_{cond}, °C	107.7	116.2
T_{reb}, °C	137.5	146.5
P_{cond}, kPa	101.3	101.3
P_{reb}, kPa	107.9	106.1

where Q_{reb} is the duty on the boiler of the column, *A* is the thermodynamic operation, and T_{cond} and T_{reb} are the absolute temperatures in the condenser and boiler of the distillation column, respectively.

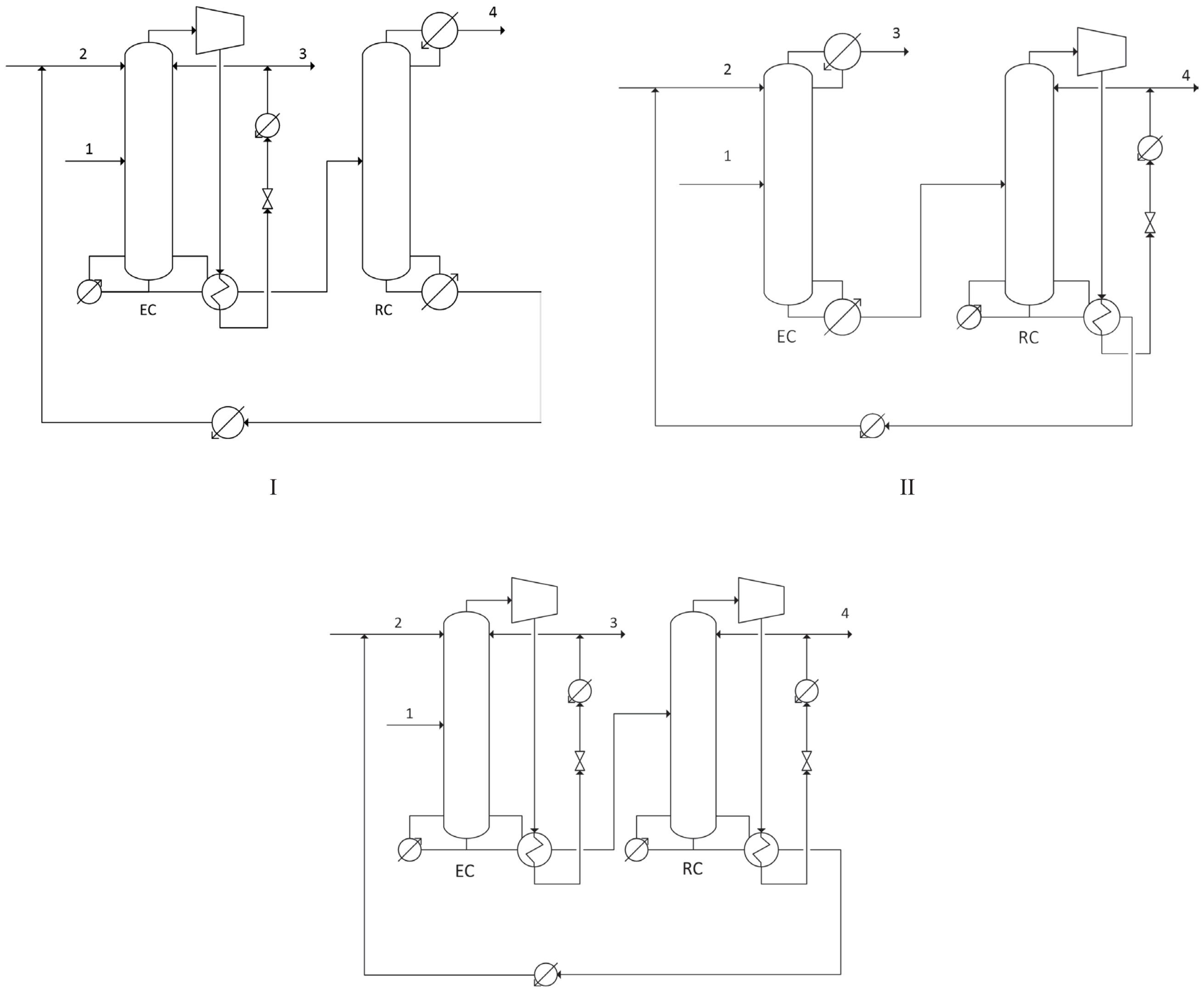
Equation (1) was obtained by Plesu *et al.* [18], based on the equation for calculating the heat required for separation and the expression for the efficiency of the Carnot heat engine. According to Plesu, with a $C_{ef} > 10$, the use of heat pumps is economically feasible in most cases. With $10 > C_{ef} > 5$, the use of heat pumps is only appropriate under certain conditions, and with a $C_{ef} < 5$, heat pumps are not practical. Notably, this approach was proposed to evaluate the effectiveness of heat pumps in the distillation of zeotropic mixtures. However, in [21–24], it was used to evaluate the effectiveness of heat pumps in the ED of azeotropic mixtures. We decided to test the validity of this approach in the separation of the IBS–IBA mixture by ED with BP.

Based on the data from Table 7, the C_{ef} is 12.76 for the EC and 12.83 for the regeneration column. High C_{ef}

values imply a significant effect attributed to the heat pumps on both columns. Moreover, literature data [4] indicate that the maximum efficiency of the heat pump is achieved with the minimum possible temperature difference in the heat exchanger. Based on these data, the temperature difference, ΔT = 25 K, was set to determine the output pressure of the compressor. At the same time, the compressor provides the design pressure for the distillate of the extractive column, $P_{\text{comp}}^{\text{EC}}$ = 506.6 kPa, and the distillate of the regeneration column, $P_{\text{comp}}^{\text{RC}}$ = 456.0 kPa.

Based on the conventional scheme of ED and the above assumptions about the effectiveness of heat pumps, three variants of schemes including vapor-recompression heat pumps were modeled (Fig. 2). In all cases, the heat pump installed on the column introduced in the scheme fully utilizes the steam flow coming from the top of the column. After compression in the compressor with the W_{comp} power input to the P_{comp} pressure and adiabatic heating, the steam flow is directed to the heat exchanger, partially heating the column cube (the amount of heat transferred in this heat exchanger is indicated by Q_{HE}). Thereafter, the flow of the vapor–liquid mixture is directed to the throttle, where the pressure is reduced to 101.3 kPa. An auxiliary capacitor is used for the complete condensation of the flow, after which the flow is divided into the product and reflux.

Since the replacement of the standard heat exchange equipment of distillation columns with a binding, which would allow the use of a heat pump, does not have significant effects on the heat and mass



I

II

III

Fig. 2. Schemes of ED including vapor-recompression heat pumps.
The compressor installed on the vapor streams of (I) EC, (II) RC, and (III) both columns.
EC is the ED column, RC is the entrainer regeneration column. (1) Feed, (2) entrainer, (3) IBA, (4) IBAC.

exchange processes inside the columns, the repeated optimization of the structural parameters of the columns is not required. It should be noted that for all three variants of the process organization for the columns with heat pumps, additional reboilers and condensers are used, the duties of which are designated as Q_{reb} and Q_{cond}, respectively. This is because in these schemes the additional supply or removal of heat was not prevented, despite that the relevant heat duty and, consequently, the costs of heating steam and cooling water, as shown below, significantly reduced compared with those of the conventional scheme.

The calculated parameters of the three variants of schemes with heat pumps are shown below (Table 8).

In comparison with the conventional scheme, significant changes have been made to the technological schemes (Fig. 2) by including additional expensive equipment, such as "hot" compressors that consume electricity when compressing steam flows. At the same time, the application of the energy consumption criterion for choosing the optimal technological scheme is incorrect. Furthermore, for the optimization process of each technological scheme, this criterion is acceptable and appropriate. To compare the options for organizing a process that includes heterogeneous technological equipment, it is customary to use the criterion of the total annual costs (TAC).

$$TAC = OC + \frac{CC}{OT}, \tag{2}$$

where OT is the lifetime of the installation in years; CC is the capital costs in USD; OC is the operating costs in USD per year.

Table 8. Operating parameters of the schemes with vapor-recompression heat pumps

Scheme I (Fig. 2)		
Columns	**EC**	**RC**
Q_{reb}, kW	64.83	394.32
Q_{HE}, kW	568.82	–
Q_{cond}, kW	−163.51	−389.81
Equipment	The compressor was installed on the vapor streams of EC	–
W_{comp}, kW	106.18	–
P_{comp}, kPa	506.63	–
Scheme II (Fig. 2)		
Columns	**EC**	**RC**
Q_{reb}, kW	618.16	91.54
Q_{HE}, kW	–	299.24
Q_{cond}, kW	−515.25	−150.15
Equipment	–	The compressor was installed on the vapor streams of RC
W_{comp}, kW	–	65.89
P_{comp}, kPa	–	455.96
Scheme III (Fig. 2)		
Columns	**EC**	**RC**
Q_{reb}, kW	64.83	91.54
Q_{HE}, kW	568.82	299.24
Q_{cond}, kW	−163.51	−150.15
Equipment	The compressor was installed on the vapor streams of both colomns	
W_{comp}, kW	106.18	65.89
P_{comp}, kPa	506.63	455.96

Since the change in the service life significantly affects the TAC, the criteria were calculated for 10- and 20-year periods. Aspen Process Economic Analyzer v10.1 (APEA) was used to calculate the capital and operating costs. The main economic parameters are shown in Tables 9 and 10, and the results of the economic assessment are shown in Table 11.

As can be observed, in a 10-year operation period, the use of technological schemes with heat pumps has very little economic impact, and practically, these technological solutions are on the verge of economic feasibility. It can also be observed that for the ED system, the most effective technical solutions are those that provide for the installation of a compressor on the steam stream of the distillate of the ED column. The use of a heat pump only on the recovery column of an entrainer is impractical. The scheme with two heat pumps is the most energy-efficient. According to the TAC criterion, the scheme with a heat pump on an extractive column is more profitable over 10 years; however, as noted above, the economic effect is insignificant. Conversely, for 20 years, the scheme with two heat pumps is more profitable.

Simulation of a circuit with an internal heat pump

The heat pump for ED can be placed not only on the steam flows of distillates of columns, but also on the steam flows between separate sections of columns.

Table 9. Utility costs (USD)

Energy resource	Cost, USD per unit
Electricity, kW	0.0775
Cooling water, t	0.03
Steam, kg	0.017

Table 10. Equipment costs (USD)

Equipment	General		Conventional scheme	
	Tower	Reflux pump	Main condenser	Main reboiler
EC	862500	4500	23600	21400
RC	404000	5200	20400	18400
Equipment	**Heat pump**			
	Compressor	**Heat exchanger**	**Support condenser**	**Support reboiler**
EC	707400	15100	8600	18400
RC	671000	11000	8500	12300

Table 11. Economical evaluation

Economic parameters	Conventional scheme (Fig. 1)	Scheme I	Scheme II	Scheme III
		Fig. 2		
Energy costs, USD per year	334155	248718	291574	201721
Energy saving, %	0	25.6	12.7	39.6
Capital costs, USD	1363800	2061400	2027100	2555800
TAC10, USD per year	470535	454858	494284	457301
TAC20, USD per year	402345	351788	392929	329511
TAC10 saving, %	0	3.3	−5.1	2.8
TAC20 saving, %	0	12.6	2.3	18.1

This solution was first proposed by Batista *et al.* [19], although it has not yet been compared with other options for organizing the process. The scheme with an internal heat pump is shown in Fig. 3.

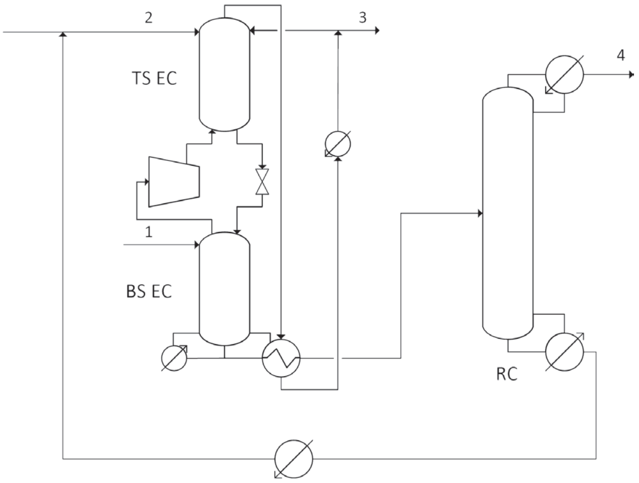


Fig. 3. Scheme of ED including an "internal" heat pump. TS EC denotes the top section of the ED column, BS EC denotes the bottom section of the ED column, and RC denotes the entrainer regeneration column. (1) Feed, (2) entrainer, (3) IBA, (4) IBAC.

In this scheme, the ED column is divided into two parts working at different pressures: 101.3 kPa in the exhaust section (bottom section – BS) and 506.64 kPa in the upper refining and extractive sections (top section – TS), with the feed being supplied to the first plate of the lower section. Partial heating of the boiler in the lower section is conducted by the steam flow of the distillate of the upper section.

When the operating pressure in the system changes, the view of the vapor–liquid equilibrium diagram changes as well. In this case, when the pressure increases, the composition of the azeotrope shifts in the direction of increasing concentration of the light-boiling component in it, up to the degeneration of azeotropy into tangential at a pressure of 506.64 kPa. Figure 4 (I) shows diagrams of the relative volatility lines (α_{12}) of the IBA (1)–IBAC (2) pair at 101.3 kPa, while Figure 4 (II) displays the same at a pressure of 506.64 kPa.

As shown, with increasing pressure in the presence of the entrainer in the system under consideration, the relative volatility of α_{12} of the IBA–IBAC pair increases; therefore, separation at increased pressure is facilitated and requires a relatively small amount of entrainer. Our calculated data on the increase in the relative volatility of the IBA–IBAC pair with increasing pressure are consistent with the data of the full-scale experiment of Monton *et al.* [25].

To model the scheme with an "internal" heat pump, it was necessary to determine the optimal operating parameters of the conventional ED scheme, in which the EC column operates at high pressure. In this case, there are additional heat costs for heating the feedstock and a heat exchanger for heating. This scheme was modeled and optimized using the previously mentioned algorithm [17]. The optimal operating parameters of this scheme are presented in Table 12. The optimal flow of entrainer is 1312 kg/h, and the entrainer temperature is 146℃.

Based on the parameters of the EC scheme operating at a pressure of 506.64 kPa and the conventional scheme (at a pressure of 101.3 kPa), the scheme with an "internal" heat pump was simulated. The parameters of the TS EC: the total number of plates, number of the entrainer feed plate, and the flow rate of the entrainer, correspond to the parameters of the refining and extractive sections of the EC in the scheme, operating at elevated pressures, and the parameters of the BS EC, i.e., the parameters of the lower section of the EC of schemes, operating at

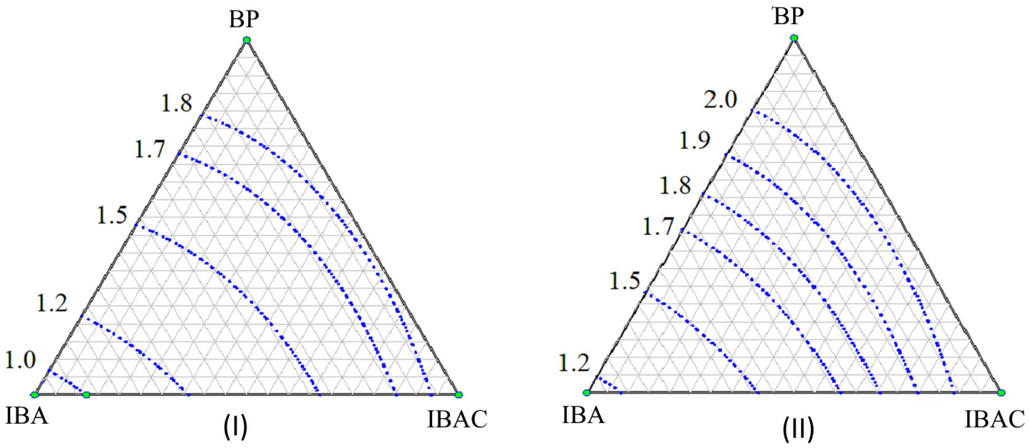


Fig. 4. Relative volatility diagrams (α_{12}) for IBA–IBAC with an entrainer at 101.3 kPa (I) and 506.64 kPa (II).

atmospheric pressure. The parameters of the scheme with an "internal" heat pump are shown in Table 13. The optimal flow of entrainer is 1312 kg/h, and the entrainer temperature is 146°C.

From the results shown, it is clear that an internal heat pump prevents additional heat supply to the reboiler of the EC column and excludes the support reboiler.

For the scheme with an internal heat pump, an economic assessment was also carried out, and the TAC value was determined. The equipment costs are shown in Table 14, and the economic analysis results in comparison with the conventional scheme are presented in Table 15.

As shown, using an internal heat pump can significantly reduce the energy costs and TACs.

Table 12. Operating parameters of the scheme of ED with EC, at 506.64 kPa

Columns	EC	RC
Total number of stages, N_{total}	56	50
Feed stage, N_F	44	23
EA, N_S	13	–
Q_{reb}, kW	473.8	214.2
Q_{cond}, kW	−408.9	−311.4
R	4.2	3.1
T_{cond}, °C	160.4	116.2
T_{reb}, °C	197.9	146.6
P_{cond}, kPa	506.6	101.3
P_{reb}, kPa	512.2	106.3
$Q_{additional\ feed\ heating}$, kW	76.6	–

Table 13. Operating parameters of the scheme with the "internal" heat pump

Columns	EC	RC
N_{total}	56	50
$N^{TS\ EC}$	43	–
$N^{BS\ EC}$	13	–
N_F	44 (1)	23
N_S	13	–
Q_{reb}, kW	0	214.2
Q_{HE}, kW	403.9	–
Q_{cond}, kW	−84.3	−311.4
R	4.2	3.1
T_{cond}, °C	160.4	116.2
T_{reb}, °C	130.8	146.5
P_{cond}, kPa	506.6	101.3
P_{reb}, kPa	102.5	106.1
Equipment	**EC**	**RC**
W_{comp}, kW	123.6	–
P_{comp}, kPa	511	–

Table 14. Equipment costs for the scheme with the "internal" heat pump

Equipment	Tower	Reflux pump	Main condenser	Main reboiler
TS EC	414000	5100	–	–
BS EC	68800	–	–	–
RC	605200	4500	21500	14600
Equipment	**Compressor**	**Heat exchanger**	**Support condenser**	
TS EC	727100	–	8300	
BS EC	–	12600	–	

Table 15. Economical evaluation

Economic parameters	Conventional scheme	Scheme with the "internal" heat pump
Energy costs, USD per year	334155	187266
Energy saving, %	0	44.0
Capital costs, USD	1363800	1881700
TAC10, USD per year	470535	375436
TAC20, USD per year	402345	281351
TAC10 saving, %	0	20.2
TAC20 saving, %	0	30.1

CONCLUSIONS

In this study, it is demonstrated that the use of heat pumps in the scheme of the ED of a mixture of isobutyl alcohol–isobutyl acetate with *n*-butylpropionate as an entrainer can be economically justified. Among the considered schemes with an external vapor-recompression heat pump, the scheme in which heat pumps are fixed on both columns has the highest energy efficiency. This scheme reduces the energy costs by 39.6% compared to the conventional ED scheme. According to the TAC criterion, when calculating based on the operating time of the installation of 10 years, the lowest value of TAC10 is achieved in the scheme with a heat pump attached to the ED column. This scheme provides a reduction of TAC10 by 3.3% compared to the conventional scheme. With a lifetime of 20 years, the lowest TACs are provided by the scheme including two heat pumps. The TAC20 of this scheme is lower by 18.1% compared to that of the conventional scheme. The proposed scheme including an internal heat pump is the most economical scheme considered in this paper, despite its somewhat non-standard configuration. This scheme provides a 44% reduction in energy costs, a 20.2% reduction in TACs with a 10-year operating life, and a 30.1% reduction over 20 years.

Thus, the incorporation of heat pumps into ED systems results in a significant reduction in energy consumption and significant economic impacts.

Key

A – thermodynamic work;
a, b – parameters of the UNIQUAC equation;
C_{ef} – efficiency coefficient;
CC – capital costs;
N – plate number;
OC – operating costs;
OT – operating time;
P – absolute pressure;

Q – heat duty;
R – reflux ratio;
S – flow rate of the extractive agent;
T – temperature;
TP – theoretical plates;
TAC – total annual costs;
TAC10 – total annual costs with a 10-year operating life;
TAC20 – total annual costs with a 20-year operating life;
W – power consumption;
Y – component concentration in the vapor phase;
DB – database of the software package;
BP – *n*-butylpropionate;
TS – top section;
IBAC – isobutyl acetate;
IBA – isobutyl alcohol;
Liter. – data from a literary source;
BS – bottom section;
VLE – vapor–liquid equilibrium;
RC – entrainer regeneration column;
EA – separating (extractive) agent;
EC – extractive distillation column;
ED – extractive distillation;

Indexes
comp – compressor;
cond – condenser;
i,j – numbers of the components;
F – feed;
HE – heat exchanger;
min – the minimum value;
opt – optimal value;
reb – reboiler;
S – extractive agent.

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The authors declare no conflicts of interest.

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About the authors:

Pavel S. Klauzner, Postgraduate Student, Department of Chemistry and Technology of Basic Organic Synthesis, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: paulklausner@mail.ru. https://orcid.org/0000-0001-5844-549X

Danila G. Rudakov, Cand. of Sci. (Engineering), Docent, Department of Chemistry and Technology of Basic Organic Synthesis, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: rudakov@mitht.ru. Scopus Author ID 37018548000, ResearcherID M-5241-2014, https://orcid.org/0000-0002-9892-7909

Elena A. Anokhina, Cand. of Sci. (Engineering), Associate Professor, Department of Chemistry and Technology of Basic Organic Synthesis of M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: anokhina.ea@mail.ru. Scopus Author ID 6701718055, ResearcherID E-5022-2016

Andrey V. Timoshenko, Dr. of Sci. (Engineering), Professor, Department of Chemistry and Technology of Basic Organic Synthesis, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: timoshenko@mitht.ru. Scopus Author ID 56576076700, ResearcherID Y-8709-2018

Об авторах:

Клаузнер Павел Сергеевич, аспирант кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: paulklausner@mail.ru. https://orcid.org/0000-0001-5844-549X

Рудаков Данила Григорьевич, кандидат технических наук, доцент кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: rudakov@mitht.ru. Scopus Author ID 37018548000, ResearcherID M-5241-2014, https://orcid.org/0000-0002-9892-7909

Анохина Елена Анатольевна, кандидат технических наук, доцент кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: anokhina.ea@mail.ru. Scopus Author ID 6701718055, ResearcherID E-5022-2016

Тимошенко Андрей Всеволодович, доктор технических наук, профессор кафедры химии и технологии основного органического синтеза Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: timoshenko@mitht.ru. Scopus Author ID 56576076700, ResearcherID Y-8709-2018

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RESEARCH ARTICLE

New approaches for the standardization of the *Monarda fistulosa* herb

Vladimir A. Kurkin@, Anastasiya S. Tsibina

Samara State Medical University, Samara, 443099 Russia
@Corresponding author, e-mail: kurkinvladimir@yandex.ru

Objectives. *The Monarda fistulosa herb of the Lamiaceae family is particularly interesting among essential oils from medicinal plants that have a wide spectrum of pharmacological activities. However, information regarding some of its flavonoids, which are found in the essential oil, is controversial. Inaccuracies in identification of the chemical composition of the herb have led to several different standardization approaches, which are cumbersome. To establish a uniform classification, here, we present confirmation for new approaches for the standardization of the Monarda fistulosa herb.*

Methods. *Silica gel column chromatography was used to extract the flavonoids. Identification was based on ultraviolet spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry, and acidic hydrolysis. The quality of the proposed quantitation methodology for total flavonoids was assessed by differential spectrophotometry at 394 nm, in isorhoifolin equivalent.*

Results. *We have verified new approaches for the standardization of the Monarda fistulosa herb. The approaches can determine the authenticity of the herb by detecting monoterpene phenols and flavonoids that have diagnostic value. We also developed a technique for quantitation of the total flavonoids.*

Conclusions. *We investigated the possibility of establishing the authenticity of the Monarda fistulosa herb based on the diagnostically significant flavonoids, isorhoifolin and linarin.*

Keywords: *flavonoids, Monarda fistulosa, isorhoifolin, linarin, spectrophotometry, thin-layer chromatography, standardization.*

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Новые подходы к стандартизации травы монарды дудчатой

В.А. Куркин[@], А.С. Цибина

Самарский государственный медицинский университет, Самара, 443099 Россия
[@]Автор для переписки, e-mail: kurkinvladimir@yandex.ru

Цели. *Среди эфиромасличных лекарственных растений, обладающих широким спектром фармакологической активности, особый интерес представляет трава монарды дудчатой (Monarda fistulosa) семейства Яснотковых. Однако информация о некоторых флавоноидах, содержащихся в ней наряду с эфирным маслом, носит противоречивый характер. Неточности, выявленные в отношении химического состава травы, становятся причиной появления различных подходов к стандартизации, что создает трудности. Для обеспечения единообразия классификации в данной работе представлено обоснование новых, ранее не применявшихся подходов к стандартизации травы монарды дудчатой.*

Методы. *Для экстракции флавоноидов использовали колоночную хроматографию на силикагеле. Идентификацию осуществляли на основании данных ультрафиолетовой спектроскопии, спектроскопии ядерного магнитного резонанса и масс-спектрометрии, а также результатов кислотного гидролиза. Оценку качества предложенной методики количественного определения суммы флавоноидов проводили методом дифференциальной спектрофотометрии при 394 нм в пересчете на изороифолин.*

Результаты. *Обоснованы подходы к стандартизации травы монарды дудчатой, заключающиеся в определении ее подлинности путем обнаружения монотерпеновых фенолов и флавоноидов, имеющих диагностическое значение. Разработана методика количественного определения суммы флавоноидов.*

Выводы. *Изучена возможность определения подлинности травы монарды дудчатой, исходя из диагностически значимых флавоноидов – изороифолина и линарина.*

Ключевые слова: *флавоноиды, монарда дудчатая, Monarda fistulosa, изороифолин, линарин, спектрофотомерия, тонкослойная хроматография, стандартизация.*

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INTRODUCTION

Currently, essential oils of medicinal plants that have a wide range of pharmacological activity are widely used in medicine owing to the chemical variety of the biologically active compounds (terpenoids, aromatic compounds, etc.). Of particular interest are plants containing monoterpene phenols, for example, thymol and carvacrol. In this regard, creeping thyme (*Thymus serpyllum* L.), common thyme (*Thymus vulgaris* L.) and oregano (*Origanum vulgare* L.), which belong to the *Lamiaceae* herb family, are the most well-known[1].

One of the promising plants for study is the *Monarda fistulosa* herb of the *Lamiaceae* family. This herb grows in North America [1]. The *Monarda fistulosa* herb contains over 3% essential oil, the components of which (thymol, carvacrol, etc.) determine the high bactericidal, fungicidal, anti-inflammatory and anthelmintic activity [1–3]. Interestingly, the dominant component in the essential oil of the *Monarda fistulosa* herb is not thymol, as in the case of creeping and common thyme, but carvacrol, for which a more pronounced antimicrobial activity has been shown [4].

To determine the authenticity of the *Monarda fistulosa* herb, thin layer chromatography (TLC) using a standard thymol sample was previously proposed. In this case, the chromatogram of the analyzed extract at the level of a standard sample of thymol should contain an orange spot with an R_f coefficient of

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[1] The State Pharmacopeia of the Russian Federation. 14th edition. Moscow: Ministry of Health of the Russian Federation; 2018. (In Russ.). Available from: http://www.femb.ru/femb/pharmacopea.php (Accessed September 09, 2019).

approximately 0.9 [4]. Taking into account the current trends in pharmacopoeia analysis, which are typically used to determine the authenticity of anthocyanins and the quality of medicinal plant raw materials via two (or more) groups of biologically active substances[2], the study of the flavonoid composition of the *Monarda fistulosa* herb seems relevant.

In addition to the essential oil, this plant also contains other valuable biologically active compounds, in particular, flavonoids (flavones, flavonols, flavonones, anthocyanins), which also contribute to the pharmacological activity [5, 6]. The literature contains information on the content of the following flavonoids in the *Monarda fistulosa* herb: hesperidin, diosmin, quercetin, luteolin, rutin, naringenin, cynaroside (luteolin-7-O-glucoside), hyperoside, and catechin [5, 6]; however, these data are controversial. The controversy also applies to methodical and methodological approaches for standardization of the *Monarda fistulosa* herb. Thus, for quantitative determination of the total flavonoid content, differential spectrophotometry at a wavelength of 390 nm calculated for rutin (0.48 ± 0.01%) has been used [5, 6]. For this technique, the extrication of substances from the raw material was performed by triple extraction with 70% ethyl alcohol.

According to the results of previously published studies, the total flavonoid content in the *Monarda fistulosa* herb is 2.14% in terms of luteolin [5, 6]. The authors used double extraction with 70% ethyl alcohol in the ratio of "raw materials to extractant" of 1 : 30 as well as differential spectrophotometry. Additionally, a method was proposed for the quantitative determination of flavonoids in the *Monarda fistulosa* herb by double (30 min each) extraction of raw materials (1 : 30) with 50% ethanol (analytical wavelength of 398 nm). The content of flavonoids in terms of luteolin was in this case 1.57 ± 0.02% [5, 6].

Previously, we developed approaches for standardization of the *Monarda fistulosa* herb that involved determining the amount of flavonoids in terms of cynaroside and the content of essential oil [7–9]. The choice of cynaroside as a standard sample was because this flavon, according the literature, is present in the *Monarda fistulosa* herb, has a pharmacopoeial status, and is widely used to standardize medicinal plant raw materials[3]. Additionally, the maximum in the absorption spectrum for the aqueous–alcoholic extract of the *Monarda fistulosa* herb (394 nm) was close to the maximum absorption of the cynaroside solution (approximately 400 nm). However, in further studies, we did not confirm the presence of cynaroside in the plant.

Thus, despite the literature data on the chemical composition of *Monarda fistulosa*, some contradictions regarding the flavonoid composition have been identified. This, in turn, has led to different approaches for standardization. Ethanol at various concentrations is used as an extractant; there is no single standard for the duration of extraction; there is no consensus on the analytical wavelength or substance used as a standard. Therefore, new steps should be taken to develop methodological approaches for standardization of the *Monarda fistulosa* herb, which was the purpose of this study.

MATERIALS AND METHODS

The object of this study was the *Monarda fistulosa* herb collected during mass flowering in the Botanical Garden of Samara University in July 2016–2018 and in the Nikitsky Botanical Garden (Republic of Crimea) in July 2018.

The flavonoid compounds, isorhoifolin (1) and linarin (2) (Fig. 1), were isolated from the *Monarda fistulosa* herb on a chromatographic column with silica gel L 40/100. Separation of the substances was monitored by TLC analysis on Sorbfil PTLC-AF-A-UV plates (*CHIMMED*, Russia). The eluent was chloroform–ethanol–water (26 : 16 : 3) and *n*-butanol–glacial acetic acid–water (4 : 1 : 2) systems. The extractables were detected by visualizing spots on the TLC plates in ultraviolet at 366 nm, including detection with a solution of aluminum chloride and then with an alkaline solution of diazobenzenesulfonic acid (DSA).

Nuclear magnetic resonance (NMR) spectra were recorded as follows: ^{1}H-spectra on a Bruker AM 300 (*Bruker,* Germany) at a frequency 300 MHz; ^{13}C-spectra on a Bruker DRX 500 (*Bruker*, Germany) at a frequency 126.76 MHz were recorded on a Kratos MS-30 (*Kratos*, United Kingdom), and absorption spectra in the ultraviolet (UV) region on a Specord 40 (*Analytik Jena*, Germany).

Isorhoifolin (7-O-apigenin rutinoside) (**1**). This crystalline substance is a light-yellow color with a composition of $C_{27}H_{30}O_{14}$; m.p. 257–260°C (water alcohol). λ_{max} EtOH 270, 340 nm; + NaOAc 270, 340 nm; + NaOAc + H_3BO_3 270, 405 nm; + $AlCl_3$ 278, 308, 345, 384 nm; + $AlCl_3$ + HCl 278, 308, 345, 384 nm; + NaOMe 254, 269, 400 nm.

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[2] The State Pharmacopeia of the Russian Federation. 14th edition. Ministry of Health of the Russian Federation. Moscow; 2018. (In Russ.). Available from: http://www.femb.ru/femb/pharmacopea.php (Accessed September 09, 2019).

[3] The State Pharmacopeia of the Russian Federation. 14th edition. Moscow: Ministry of Health of the Russian Federation; 2018. (In Russ.). Available from: http://www.femb.ru/femb/pharmacopea.php (Accessed September 09, 2019).

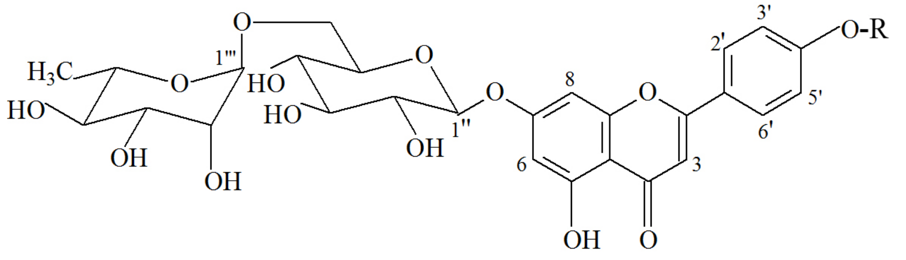

Fig. 1. Flavonoids isolated from *Monarda fistulosa* herb: R = H: isorhoifolin; R = CH_3: linarin.

^{1}H-NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.07 (3H, d, J = 6, CH_3 rhamnose), 3.0–5.2 (10H routines), 4.56 (1H, br. s, H-1’’’ rhamnopyranose), 5.07 (1H, d, J = 7, H-1’’ glucopyranose), 6.46 (1H, d, J = 2, H-6), 6.77 (1H, d, J = 2, H-8), 6.87 (1H, s, H-3), 6.93 (2H, d, J = 8.5, H-3’ and H-5’), 7.94 (2H, d, J = 8.5, H-2’ and H-6’), 12.95 (1H, s, 5-OH group).

^{13}C-NMR spectrum (126.76 MHz, DMSO-d_6, δ_C, ppm): C-2 (162.87), C-3 (103.11), C-4 (181.97), C-5 (161.17), C-6 (99.54), C-7 (164.37), C-8 (94.79), C-9 (156.92), C-10 (105.38), C-1’ (121.03), C-2’ and C-6’ (128.62), C-3’ and C-5’ (116.06), C-4’ (161.32), C-1’’ glucose (99.91), C-2’’ (72.06), C-3’’ (75.62), C-4’’ (70.74), C-5’’ (76.27), C-6’’ (66.05), C-1’’’ rhamnose (100.52), C-2’’’ (70.32), C-3’’’ (69.57), C-4’’’ (73.08), C-5’’’ (68.31), C-6’’’ (CH_3 rhamnose) (17.79).

Mass spectrum (ESI-MS, 180°C, *m/z*): *m/z* 579.1739 $[M+H]^+$, *m/z* 601.1554 $[M+Na]^+$, *m/z* 617.1285 $[M+K]^+$.

Linarin (7-O-rutinoside acacetin) (**2**). This crystalline substance is a white color with a composition of $C_{28}H_{32}O_{14}$; m.p. 260°C (dec.) (water alcohol). λ_{max} EtOH 272, 330 nm; + NaOAc 272, 330 nm; + NaOAc + H_3BO_3 272, 330 nm; + $AlCl_3$ 280, 384 nm; + $AlCl_3$ + HCl 280, 384 nm; + NaOMe 287, 372 nm.

^{1}H-NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.07 (3H, d, J = 6, CH_3 rhamnose), 3.0–5.3 (10H routines), 3.83 (s, 3H, CH_3O), 4.54 (1H, br. s, H-1’’’ rhamnopyranose), 5.07 (1H, d, J = 7, H-1’’ glucopyranose), 6.45 (1H, d, J = 2, H-6), 6.78 (1H, d, J = 2, H-8), 6.92 (1H, s, H-3), 7.14 (2H, d, J = 8.5, H-3’ and H-5’), 8.04 (2H, d, J = 8.5, H-2’ and H-6’), 12.90 (1H, s, 5-OH group).

^{13}C-NMR spectrum (126.76 MHz, DMSO-d_6, δ_C, ppm): C-2 (163.94), C-3 (103.80), C-4 (182.01), C-5 (161.13), C-6 (99.65), C-7 (165.11), C-8 (96.45), C-9 (156.96), C-10 (105.45), C-1’ (122.66), C-2’ and C-6’ (128.44), C-3’ and C-5’ (114.70), C-4’ (162.42), C-1’’ glucose (99.94), C-2’’ (73.06), C-3’’ (75.66), C-4’’ (70.34), C-5’’ (76.24), C-6’’ (68.31), C-1’’’ rhamnose (100.51), C-2’’’ (70.74), C-3’’’ (70.25), C-4’’’ (72.05), C-5’’’ (69.60), C-6’’’ (CH_3 rhamnose) (17.79), CH_3O (55.55).

Mass spectrum (ESI-MS, 180°C, *m/z*): *m/z* 593.1888 $[M+H]^+$, *m/z* 615.1710 $[M+Na]^+$.

Method for the quantitative determination of the total flavonoids in the *Monarda fistulosa* herb. The raw material was crushed so that its particles passed through a sieve with holes 1 mm in diameter. An accurate weighed sample of the ground material (approximately 1 g) was placed in a 100 mL flask, and 50 mL of 60% ethyl alcohol was added. The flask was closed with a stopper and weighed on a balance that is accurate to 0.01 g. The flask was attached to a reflux condenser and heated in a boiling water bath for 60 min. After boiling, the flask was cooled for 30 min, closed with the same stopper and weighed again, and the extractant was added to its original weight. The resulting aqueous–alcoholic extract was filtered through a paper filter (red, grade 589/5).

Preparation of the test solution. The resulting extract (1 mL) was poured into a 50-mL volumetric flask, and 2 mL of a 3% alcohol solution of aluminum chloride was added; then, the solution volume was adjusted to the mark with 96% ethyl alcohol (test solution). The optical density of the test solution was determined 40 min after preparation using a spectrophotometer at a wavelength of 394 nm (to calculate the content of flavonoids). The comparison solution was a solution containing 1 mL of an aqueous–alcoholic extract (1 : 50) with 96% ethyl alcohol, which was adjusted to the mark in a 50-mL flask.

Preparation of the isolated substance solution. An exact weighed portion (approximately 0.02 g) of isorhoifolin was placed in a 50-mL flask and dissolved in 30 mL of 70% ethanol while heating. After cooling to room temperature, the volume of the solution was adjusted to the mark with 70% ethanol (isorhoifolin solution A). Then, 1 mL of isorhoifolin solution A was placed in a 25-mL volumetric flask, 2 mL of a 3% alcohol solution of aluminum chloride was added, and the solution volume was adjusted to the mark with 96% ethyl alcohol (isorhoifolin solution B). The optical density of solution B was determined using a spectrophotometer at a wavelength of 394 nm. The comparison solution was a solution containing 1 mL of isorhoifolin solution A and 96% ethanol, which was adjusted to the mark in a 25-mL flask (comparison solution B of isorhoifolin).

The content of flavonoids in percent (X) in terms of isorhoifolin and absolute dry raw materials was calculated by the formula:

$$X = \frac{D \times m_0 \times 50 \times 50 \times 1 \times 50 \times 100 \times 100}{D_0 \times m \times 50 \times 1 \times 25 \times (100 - W)}$$

where

D – optical density of the test solution;

D_0 – optical density of an isorhoifolin standard sample solution;

m – mass of raw materials, g;

m_0 – the mass of the isorhoifolin standard sample, g;

W – mass loss on drying, %.

In the absence of a standard sample of isorhoifolin in the formula for the calculation, it is advisable to use the theoretical value of the specific absorption index equal to 195:

$$X = \frac{D \times 50 \times 50 \times 100}{m \times 195 \times (100 - W)}$$

where

D – optical density of the test solution;

m – mass of raw materials, g;

195 – specific absorbance ($E_{1sm}^{1\%}$) of isorhoifolin at 394 nm;

W – mass loss on drying, %.

RESULTS AND DISCUSSION

Using column chromatography on silica gel L 40/100, flavonoids 1 and 2, identified as isorhoifolin (apigenin 7-O-rutinoside) [10] and linarin (acacetin 7-O-rutinoside) [11–13], were first isolated from the *Monarda fistulosa* herb. Identification was based on data from UV spectra, ^{1}H-NMR and ^{13}C-NMR spectra, mass spectra, and acid hydrolysis.

Because the isolated substances are the dominant flavonoids in this plant, we studied the possibility of determining the authenticity of the *Monarda fistulosa* herb by the presence of not only thymol and carvacrol but also the diagnostically significant flavonoids, isorhoifolin (**1**) and linarin (**2**). Moreover, in our opinion, it is advisable to carry out TLC analysis using not only thymol [5] but also a standard sample of rutin, which is most widely used in the pharmacopoeial analysis of medicinal plant raw materials[4].

TLC analysis of an aqueous–alcoholic extract obtained using 60% ethanol showed that two flavonoids close to the chromatographic mobility, isorhoifolin (**1**) and linarin (**2**), were found in the chromatogram of the test solution at 366 nm. The values of R_{st} relative to rutin for them are approximately 1.15 and 1.30, respectively (Figs. 2 and 3). Upon subsequent development with an alkaline DSA solution (Fig. 4), an orange-red spot (thymol + carvacrol) was found on the chromatogram at the level of the thymol spot.

To develop a method for the quantitative determination of the flavonoids in the *Monarda fistulosa* herb, we studied the absorption spectra of an aqueous–alcoholic extract and solutions of the selected substances, isorhoifolin and linarin. We found that the isolated flavonoids, and in particular isorhoifolin (Figs. 5 and 6), largely determine the nature of the absorption curve of the water–alcohol extract, especially under differential UV spectroscopy (Figs. 7 and 8). In the spectrum, a bathochromic shift of the long-wavelength

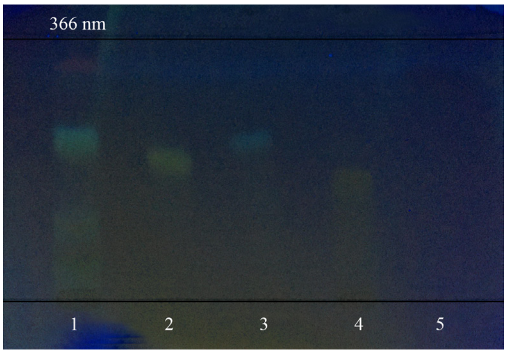

Fig. 2. Chromatogram of the water-alcohol extract from *Monarda fistulosa* in the chloroform–ethanol–water (26 : 16 : 3) system. Detection at 366 nm. Designations: 1 – extract from *Monarda fistulosa*; 2 – isorhoifolin; 3 – linarin; 4 – rutin; 5 – thymol.

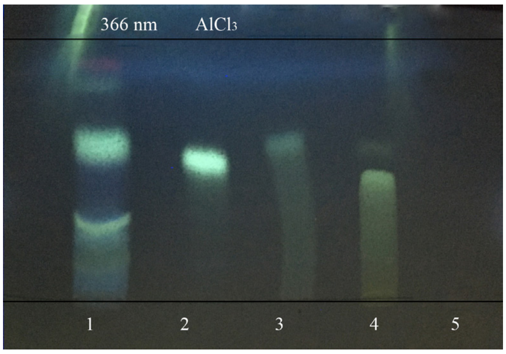

Fig. 3. Chromatogram of the water-alcohol extract from *Monarda fistulosa* in the chloroform–ethanol–water (26 : 16 : 3) system. Detection at 366 nm after treatment with $AlCl_3$ alcohol solution. Designations: 1 – extract from *Monarda fistulosa*; 2 – isorhoifolin; 3 – linarin; 4 – rutin; 5 – thymol.

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absorption band of flavonoids was observed (Fig. 7) as in the case of isorhoifolin (Fig. 5). A study of the absorption spectra of isorhoifolin and the test solutionshowed that in both cases in the presence of aluminum chloride (differential spectrophotometry) there is an absorption maximum at 394 nm (Figs. 6 and 8).

Taking into account the fact that the absorption maxima of the solution of the isolated flavonoid and water–alcohol extract from the *Monarda fistulosa* herb are in the region of 394 nm (differential version), it was advisable to determine the flavonoid amount in terms of isorhoifolin at 394 nm. During the development of a method for quantitative determination of the flavonoid amount, we used

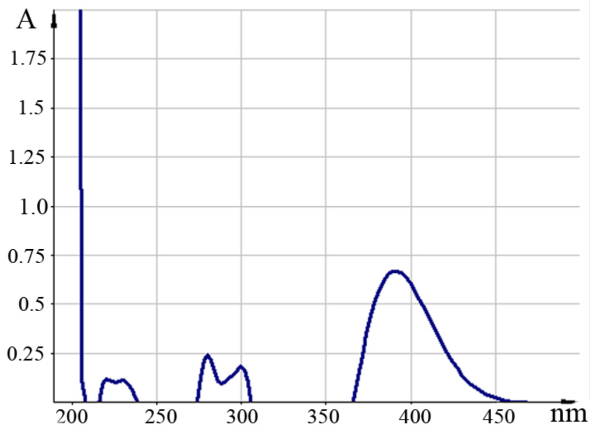

Fig. 6. Differential absorption spectrum of the isorhoifolin solution.

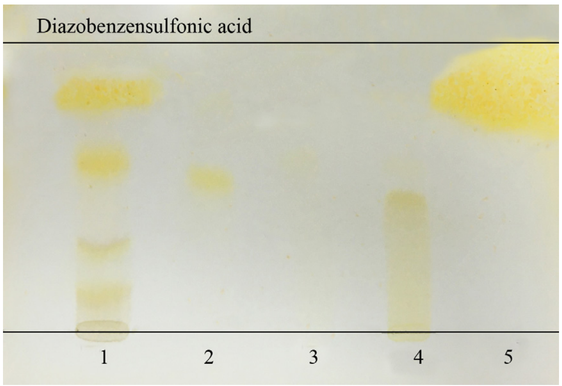

Fig. 4. Chromatogram of the water-alcohol extract from *Monarda fistulosa* in the chloroform–ethanol–water (26 : 16 : 3) system. Detection in visible light after treatment with the alkaline solution of diazobenzenesulfonic acid. Designations: 1 – extract from *Monarda fistulosa*; 2 – isorhoifolin; 3 – linarin; 4 – rutin; 5 – thymol.

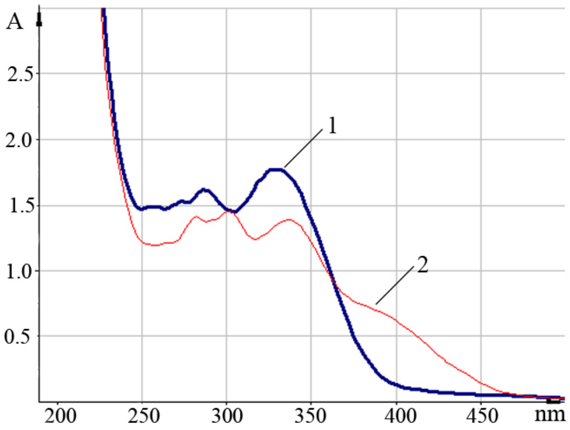

Fig. 7. Absorption spectra of water–alcohol extracts from *Monarda fistulosa*. Designations: 1 – extract solution; 2 – extract solution with added aluminum chloride.

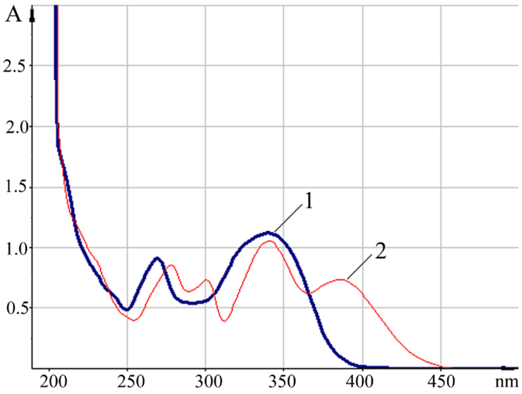

Fig. 5. Absorption spectra of isorhoifolin alcohol solutions. Designations: 1 – initial solution; 2 – solution with added aluminum chloride.

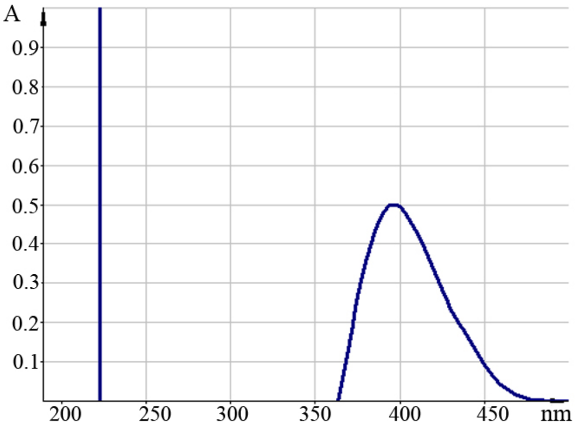

Fig. 8. Differential absorption spectrum of the water-alcohol extract from *Monarda fistulosa.*

previously determined optimal parameters for the extraction of flavonoids from the *Monarda fistulosa* herb: extractant – 60% ethyl alcohol; ratio of raw materials : extractant = 1 : 50; extraction time – 60 min; the extraction was carried out in a boiling water bath [7]. The metrological characteristics of the method for quantitative determination of the total flavonoid content in the *Monarda fistulosa* herb are presented in Table 1.

The results of statistical processing of the results indicated that the error for single determination of the flavonoid amount in the *Monarda fistulosa* herb with a confidence probability of 95% was ± 4.65%. Additionally, the content of flavonoids in the *Monarda fistulosa* herb varied from 5.96 ± 0.08% to 7.68 ± 0.12% (Table 2).

Validation of the developed methodology was performed according to the indicators of specificity, linearity, correctness, and reproducibility. The specificity of the technique was confirmed by the correspondence of the absorption maxima of the *Monarda fistulosa* herb flavonoid complex and isorhoifolin with the aluminum chloride solution. The linearity of the method was determined for a series of solutions of isorhoifolin in the concentration range of 0.01272 to 0.03816 mg/mL. The correlation coefficient was 0.99974. The correctness of the methodology was established by the method of standard addition via injection of isorhoifolin solutions with known concentrations of 25%, 50%, and 75% to the test solution. The average recovery percentage was 98%.

CONCLUSIONS

The feasibility of determining the authenticity of the *Monarda fistulosa* herb using thin-layer chromatography by detecting monoterpene phenols (thymol and carvacrol) and the flavonoids of isorhoifolin and linarin, the dominant and diagnostically significant components of the plant, was confirmed. To assess the quality of the *Monarda fistulosa* herb, a method for the quantitative determination of the flavonoid contents using differential spectrophotometry at 394 nm in terms of isorhoifolin was proposed.

The authors declare no conflicts of interest.

Table 1. Metrological parameters of the quantitation technique for the total flavonoids in *Monarda fistulosa*

f **(number of degrees of freedom)**	$\overline{X}$ **(sample average)**	***S*, (standard deviate)**	***P*, % (confidence figure)**	***t* (*P, f*) (Student t-test)**	**±*X* (credible interval)**	***E*, % (relative error single determination)**
10	6.51	0.1332	95	2.23	±0.11	±4.65

Table 2. Content of the total flavonoids in the *Monarda fistulosa* samples

No.	**Sample origin**	**Total flavonoid content in an absolutely dry sample in isorhoifolin equivalent, %**
1	Samara University Botanical Garden (July 2016)	5.97 ± 0.08
2	Samara University Botanical Garden (July 2017)	7.68 ± 0.12
3	Samara University Botanical Garden (July 2018)	6.61 ± 0.10
4	Nikitsky Botanical Garden, Crimea (July 2018)	5.96 ± 0.10

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About the authors:

Vladimir A. Kurkin, Dr. of Sci. (Pharmaceuticals), Professor, Head of the Department of Pharmacognosy with Botany and Elements of Phytotherapy, Samara State Medical University (89, Chapaevskaya ul., Samara, 443099, Russia). E-mail: kurkinvladimir@yandex.ru. https://orcid.org/0000-0002-7513-9352

Anastasiya S. Tsibina, Postgraduate Student, Department of Pharmacognosy with Botany and Elements of Phytotherapy, Samara State Medical University (89, Chapaevskaya ul., Samara, 443099, Russia). E-mail: nastylapochka@mail.ru. https://orcid.org/0000-0002-0384-5522

Об авторах:

Куркин Владимир Александрович, доктор фармацевтических наук, профессор, заведующий кафедрой фармакогнозии с ботаникой и основами фитотерапии Самарского государственного медицинского университета (443099, Россия, Самара, ул. Чапаевская, д. 89). E-mail: kurkinvladimir@yandex.ru. https://orcid.org/0000-0002-7513-9352

Цибина Анастасия Сергеевна, аспирант кафедры фармакогнозии с ботаникой и основами фитотерапии Самарского государственного медицинского университета (443099, Россия, Самара, ул. Чапаевская, д. 89). E-mail: nastylapochka@mail.ru. https://orcid.org/0000-0002-0384-5522

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CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Optimization of total flavonoid content of ethanolic extract of *Persicaria pulchra* (Bl.) Soják for the inhibition of *α*-glucosidase enzyme

Nga H.N. Do[1,2], Tan M. Le[1,2], Chinh D.P. Nguyen[1,2], Anh C. Ha[1,2,@]

[1]Faculty of Chemical Engineering, Ho Chi Minh City University of Technology, 268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam
[2]Vietnam National University Ho Chi Minh City, Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam
[@]Corresponding author, e-mail: hcanh@hcmut.edu.vn

Objectives. *There has been a rapid increase in the number of diabetic patients since the past few decades in developed and developing countries. This rapid increase is accompanied by alarming costs of treatment. α-Glucosidase inhibitors are one of the most effective drugs employed for the reduction of postprandial hyperglycemia to manage Type 2 diabetes mellitus. Additionally, flavonoids, a group of natural substances, which are widely distributed in plants and possess variable phenolic structures, exhibit outstanding hypoglycemic activity and are considered as potential α-glucosidase inhibitors. In Vietnam, Persicaria pulchra (Bl.) Soják (P. pulchra) is employed in traditional medications. It possesses high flavonoid contents and its anti-diabetes ability has been hypothesized, although it has attracted less attention for investigation. Hence, the aim of this study is to optimize the condition of the P. pulchra extract to obtain the highest total flavonoid content and measure the bioactivities of P. pulchra, such as the anti-α-glucosidase and antioxidant activities.*

Methods. *The effects of the extracting conditions, including the temperature, extraction time, liquid-to-solid ratio (LSR), and ethanol (C_2H_5OH) concentration, on the total flavonoid content are investigated via experiments and analyzed by the response surface methodology (RSM). Concurrently, the optimal extraction also determines the anti-α-glucosidase and antioxidant activities.*

Results. *The optimal extraction condition for the highest flavonoid content (530 mg quercetin/g) is determined in 60 min, at 53°C, with LSR of 9.46 g/g and C_2H_5OH concentration of 62%. Moreover, the optimal plant extract exhibits good α-glucosidase inhibition with a half-maximal inhibitory concentration (IC_{50}) of 22.67 mg/mL, compared to the positive control (acarbose −7.77 g/mL). Additionally, P. pulchra is proposed to be a potential antioxidant with an IC_{50} of ~12.68 µg/mL.*

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Conclusions. *The study confirmed the optimal extraction condition of P. pulchra that will obtain the highest total flavonoid content and revealed the potentials of P. pulchra in α-glucosidase inhibition and antioxidation.*

Keywords: *flavonoid, plant extraction, optimization, anti-diabetes, response surface methodology.*

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Оптимизация общего содержания флавоноидов в спиртовом экстракте *Persicaria pulchra* (Bl.) Soják для ингибирования фермента *α*-глюкозидазы

Н.Х.Н. До[1,2], Т.М. Ле[1,2], Ч.Д.П. Нгуен[1,2], А.К. Ха[1,2,@]

[1]Химико-технологический факультет, Технологический университет Хошимина, 268 Ли Тхыонг Кьет ул., г. Хошимин, Вьетнам
[2]Вьетнамский национальный университет, Район Тхёк, г. Хошимин, Вьетнам
[@]Автор для переписки, e-mail: hcanh@hcmut.edu.vn

Цели. *В последние десятилетия в развитых и развивающихся странах наблюдается быстрый рост числа больных диабетом, который сопровождается ростом стоимости лечения. Ингибиторы α-глюкозидазы являются одним из наиболее эффективных препаратов, применяемых для снижения постпрандиальной гипергликемии при лечении сахарного диабета 2 типа. Кроме того, флавоноиды, группа природных веществ, широко распространенных в растениях и содержащих различные производные фенола, проявляют значительную гипогликемическую активность и могут служить потенциальными ингибиторами α-глюкозидазы. Во Вьетнаме Persicaria pulchra (Bl.) Soják (P. pulchra) используется в народной медицине. Он обладает высоким содержанием флавоноидов и, предположительно, противодиабетическими свойствами, хотя исследован мало. Таким образом, целью настоящего исследования является оптимизация экстрагирования P. pulchra для получения наиболее высокого общего содержания флавоноидов, а также определение его биологической активности – анти-α-глюкозидазной и антиоксидантной.*

Методы. *Экспериментально исследовано влияние условий экстрагирования, а именно температуры, времени экстракции, соотношения жидкость : твердое вещество и концентрации этанола, на общее содержание флавоноидов с помощью методологии анализа поверхности отклика. Показано, что оптимальные условия экстракции определяют анти-α-глюкозидазную и антиоксидантную активность.*

Результаты. *Найдены оптимальные условия экстракции для получения максимального содержания флавоноидов (530 мг кверцетина/г): время экстракции 60 мин, температура 53 °С, отношение жидкость : твердое вещество 9.46 г/г и концентрация этанола 62%. Растительный экстракт, полученный в оптимальных условиях, проявляет хорошее ингибирование α-глюкозидазы с концентрацией полумаксимального ингибирования (IC_{50}) 22.67 мг/мл по сравнению с положительным контролем (акарбоза – 7.77 г/мл).*

Выводы. *Исследование выявило оптимальные условия экстракции P. pulchra, позволяющие получить наиболее высокое общее содержание флавоноидов, и подтвердило перспективы применения P. pulchra для ингибировании α-глюкозидазы и антиоксидантного окисления.*

Ключевые слова: *флавоноид, экстракция растений, оптимизация, противодиабетические средства, методология поверхности отклика.*

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INTRODUCTION

Diabetes is rapidly becoming one of the most severe diseases of the 21st century largely because of current unhealthy lifestyles, like the consumption of greasy food and lack of exercise [1]. Particularly, this disease accounted for the deaths of about 4 mln people in 2017, along with its accompanying huge cost of treatment (about USD 850 mln, which is expected to increase significantly by the year 2030 [2]. Moreover, the prevalence of diabetes has increased sharply in recent decades. In 1980, the number of diabetic patients was about 108 mln, which increased to 425 mln in 2017 and is predicted to be nearly 630 mln by 2045 [2, 3]. The disease is mainly divided into three groups: Type 1, Type 2, and gestational diabetes [4]. Type 1 diabetes is an autoimmune disease that is caused by the self-destruction of β-pancreatic cells, which are key to insulin production while Type 2 diabetes is caused by insufficient insulin secretion or insulin resistance of cells [5, 6]. Actually, Type 2 diabetes accounts for up to 95% of the cases, thereby demonstrating its widespread prevalence. The third form of diabetes is common with pregnant women because of significant changes in their hormones during pregnancy, which could manifest in an increase in the blood glucose level [4]. According to a previous study, diabetes mellitus is risky and can cause death because of its life-threatening complications, such as coronary artery disease, heart failure, retinopathy, nephropathy, and atherosclerosis [4, 7].

Diabetes mellitus is generally caused by unhealthy lifestyles and can be effectively treated by proper diets and exercises. However, the utilization of medicine is still the main therapy [8]. Some typical drugs that are employed presently to treat the disease are sulphonylurea, biguanide, thiazolidinediones, and α-glucosidase inhibitors [9–12]. Nevertheless, these drugs exhibit side effects on the health of patients. For instance, biguanide negatively affects the digestive system, kidneys, and increases the risk of contracting ketone infection [13]. Thiazolidinediones are a new approach to the treatment of insulin resistance but can cause heart failure, edema, and weight gain [13]. Alternative therapy has been developed so far and involves the utilization of bioactive compounds, which are extracted from natural plants, as a dietary supplement for the treatment of diabetes mellitus. Some natural substances, such as polyphenols, flavonoids, alkaloids, glycosides, and saponins, have been demonstrated to cure the disease through their structure–activity relationship (SAR) [14]. Therein, researchers have invested much attention to flavonoids because they exhibit diverse biological activities, especially their ability to promote the treatment of Type 2 diabetes and its resulting complications [15, 16]. Flavonoids have demonstrated a wide range of hypoglycemic functions and counteracted hyperglycemia by stimulating insulin production and enhancing its absorption into cells and inhibiting the enzyme, α-glucosidase, which is mainly responsible for the breakdown of oligosaccharides, trisaccharides, and disaccharides into glucose in the mucosa [17, 18]. The enzyme is inhibited by flavonoids via either competitive or non-competitive inhibition [17].

Amongst the anti-diabetic herbals, *Persicaria* plants demonstrated their ability to combat diabetes with an inhibitory capacity of ~70%, compared to rutin (86%) [19]. Many species belonging to the *Persicaria* genus, like *Persicaria hydropiper* and *Polygonum perfoliatum* L. are biologically active and are employed in traditional medicines because they include phenolics, flavonoids, phenylpropanoids, steroids, and benzoquinones [20, 21]. Nevertheless, a lot of other *Persicaria* plants, e.g., *P. pulchra*, which is utilized frequently in Vietnamese traditional medicine, have not been investigated for the treatment of diabetes. Based on previous studies on the bioactive compounds of other *Persicaria* plants, *P. pulchra* is well expected to contain high flavonoid contents to cure diabetes mellitus via α-glucosidase inhibition [22].

In this study, the optimal condition for the one-time ethanolic extraction of *P. pulchra* to obtain the highest flavonoid contents was determined by the response surface methodology (RSM). The method was introduced by Box and Wilson, in 1951, and has been applied to the determinations of the best conditions of extraction ever since [23]. The effects of the concentration of ethanol (C_2H_5OH), the extraction temperature, extraction time, and liquid-to-solid ratio (LSR) on the flavonoid contents were comprehensively investigated. Finally, the α-glucosidase inhibition and antioxidation of the optimal plant extract were evaluated.

MATERIALS AND METHOD

Materials

P. pulchra leaves were harvested from Binh Chanh District, Ho Chi Minh City, Vietnam. The plant was authenticated by the Department of Ecology and Evolutionary Biology of the Faculty of Biology and Biotechnology, Ho Chi Minh City University of Science, Vietnam National University. The following reagents were purchased from commercial suppliers in pure grade: C_2H_5OH, methanol (CH_3OH), distilled water, sodium nitrite ($NaNO_2$), sodium carbonate (Na_2CO_3), sodium hydroxide (NaOH), aluminum chloride ($AlCl_3$), and dimethyl sulfoxide (DMSO). The Folin–Ciocalteau reagent, quercetin (QUE), gallic acid (GA), *para*-nitrophenyl-α-D-glucopyranoside (*p*-NPG), α-glucosidase, and 1,1-diphenyl-2-picryhydrazyl (DPPH) were obtained from *Merck* (Germany).

Preparation of the ethanolic extract

Freshly harvested leaves of *P. pulchra* were rinsed with tap water to remove dirt and impurities. Thereafter, the leaves were air-dried, pulverized, and stored in a sealed container for the experiment. Before the extraction, the moisture content of the sample was determined by a moisture analyzer Sartorius MB45 (*Sartorius*, Germany) to be ~11%.

The extracts were prepared, at controlled temperatures, extraction times, C_2H_5OH concentrations, and LSR (Table 1). Next, 5.00 g of the dried sample was extracted by aqueous C_2H_5OH in a 100 mL beaker, which was assisted by an agitator (300–400 rpm). The primary extract was filtered afterward, under vacuum condition, followed by rotary vacuum evaporation, until the excess solvent was completely removed. The extraction yield was determined by Eq. (1):

$$H = \frac{m_{extract}}{m_{sample}} \times 100\%, \tag{1}$$

where $m_{extract}$ is the weight of dry extract (g) and m_{sample} is the weight of the dry leaf powder (g).

Determination of the total polyphenol content (TPC)

TPC in the extracts was determined, utilizing the Folin–Ciocalteu colorimetric method, according to Sánchez-Rangel [24]. Briefly, ~10 mg of the primary ethanolic extract was dissolved in 1 mL of pure DMSO to form a concentrated sample solution, which was diluted to different concentrations before the measurement. Next, 200 µL of the Folin–Ciocalteau reagent was mixed with 40 µL of the sample solution. The mixture was thereafter homogenized in a sonication bath for 5 min, at room temperature. Afterward, 600 µL of 20% Na_2CO_3 and 3.16×10^3 µL of distilled water were added to the mixture. A homogenous solution was obtained in the sonication bath after 30 min. Thereafter, the absorbance of the mixture was measured, at a wavelength of 760 nm. Moreover, GA was employed as a standard to depict the calibration graph.

Determination of the total flavonoid content (TFC)

A colorimetric method was applied to measure TFC [25]. Therein, ~10 mg of the extract was dissolved in 1 mL of CH_3OH to yield the mother liquor. To measure the sample absorbance, it was diluted to appropriate concentrations to obtain various sample solutions. Further, 2 mL of distilled water, 0.5 mL of the sample, and 0.15 mL of 5% $NaNO_2$ were mixed. After 5 min, 0.15 mL of 10% $AlCl_3$ was added to the mixture. Within 1 min, 1 mL of 1 M NaOH and 1.2 mL of distilled water were added. The absorbance of the mixture was measured, at a wavelength of 425 nm. QUE was utilized as a standard to illustrate the calibration graph.

Experimental design

The experiments adopted the rotatable central composite design (CCD) to determine the most suitable regression equation [23]. Compared to a single-factor optimization, this highly effective mathematical and statistical technique exploits higher accuracy by considering the interactions between variables. The objective is to determine the relationship between the factors and response values to determine optimal conditions. The Design Expert® 11 software (*Stat-Ease Inc.*, USA) was applied to this study.

The design consisted of 36 experiments, including 12 replicates, at the center points. The center points defined the experimental error and reproducibility of the data. The independent variables in this study are temperature (X_1: 45–65°C), time (X_2: 40–100 min), LSR (X_3: 8–12 g/g), and C_2H_5OH concentration (X_4: 50–80%). The coded and uncoded levels of the independent variables are described in Table 1. The values of the independent variables are expressed in codes, as −1, 0, and +1 interval, corresponding to the lower, center, and upper levels of each variable, respectively. Each experiment was performed three times to obtain the average TFC value, which was expressed as a response, Y, variable.

In vitro α-glucosidase inhibitory assay

The investigation of the α-glucosidase enzyme inhibitory activity of the extract was conducted following Mahomoodally's method [26]. The test was performed on 96-well plates. The extract was dissolved in DMSO before the test. Additionally, 40 and 20 µL of the sample solution and α-glucosidase enzyme (1 U/mL) were added to the well, respectively. Next, 100 µL of a phosphate buffer (pH 6.8) was added to the mixture. Thereafter, the plate was incubated for 5 min, at 37°C. After that, 40 µL of 0.1 mM *p*-NPG was added to the reacting mixture. Incubation proceeded for 30 min, at 37°C. Subsequently, ~100 µL of 0.1 M Na_2CO_3 was added to terminate the reaction, and the absorbance of the sample was measured, at 405 nm. Acarbose was employed as a positive control. The percent inhibition of the α-glucosidase reaction was calculated as follows:

$$I\% = \left(\frac{A - B}{A}\right) \times 100\%, \tag{2}$$

A: absorbance, at 405 nm of the blank (α-glucosidase and the substrate),
B: absorbance, at 405 nm of the subject (α-glucosidase, the substrate, and the sample).

In vitro antioxidant assay

The antioxidant activity of the plant extract was investigated according to Sharma's method [27]. The antioxidative substances in the extract neutralized the DPPH radical by donating hydrogen. Thus, the reactive solution changed from violet to light-yellow, and its absorbance was measured, at 517 nm. Next, 180 µL of DPPH, which was dissolved in 80% CH_3OH, was added to 120 µL of the sample. The mixture was incubated for 30 min, at 30°C, in the dark. This was followed by the measurement of its absorbance, at 517 nm. Ascorbic acid

Table 1. Rotatable CCD with four factors and TFC (Y)

No.	Coded variables (Real variables)				TFC Y
	X_1	X_2	X_3	X_4	
1	−1 (45)	−1 (40)	−1 (8)	−1 (50)	469 ± 14
2	1 (65)	−1 (40)	−1 (8)	−1 (50)	478 ± 15
3	−1 (45)	1 (100)	−1 (8)	−1 (50)	460 ± 12
4	1 (65)	1 (100)	−1 (8)	−1 (50)	467 ± 7
5	−1 (45)	−1 (40)	1 (12)	−1 (50)	472 ± 14
6	1 (65)	−1 (40)	1 (12)	−1 (50)	491 ± 11
7	−1 (45)	1 (100)	1 (12)	−1 (50)	441 ± 11
8	1 (65)	1 (100)	1 (12)	−1 (50)	444 ± 11
9	−1 (45)	−1 (40)	−1 (8)	1 (80)	457 ± 21
10	1 (65)	−1 (40)	−1 (8)	1 (80)	461 ± 22
11	−1 (45)	1 (100)	−1 (8)	1 (80)	459 ± 12
12	1 (65)	1 (100)	−1 (8)	1 (80)	456 ± 16
13	−1 (45)	−1 (40)	1 (12)	1 (80)	444 ± 15
14	1 (65)	−1 (40)	1 (12)	1 (80)	453 ± 11
15	−1 (45)	1 (100)	1 (12)	1 (80)	424 ± 13
16	1 (65)	1 (100)	1 (12)	1 (80)	431 ± 15
17	−2 (35)	0 (70)	0 (10)	0 (65)	437 ± 11
18	2 (75)	0 (70)	0 (10)	0 (65)	440 ± 9
19	0 (55)	−2 (10)	0 (10)	0 (65)	449 ± 4
20	0 (55)	2 (130)	0 (10)	0 (65)	426 ± 14
21	0 (55)	0 (70)	−2 (6)	0 (65)	504 ± 10
22	0 (55)	0 (70)	2 (14)	0 (65)	474 ± 14
23	0 (55)	0 (70)	0 (10)	−2 (35)	461 ± 12
24	0 (55)	0 (70)	0 (10)	2 (95)	456 ± 13
25	0 (55)	0 (70)	0 (10)	0 (65)	534 ± 10
26	0 (55)	0 (70)	0 (10)	0 (65)	529 ± 9
27	0 (55)	0 (70)	0 (10)	0 (65)	536 ± 12
28	0 (55)	0 (70)	0 (10)	0 (65)	521 ± 14
29	0 (55)	0 (70)	0 (10)	0 (65)	529 ± 7
30	0 (55)	0 (70)	0 (10)	0 (65)	521 ± 12
31	0 (55)	0 (70)	0 (10)	0 (65)	528 ± 8
32	0 (55)	0 (70)	0 (10)	0 (65)	530 ± 7
33	0 (55)	0 (70)	0 (10)	0 (65)	532 ± 15
34	0 (55)	0 (70)	0 (10)	0 (65)	536 ± 7
35	0 (55)	0 (70)	0 (10)	0 (65)	522 ± 10
36	0 (55)	0 (70)	0 (10)	0 (65)	529 ± 9

was employed as a positive standard. The percentage inhibition can be calculated by the following equation:

$$I\% = \left(\frac{A - B}{A}\right) \times 100\% \qquad (3)$$

A: Absorbance, at 517 nm, of the DPPH radical in CH_3OH, B: Absorbance, at 517 nm, of the DPPH radical solution, mixed with the sample.

RESULTS AND DISCUSSION

Extraction efficiency, TPC, TFC, and α-glucosidase inhibition

Table 2 presents the bioactive compound contents in the highly concentrated ethanolic (96%) extract with LSR of 10 g/g, obtained after 60 min, at 50°C. TPC and TFC of the plant are 388 mg GA/g and 423 mg QUE/g, respectively. Interestingly, TPC and TFC of *P. pulchra* were much higher

Table 2. Total polyphenol content, total poly flavonoids content and *α*-glucosidase inhibition of *P. pulchra* compared to some bioactive plant extracts

Plant	TPC, mg GA/g	TFC, mg QUE/g	IC_{50} of *α*-glucosidase inhibition, µg/mL
P. pulchra	388 ± 16	423 ± 16	33.53 ± 1.25
P. odoratum	52.59	19.97	–
P. minus	174	53.19	–
N. mirabilis	–	–	32.7
P. urinaria	–	–	39.7
K. candel	–	–	35.4

than those of other plants in the *Persicaria* family, such as *P. odoratum* and *P. minus* [28, 29]. The crude ethanolic extract of *P. pulchra* exhibited good inhibition of *α*-glucosidase with IC_{50} of 33.53 ± 1.25 µg/mL, which is comparable to those of some anti-diabetic Vietnamese plants, like *N. mirabilis*, *P. urinaria*, and *K. candel* [30].

The extraction of bioactive compounds from dried P. pulchra, employing 96% C_2H_5OH obtained the highest yield, ~12%, in the one-time extraction. Figure 1 indicates that the extract recoveries, at the 2nd and 3rd extractions, decreased three to six times, compared to the 1st extraction, along with a decrease in the TPC and TFC contents. This was mainly caused by the reduced diffusivities of the bioactive compounds with several extraction rounds. In the one-time extraction, the substances in the plant readily diffused into C_2H_5OH because of the large concentration difference between the plant and the solvent. During subsequent extractions, those compounds were hardly extracted owing to their low concentrations in the plant. Consequently, more extractions, resulting in the utilization of more solvent and increase in the consumption of energy and time, were conducted. Therefore, the objective of this work was to investigate an optimal condition that would obtain the highest TFC content in the first extraction. Moreover, the *α*-glucosidase inhibition of the optimal extract was evaluated based on SAR between the flavonoids and diabetes treatment [31].

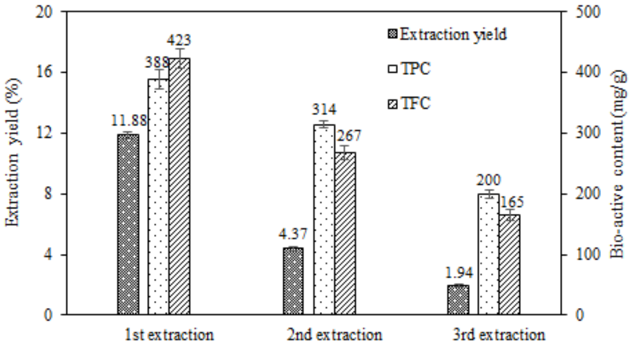

Fig. 1. Extraction yield, TPC, and TFC content of the ethanolic extract, at different extraction times.

Effect of the extraction parameters on TFC

Some extraction conditions, such as the solvent concentration (%), temperature (°C), time (min), and LSR (g/g) exert significant impacts on flavonoid yields of natural plants. The effects of the extraction parameters on TFC are shown in Fig. 2. One of the important steps to optimize the bioactive compounds obtained from the plant is to select an appropriate solvent. CH_3OH and C_2H_5OH are "universal" solvents that could penetrate cell membranes and extract compounds via hydrogen bonds [32]. However, in the pharmaceutical industry, C_2H_5OH is mostly utilized, compared to CH_3OH, because it is less toxic.

Employing different solvent concentrations, from 35 to 95% (Fig. 2a), TFC of the plant extract peaked at 536 mg QUE/g with 65% C_2H_5OH, which is consistent with the result of previous studies [33]. It was predicted that the flavonoids in the plant were highly polar while higher concentrations of C_2H_5OH are averagely polar, thereby reducing its extraction capacity. The 65% C_2H_5OH was utilized afterward for the next experiments. As could be observed from Fig. 2b, the temperature greatly influenced the extraction of flavonoids from the plant. When the extraction temperature increased from 35 to 55°C, a corresponding increase in TFC, from 437 to 529 mg QUE/g, was observed and followed by a decrease in TFC, at a higher temperature, due to the thermal degradation of the flavonoids. According to the previous study, some thermally susceptible flavonoids, such as myricetin, kaempferol, rhamnetin, and QUE might be present in the plant extract [34]. A similar phenomenon could be observed in Fig. 2c in which TFC approached a peak of 534 mg QUE/g after 70 min. The temperature, at 55°C, and time, 70 min, were applied to the next experiments to investigate the effect of LSR on TFC. However, this factor did not affect TFC as significantly as the others. TFC of the extract was low at low ratios (6 : 1 and 8 : 1) because the difference between the concentration of the plant and the environment was not enough to induce the diffusion of the flavonoids into the solvent. The TFC value reached a peak of 532 mg QUE/g with a 10 : 1 ratio and decreased with increasing solvent. Other compounds, like tannins and saponins, in the plant could be extracted along with the flavonoids when a higher amount of the solvent was utilized. Therefore, TFC of the extract was reduced.

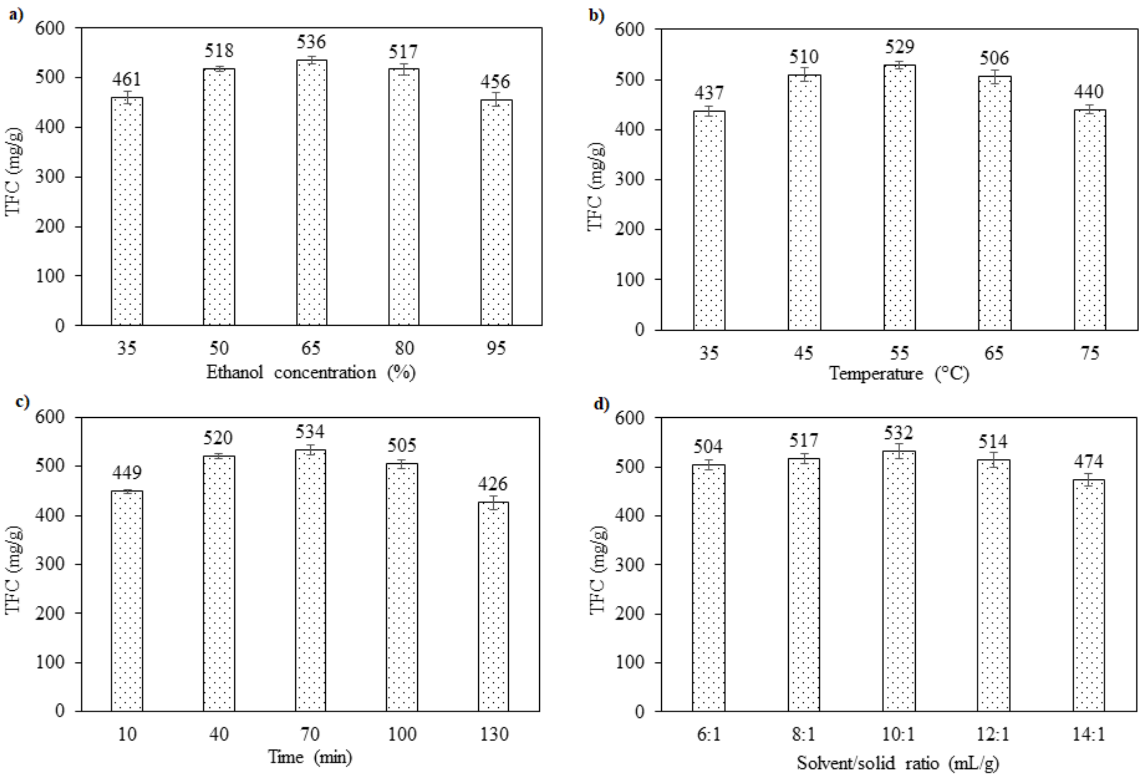

Fig. 2. Effects of (a) C_2H_5OH concentration, (b) temperature, (c) time, and (d) LSR on TFC.

Optimization of TFC in the first-time extract by RSM

Because of the effects of the C_2H_5OH concentration, time, temperature, and LSR on the TFC, those four factors were selected, as variables, to determine the optimal extraction condition. Generally, TFC of the ethanolic extract ranged significantly, from 424 to 536 mg QUE/g. Therein, the experiments at the center point resulted in the highest TFC, thus strongly indicating that the optimal point was close to the center (Fig. 3). Conversely, the two experiments that obtained the lowest TFC were those at the upper point (65°C, 100 min, and LSR of 12 : 1) because of a combination of disadvantageous factors against the extraction.

By applying the orthogonal planning method and employing the Design Expert® software, the regression coefficients of the objective functions were calculated. The compatibility of the build model with the experiment was validated via the coefficient of determination (R^2 value). Table 3 presents the ANOVA analysis of the response surface model, which was extracted from the software. The F-value of the model, 106.10, implied the quadratic model whose *p*-value of <0.0001 was adequate to predict the TFC value. R^2 of 0.9861 indicated that the regression model accounted for 98.61% of the total variability.

The coefficients of the regression equation were derived from the formula of orthogonal matrices, after which they are tested to determine their significance level. There was only a 0.01% chance that an F-value, this large, could occur due to noise. *p*-Values, <0.0500,

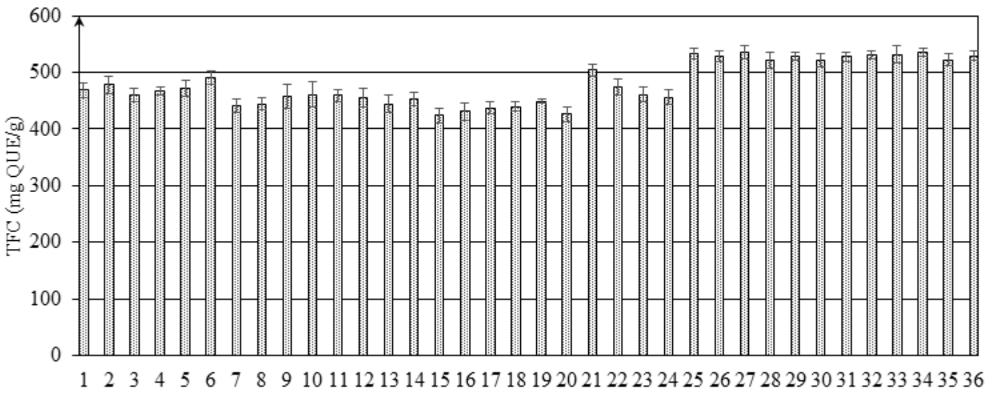

Fig. 3. TFC values of the plant extract, at 36 planning points.

Table 3. ANOVA table for the effects of the extraction parameters on TFC in the *P. pulchra* extracts

Source	DF (Degree of Freedom)	SS (Sum of Squares)	Mean square	F-value	*p*-value
Model	14	50341.02	3595.79	106.10	<0.0001
X_1	1	168.13	168.13	4.96	0.0370
X_2	1	1947.97	1947.97	57.48	<0.0001
X_3	1	1162.04	1162.04	34.29	<0.0001
X_4	1	900.38	900.38	26.57	<0.0001
X_1X_2	1	66.53	66.53	1.96	0.1758
X_1X_3	1	27.56	27.56	0.8132	0.3774
X_1X_4	1	27.56	27.56	0.8132	0.3774
X_2X_3	1	588.06	588.06	17.35	0.0004
X_2X_4	1	175.56	175.56	5.18	0.0334
X_3X_4	1	189.06	189.06	5.58	0.0279
X_1^2	1	16078.86	16078.86	474.41	<0.0001
X_2^2	1	12832.51	12832.51	378.63	<0.0001
X_3^2	1	3304.03	3304.03	97.49	<0.0001
X_4^2	1	10105.48	10105.48	298.17	<0.0001
Residual	21	711.73	33.89	–	–
Lack of fit	10	400.82	40.08	1.42	0.2870
Linear	0.6789				
Quadratic	<0.0001				
Cubic	0.2477				
R^2	0.9861				
Adjusted R^2	0.9768				

indicated that the terms of the model were significant. In this case, X_1, X_2, X_3, X_4, X_2X_3, X_2X_4, X_3X_4, X_1^2, X_2^2, X_3^2, X_4^2, were significant model terms. After the analysis, the Design Expert® software results of the second-degree regression equation for the virtual variables are as described in Eq. (4).

$$\begin{aligned} Y &= 528.87 + 2.63X_1 - 9.23X_2 - 6.96X_3 - \\ &6.13X_4 - 6.06X_2X_3 + 3.31X_2X_4 - 3.44X_3X_4 - \\ &-22.74X_1^2 - 21.03X_2^2 - 10.18X_3^2 - 17.81X_4^2 \end{aligned} \tag{4}$$

As could be seen in Eq. (4), all the four variables were captured in the equation, thus confirming the influence of the investigated factors on the extraction process. Additionally, the second-order regression coefficients were negative, indicating that the response surface was convex, and presented the maximum point. The temperature and time variables possessed the highest coefficients (22.74 and 21.03, respectively), proving that they exerted significant impacts on TFC. Moreover, the coefficient of the slope was close to the TFC value that was measured in the experiments, at the center point, and was significantly higher than the other coefficients in the resulting equation. Therefore, the predicted maximum point was around the center point and was approximately the value of the slope. The response surfaces were plotted from Eq. (2) to determine the optimal point and visually evaluate the interactions of variables with TFC. Due to the great impacts of the temperature and time parameters on the response variable, they were selected, at different LSR and C_2H_5OH concentrations, as illustrated in Fig. 4. Generally, the peaks of the response surfaces were near the center point of the temperature and time variables. At an LSR of 8 g/g (Figs. 4a, 4b, and 4c), the highest TFC was ~526 mg QUE/g with 65% C_2H_5OH, and the lowest value was 505 mg QUE/g with 80% C_2H_5OH. It was predicted that the optimal point of solvent concentration was near the 65% C_2H_5OH concentration. Additionally, the peaks of the response surfaces with LSR of 10 g/g were all higher than those with LSR of 8 g/g (Figs. 4d, 4e, and 4f). The TFC value simultaneously reached a peak with 65% C_2H_5OH and hit the low with 80% ethanol. With a higher LSR of 12 g/g (Figs. 4g, 4h, and 4i), a decrease in TFC was observed, along with an increase in the C_2H_5OH concentration. Therefore, it is possible to predict that the optimal conditions were close to LSR of 10 g/g and 65% C_2H_5OH. Summarily, the optimal conditions were close to the center points of the temperature (55°C), time (70 min), and C_2H_5OH concentration (65%) with LSR of ~10 g/g.

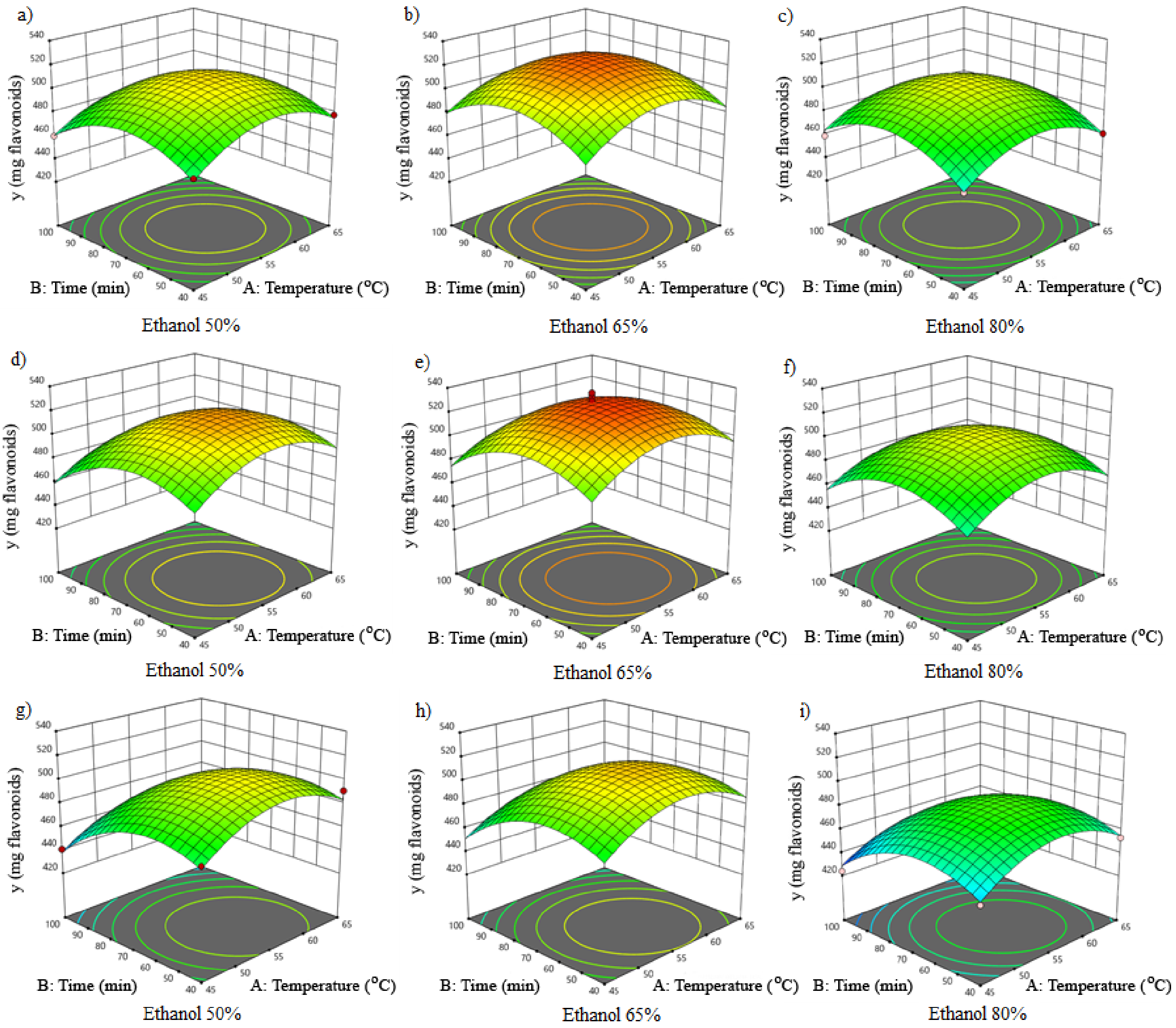

Fig 4. 3D response surfaces, plotted at LSRs of (a, b, c) 8 g/g, (d, e, f) 10 g/g, and (g, h, i) 12 g/g.

Employing the Design Expert® software, the optimal extraction conditions to obtain the maximum TFC were 52.25°C, 59.76 min, LSR of 9.201, and with 61.17% C_2H_5OH. The predicted TFC was 528 ± 11 mg QUE/g. To verify the obtained result, three experiments were performed, under the optimal conditions. As presented in Table 4, the plant extract obtained TFC of 531 ± 7, under the conditions of 53°C, 60 min, LSR of 9.46, and 62% C_2H_5OH, which is close to the predicted value. Generally, the error between the experimental and calculated values was <5%, indicating that the obtained model was reliable and meaningful, in practice.

α-Glucosidase inhibition and the antioxidant activity of the optimal extract

The crude extract of *P. pulchra* exhibited good *α*-glucosidase inhibition with IC_{50} of 33.53 μg/mL. To determine the effect of the flavonoid content on this bioactivity, the relationship between TFC and IC_{50} should be investigated. As shown in Fig. 5, when TFC of the extract increased (from 423 to 526 mg QUE/g),

Table 4. Comparison of the experimental and predicted values, under the optimal condition.

Temperature, °C	Time, min	LSR, g/g	C_2H_5OH concentration, %	Predicted TFC, mg QUE/g	Experimental TFC, mg QUE/g	Error with the model, %
53 ± 2	60	9.46	62 ± 0.5	528 ± 11	526	0.38
					539	2.08
					529	0.20

IC_{50} decreased (from 33.53 to 22.67 μg/mL), indicating an increase in the *α*-glucosidase inhibition. Because of the positive correlation between TFC and the enzyme inhibition, the optimal extraction condition for the highest TFC resulted in the best inhibitory capacity without the optimization of the IC_{50} value, thus reducing the time and cost of the analysis.

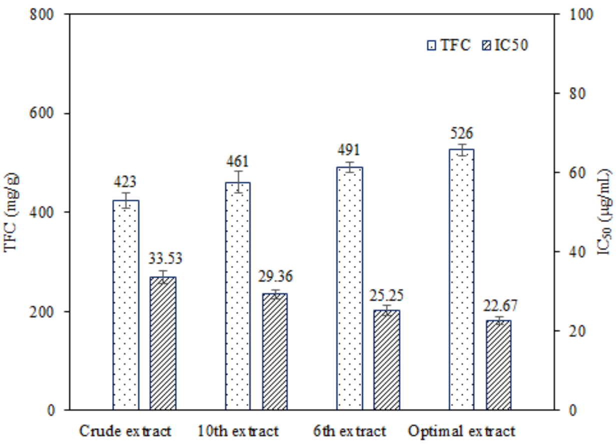

Fig. 5. Effect of TFC on the *α*-glucosidase inhibition of the plant extract.

Moreover, the IC_{50} value of the optimal extract (22.67 ± 1.00 μg/mL) is only triple of that of acarbose (7.77 ± 0.36 μg/mL), which is a common *α*-glucosidase inhibitor for Type 2 diabetes. It was safely claimed that an optimal extract could be utilized as an alternative to acarbose to reduce its adverse effects [35, 36]. Flavonoids are not only *α*-glucosidase inhibitors; they are also great antioxidants, which neutralize free radicals, produce complexes with several metal ions or induce antioxidative enzymes in the body [37]. The antioxidant assay exhibited an IC_{50} value of the optimal extract to be 12.68 ± 0.10 μg/mL, which is three times greater than that of ascorbic acid (2.82 ± 0.14 μg/mL). These results could broaden the knowledge of and avail new insights on the bioactivity of *P. pulchra*, particularly its potentials to inhibit *α*-glucosidase and its potential antioxidant activity for the treatment of diabetes.

CONCLUSIONS

Extraction factors, such as temperature, time, C_2H_5OH concentration, and LSR, were proven to exert significant effects on TFC in the one-time extraction of *P. pulchra.* The highest TFC was ~526 mg QUE/g of the sample, under the 53°C, 60 min, 62% C_2H_5OH, and LSR of 9.46 g/g conditions. Moreover, the relationship between TFC and the *α*-glucosidase inhibition of the plant extract was determined therein the optimal extract exhibited the lowest IC_{50} value of 22.67 μg/mL.

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No potential conflict of interest was reported by the authors.

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About the authors:

Nga H.N. Do, BEng., Postgraduate Student, Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam); Vietnam National University Ho Chi Minh City (Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam). E-mail: 1870411@hcmut.edu.vn. https://orcid.org/0000-0002-1606-4522

Tan M. Le, BEng., Postgraduate Student, Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam); Vietnam National University Ho Chi Minh City (Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam). E-mail: lmtan.sdh20@hcmut.edu.vn. https://orcid.org/0000-0002-7956-1067

Chinh D.P. Nguyen, BEng., Postgraduate Student, Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam); Vietnam National University Ho Chi Minh City (Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam). E-mail: npdchinh.sdh19@hcmut.edu.vn. https://orcid.org/0000-0002-2820-3913

Anh C. Ha, PhD, Dr. of Chemical Engineering, Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (268 Ly Thuong Kiet Street, District 10, Ho Chi Minh City, Vietnam); Vietnam National University Ho Chi Minh City (Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam). E-mail: hcanh@hcmut.edu.vn. https://orcid.org/0000-0001-7919-4028

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RESEARCH ARTICLE

Solvent extraction of europium(III) from technogenic solutions with the use of surfactants

Natalia V. Dzhevaga, Olga L. Lobacheva@

Saint Petersburg Mining University, Saint Petersburg, 199106 Russia
@*Corresponding author, e-mail:* Olga-59@yandex.ru

Objectives. *The extraction and separation of rare-earth metals is a complicated process that requires a multidisciplinary and detailed investigation. Liquid-liquid extraction with the use of surfactant, along with the thermodynamic analysis of the parameters is considered a promising approach. The extraction and separation of rare-earth metals from low-concentration solutions represents an attractive research opportunity. The extraction of europium(III) from nitric acid solutions in the form of dodecyl sulfates has been experimentally studied. This work focuses on the study of fundamental and alternative sources of rare-earth metals and their extraction and separation.*

Methods. *The extraction was performed on a top drive ES-8300 D equipment for 30 min at about 700 rpm. Infrared spectroscopy (Nicolet 6700 spectrometer) was used to determine the type of salts extracted into the organic phase. Extraction was studied in solutions with single cations and with a combination of the target element and interfering cations. For the latter, the concentrations of extracted elements in the aqueous phase were determined by optical emission spectroscopy with inductively coupled plasma on an ICPE-9000 (Shimadzu) spectrometer. The spectrometer was calibrated using standard samples for ICP CertiPUR (Merck).*

Results. *The dependence of the distribution and separation coefficients of rare-earth metals during extraction on the pH value of the aqueous phase at equilibrium was investigated. Moreover, the form in which the elements are extracted was analyzed based on thermodynamic parameters. The minimum concentration of the target component in the aqueous phase was observed at pH 4.0. In general, the dependence of the distribution coefficient on the pH value of the medium is poorly expressed over the entire range of the pH range of the water phase. Based on the spectra of spent and pure isooctyl alcohol, it was concluded that europium dodecyl sulfates are extracted into the organic phase as* $Eu(C_{12}H_{25}OSO_3)_3$ *solvates.*

Conclusions. *The extraction of europium(III) from nitric acid solutions in the form of dodecyl sulfates was demonstrated. The advantages of the proposed method are the possibility of selective extraction of the target component from dilute solutions and the use of an easily available surfactant (sodium dodecyl sulfate). The efficiency of extraction of europium dodecyl sulfates was maximal in the pH range from 2.0 to 7.5, which reflects a weak dependence on the acidity of the aqueous phase. In addition, in the highly alkaline pH region, the extraction efficiency is reduced.*

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Keywords: *extraction, rare-earth elements, extraction efficiency, distribution and separation coefficients, sodium dodecyl sulfate.*

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Жидкостная экстракция европия(III) из техногенных растворов с использованием поверхностно-активного вещества

Н.В. Джевага, О.Л. Лобачева@

Санкт-Петербургский Горный университет, Санкт-Петербург, 199106 Россия
@Автор для переписки, e-mail: Olga-59@yandex.ru

Цели. *Литературные данные свидетельствуют о сложности извлечения и разделения редкоземельных металлов экстракционными методами и доказывают необходимость многостороннего и детального изучения данных процессов. Перспективным является осуществление экстракции с применением поверхностно-активного вещества и термодинамическим обоснованием полученных технологических величин. Инновационной идеей научного исследования является применение экстракционного метода для извлечения и разделения редкоземельных металлов из низкоконцентрированных растворов. Экспериментально изучен процесс извлечения европия(III) из азотнокислых растворов в форме додецилсульфатов экстракцией. Исследования ориентированы на изучение основных и альтернативных источников редкоземельных металлов, способов их извлечения и разделения.*
Методы. *Процесс проводили на верхнеприводном экстракторе ES-8300 D в течение 30 мин со скоростью около 700 об/мин. Для определения формы экстрагируемых солей в органической фазе применяли метод инфракрасной спектроскопии (спектрометр Nicolet 6700). Экстракцию изучали в растворах с единичными катионами и с комбинацией целевого компонента и интерферирующих катионов. Для последних растворов концентрации экстрагируемых элементов в совместном присутствии в водной фазе определяли методом оптической эмиссионной спектроскопии с индуктивно-связанной плазмой на спектрометре ICPE-9000 (Shimadzu). Калибровка спектрометра проводилась по стандартным образцам для ICP CertiPUR (Merck).*
Результаты. *Получены зависимости коэффициентов распределения и разделения редкоземельных металлов в процессе экстракционных процессов от величины pH равновесной водной фазы с установлением и термодинамическим обоснованием формы извлекаемых соединений. Установлено, что в процессе экстракции минимальная концентрация целевого компонента в водной фазе наблюдается при pH = 4.0. В целом на всем интервале исследуемого диапазона pH водной фазы зависимость коэффициента распределения от величины кислотности среды выражена слабо. По результатам анализа спектров отработанного и чистого изооктилового спирта сделано заключение, что додецилсульфаты европия извлекаются в органическую фазу в виде сольватов* $Eu(C_{12}H_{25}OSO_3)_3$.
Выводы. *Экспериментально показана возможность извлечения европия(III) из азотнокислых растворов в форме додецилсульфатов экстракцией. Преимуществами предлагаемого метода являются возможность избирательного извлечения целевого компонента из разбавленных техногенных растворов и использование поверхностно-активного вещества (додецилсульфата натрия). Эффективность извлечения додецилсульфатов европия при экстракции максимальна в исследуемом диапазоне pH от 2.0 до 7.5, что отражает слабую зависимость от кислотности водной фазы. Кроме того, в сильнощелочной области pH эффективность извлечения экстракцией понижается.*

Ключевые слова: *экстракция, редкоземельные элементы, эффективность извлечения, коэффициенты распределения и разделения, додецилсульфат натрия.*

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INTRODUCTION

The use of metal extraction processes has increased in various sectors of the national economy [1, 2]. This is due to the selectivity and simplicity of such processes, their speed, and high efficiency at low initial concentrations of metal cations.

The extraction of rare-earth metals by carboxylic acids has been widely studied because their use in sulfuric and hydrochloric acid industries for processing rare-metal raw materials is more effective than, for example, organophosphates [1, 2]. The degree of extraction and separation of rare-earth elements (REE) and aluminum with octyl-phenoxy isopropionic acid (OPIPA) presented in [3] reaches 86.43% with a purity of 99.69%. Cerium(III) extraction with a solution of oxine and 2-methyloxine in various organic solvents under conditions similar to industrial scenarios (a strongly acidic solution with a 0.3–4.4 mol/kg content of sulfuric acid) is reported in [4].

The chemistry of the extraction of lanthanide(III) nitrates with trialkylbenzylammonium naphthenate has also been investigated [5]. With a phase ratio of 2 : 1, rare-earth metals were extracted into the organic phase as $(R_4N)_2[Ln(NO_3)_3(RCOO)_2]$. In the lanthanum–lutetium series, extraction is reduced, while the degree of yttrium extraction is significantly lower than for lanthanides. Trialkylbenzylammonium naphthenate can be used to separate lanthanides with lower ordinal numbers from other lanthanides and also in systems for removing lanthanides from yttrium compounds.

The extraction of lanthanum, thorium, and yttrium with composite materials using porous carriers and liquid extractants is a promising method. When thorium(IV), lanthanum(III), and yttrium(III) are extracted together from water-salt solutions by a composite material based on super-crosslinked polystyrene with trialkylamine (TAA), lanthanum(III) and yttrium(III) nitrates are practically not absorbed; when the concentration of lanthanum(III) and yttrium(III) increases in the aqueous phase, the content of thorium(IV) nitrate in the composite material phase increases [6]. This system can be used for removing thorium(IV) impurities from concentrated solutions of rare-earth metal nitrates.

In addition, the extraction of rare-earth metals from nitric acid solutions with fluoride ions has been reported [7, 8]. Moreover, the extraction of zirconium(IV) cations from hydrochloric acid solutions in the presence of potassium fluoride with 1-octanol was investigated [9]. Extraction methods can be thus used to obtain metal cations from industrial waste dilute solutions (processing of molybdenum, copper, copper nickel ores, apatite-nepheline, eudialite ores, and red slurries).

It is clear that the extraction and separation of rare-earth metals is a complex process that must be investigated from different perspectives in a detailed manner. Using a surfactant for the extraction, along with the thermodynamic analysis of the process' parameters, seems like a promising approach.

The primary objectives of this work are:

- developing a method for the extraction and separation of rare-earth metals using surfactants and for the experimental assessment of distribution and separation coefficients and degree of extraction, followed by their implementation in the industrial processing of low-concentrated mineral raw materials;
- studying the dependence of the distribution and separation coefficients of rare-earth metals on the pH of the aqueous phase during extraction by determining the form in which the target elements are extracted, based on thermodynamic parameters.

During the extraction of rare-earth metals from aqueous solutions, sodium dodecyl sulfate (NaDS), known as a foamer and collector, is used as surfactant because of its many advantages in comparison with other surfactants. NaDS is non-toxic (hazard class IV) and cheap and can be regenerated from the obtained products. In addition, extraction processes require amounts of NaDS, depending on stoichiometry of the chemical reaction. NaDS can be used in a wide range of acidity of the liquid phase. Compared with similar surfactants, the degree of recovery of rare-earth metals by NaDS has the maximum values [10–12].

This work focuses on the study of fundamental alternative sources of rare-earth metals, and their extraction and separation. According to the literature [13–18], cost-effective sources of rare-metal raw materials are the minerals bastnesite $Ln(CO_3)F$ (70–75%), monazite $LnPO_4$ (55–60%), laparite $NaCaLn(TiO_3)_2(NbO_3)_2$ (30–35%), and xenotima (Y, Eu, Gd)PO_4 (55–60%). Alternative sources of rare-earth metals are waste products of industrial processes with a poor rare-earth metals content, converter dusts, slags, red slurries of aluminum production, and mineral raw materials with low concentrations of the desired elements.

Modern technologies to obtain rare-metal raw materials focus on minerals of different types of deposits as sources. Russia does not have reserves of pure rare-metal raw materials, such as bastnesite, monazite, and xenotima, which are used by the rare-earth industry abroad. In the Russian Federation, the most accessible and efficient sources for processing are the Lovozero loparite, eudialite, and Khibiny apatite-nepheline ores from the Kola Peninsula. These sources have low contents of rare-earth metals. The Russian rare-earth industry is currently working in the development of new deposits, which is far from sufficient to meet the growing demand for rare metals and their derivatives. For the progress of the Russian rare-metal industry, special attention should be paid to the associated extraction of individual rare-earth metals in the processing of multicomponent ores, and not only to the development of new deposits. Complex use of mineral raw materials is of the utmost importance in efficient resource usage. Since pure rare-earth metals are of great value, it is crucial to increase the efficiency of extraction and separation of rare-earth metals with similar physical and chemical properties, which will reduce the cost of these elements and their compounds, and expand the possibilities of their use [13–18].

This work proposes a method for the extraction and separation of rare-earth metals from low-concentration solutions. The advantages of the method over existing processes are the possibility of selective extraction of the target component from dilute solutions and the use of easily accessible surfactants.

MATERIALS AND METHODS

All reagents were chemically pure. A 0.01 M europium nitrate solution was prepared by dissolving $Eu(NO_3)_3 \cdot 5H_2O$ in 99.9% pure distilled water. All subsequent working solutions (0.001 M) were prepared from this stock. The exact concentration was confirmed by titration with Triton B and xylenol orange. For the total extraction of REE, solutions of $Er(NO_3)_3 \cdot 5H_2O$, $Ho(NO_3)_3 \cdot 5H_2O$, and $Sm(NO_3)_3 \cdot 6H_2O$ were prepared and titrated, similar to $Eu(NO_3)_3 \cdot 5H_2O$. Sodium dodecyl sulfate (NaDS) for biochemistry (*Acros Organics*, USA, 99%, $C_{12}H_{25}OSO_3Na$) was used as surfactant. For the experiments, a dry NaDS suspension was added to the working solution. Nitric acid and sodium hydroxide, added before setting the desired pH value, were freshly prepared before use. Isooctyl alcohol (*Aldrich*, USA, 96%, 2-ethyl-1-hexanol) was used as extractant.

Liquid-liquid extraction was performed to separate europium dodecyl sulfate using isooctyl alcohol as the extractant. NaDS was used as the transport agent of europium cations from the aqueous to the organic phase. The surfactant (0.003 M) was added according to the stoichiometry of the following reaction:

$$Eu^{3+} + 3C_{12}H_{25}OSO_3^- = Eu(C_{12}H_{25}OSO_3)_3$$

The pH value was adjusted to a specific value by adding a 1 N NaOH solution or diluted HNO_3. The pH value of the aqueous solutions was determined using a pH-150 MA pHmeter (*AQUA-LAB*, Russia).

The volumes of the aqueous and organic phases were 200 and 5 mL, respectively. The process was performed on a top drive ES-8300 D extractor (*ECROSKHIM*, Russia) for 30 min at about 700 rpm. The parameters of the extraction were experimentally set to achieve optimum results. The type of salts extracted into the organic phase was determined using infrared spectroscopy using a Nicolet 6700 (*Thermo Fisher Scientific*, USA) spectrometer.

Extraction of europium(III) cations in the presence of holmium(III), erbium(III), and samarium(III) cations was performed using the method described above. Working solutions containing Sm^{3+}, Eu^{3+}, Ho^{3+}, and Er^{3+} were prepared by mixing 50 mL of 0.001 M solutions of each element. The volume of the solution with a final total concentration of 0.001 M was 200 mL. The concentration of the extractable elements in the aqueous phase was determined by optical emission spectroscopy with inductively coupled plasma (ICP) on an ICPE-9000 spectrometer (*Shimadzu*, Japan), which was calibrated using CertiPUR ICP standard samples (*Merck*, Germany).

The concentration of europium cations extracted into the organic phase was determined by the difference in concentration in the initial and equilibrium aqueous phases, considering the volume ratio of the phases:

$$C_{org} = \frac{\left(C_0 - C_{aq}\right) \cdot V_{aq}}{V_{org}}, \tag{1}$$

where C_0 is the initial europium concentration in the aqueous phase, mol/L; C_{org} and C_{aq} correspond to the concentration of europium cations in the organic and aqueous phases at equilibrium, mol/L; V_{aq} and V_{org} are the volume of the organic and aqueous phases, mL.

The distribution coefficient of Eu^{3+} in individual solutions (K_{distr}) and in the presence of Sm^{3+}, Ho^{3+}, and Er^{3+} ($K_{distr\Sigma}$) was calculated from the ratio of molar concentrations of the target component in the organic and aqueous phases according to [16].

The degree of extraction was calculated using the following equation:

$$\alpha = \frac{C_{org} \cdot V_{org}}{C_{aq} \cdot V_{aq} + C_{org} \cdot V_{org}} \cdot 100\% \tag{2}$$

RESULTS AND DISCUSSION

Table 1 shows the results of extraction of europium dodecyl sulfates from nitrate solutions in the pH range 2.0–11.0. As seen from the data, the maximum distribution coefficient during extraction was obtained at pH = 4.0.

According to the results reported in references [11, 12], the Gibbs energy of formation of $Eu(OH)^{2+}$ monohydroxocomplexes from its elements, $\Delta_f G^0_{298}$, and from ions, $\Delta_{compl} G^0_{298}$, is 782.60 and 47.42 kJ/mol, respectively; that of $Eu(OH)_3$ hydroxide is 1199.11 and 149.23 kJ/mol, respectively. In addition, pH of complexation, pH_{compl}, is 5.80, and pH of hydrate formation, pH_{hydr}, is 6.52; i.e. these are the pH values where the formation $Eu(OH)^{2+}$ and $Eu(OH)_3$ hydroxides begins.

During extraction, the minimum concentration of the target component in the aqueous phase is observed at pH = 4.0. In general, the dependence of the distribution coefficient of rare-earth metals during extraction on the pH value of the medium is poorly expressed over the entire pH range. Based on the spectra of spent and pure isooctyl alcohol, europium dodecyl sulfates are extracted into the organic phase as $Eu(C_{12}H_{25}OSO_3)_3$ solvates (Figs. 1 and 2). The interaction between alcohol molecules and europium cations is confirmed by a shift in the frequency of ν_{O-H} valence vibrations. However, in nitrate solutions that do not contain NaDS, the extraction of europium cations does not occur due to the lack of shielding of the target component by non-polar hydrocarbon radicals.

The efficiency of extraction of europium dodecyl sulfates is maximal from pH 2.0 to 7.5, which reflects a weak dependence on the acidity of the aqueous phase. In the highly alkaline pH region, the extraction efficiency is reduced.

Table 2 shows the results of extraction of europium dodecyl sulfates with isooctyl alcohol as an extractant in the presence of erbium(III), samarium(III), and holmium(III).

When extracting REE from individual solutions, the maximum distribution coefficients are found at pH 4.0–4.5, where REE is extracted into the organic

Table 1. Europium(III) cation extraction

pH	$[Eu^{3+}]_{aq}$ ×10^4 mol/kg	$[Eu^{3+}]_{org}$ ×10^2 mol/kg	K_{distr}
3.0	1.93	3.88	200.5
3.5	1.82	3.93	216.1
4.0	1.70	3.99	233.9
4.5	1.84	3.92	213.8
5.0	1.97	3.86	196.3
5.5	1.94	3.87	199.4
6.0	1.93	3.88	201.5

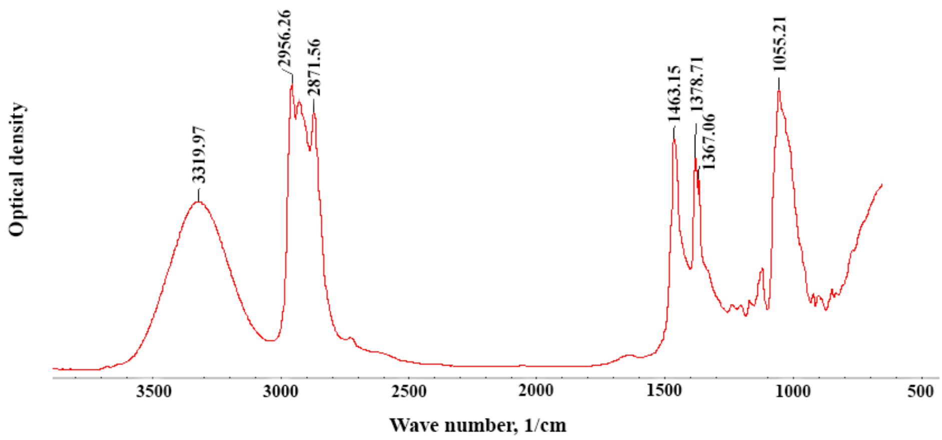

Fig. 1. Absorption spectrum of isooctyl alcohol.

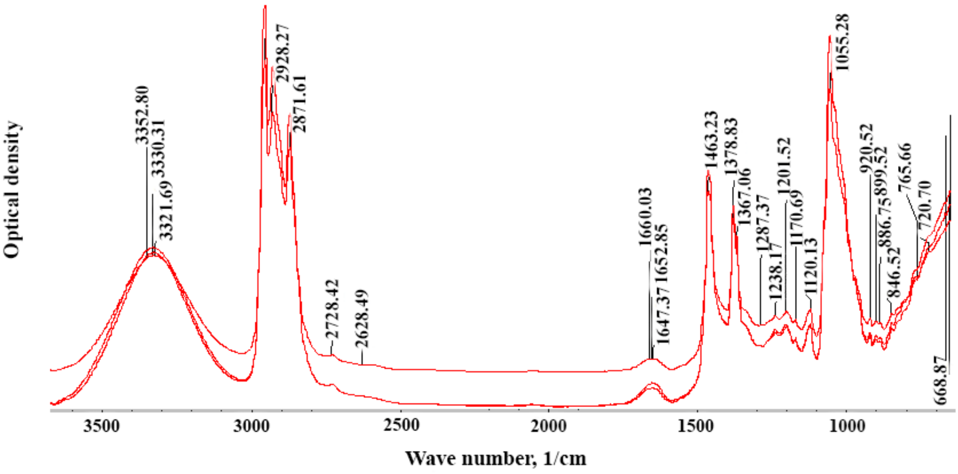

Fig. 2. Absorption spectrum of Eu extract.

Table 2. Coefficients of distribution of rare-earth elements (III) cations depending on the pH for extraction in the presence of interfering cations ($K_{\text{distr}\Sigma}$) and individually (K_{distr})

pH	Sm		Eu		Ho		Er	
	$K_{\text{distr}\Sigma}$	K_{distr}	$K_{\text{distr}\Sigma}$	K_{distr}	$K_{\text{distr}\Sigma}$	K_{distr}	$K_{\text{distr}\Sigma}$	K_{distr}
3.0	1437.3	306.9	1355.6	200.5	1282.5	443.1	1355.6	122.9
4.0	1752.4	326.2	1690.9	233.9	1481.9	481.4	1752.4	163.0
5.0	1752.4	426.2	1690.9	196.3	1529.2	404.9	1818.6	147.7
6.0	3091.7	395.6	3300.0	201.5	3300.0	359.6	4512.2	132.1

phase as alcohol solvates of medium dodecyl sulfates. As a result, the concentration of dodecyl sulfate in the aqueous phase at equilibrium is negligible. In the presence of interfering cations, the REE distribution coefficients increase by an order of magnitude and are maximum at pH ~ 6. At this value, REE in the aqueous phase are mostly found in the form of $Ln(OH)^{2+}$ monohydroxocomplexes and are extracted as solvates of the main salts of $Ln(OH)(DS)_2 \cdot nROH$. Thus, the consumption of dodecyl sulfate decreases, and the balance shifts toward extraction.

CONCLUSIONS

The extraction of europium(III) cations from aqueous solutions with and without the presence of interfering REE cations was studied. The extraction was successful at low concentrations, i.e., for concentrating components wastewater treatment.

The maximum extraction of europium(III) cations was at pH 3.0–4.5, 92%, using isooctyl alcohol as an extractant. Moreover, compared to extraction from individual solutions, the distribution coefficient of europium(III) cations significantly increased during extraction in the presence of interfering ions, and the pH of maximum extraction shifted to higher values (pH ~6).

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The authors declare no conflicts of interest.

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About the authors:

Natalia V. Dzhevaga, Cand. of Sci. (Chemistry), Associate Professor, Saint-Petersburg Mining University (2, 21 Liniya, Vasil'evskii ostrov, St. Petersburg, 199106). E-mail: dzhevaga331@mail.ru. Scopus Author ID 37060535100, ResearcherID L-6217-2016, https://orcid.org/0000-0001-5150-3415

Olga L. Lobacheva, Cand. of Sci. (Chemistry), Associated Professor, Saint-Petersburg Mining University, (2, 21 Liniya, Vasil'evskii ostrov, St. Petersburg, 199106). E-mail: Olga-59@yandex.ru. Scopus Author ID 17233818000, ResearcherID G-6008-2011, https://orcid.org/0000-0002-8383-8890

Об авторах:

Джевага Наталья Владимировна, кандидат химических наук, доцент, Санкт-Петербургский горный университет (199106, Санкт-Петербург, 21-я линия В.О., д. 2). E-mail: dzhevaga331@mail.ru. Scopus Author ID 37060535100, ResearcherID L-6217-2016, https://orcid.org/0000-0001-5150-3415

Лобачева Ольга Леонидовна, кандидат химических наук, доцент, Санкт-Петербургский горный университет (199106, Санкт-Петербург, 21-я линия В.О., д. 2). E-mail: Olga-59@yandex.ru. Scopus Author ID 17233818000, ResearcherID G-6008-2011, https://orcid.org/0000-0002-8383-8890

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ANALYTICAL METHODS IN CHEMISTRY AND CHEMICAL TECHNOLOGY

АНАЛИТИЧЕСКИЕ МЕТОДЫ В ХИМИИ И ХИМИЧЕСКОЙ ТЕХНОЛОГИИ

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RESEARCH ARTICLE

Shifts in the pK_a value of acid–base indicators caused by immobilization on solid substrates via water-soluble polycationic polymers: a case study of Congo Red

Alina O. Naumova@, Pavel V. Melnikov, Elena V. Dolganova, Nikolai A. Yashtulov, Nikolai K. Zaitsev

MIREA – Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia
@Corresponding author, e-mail: alina.naumova.92@bk.ru

Objectives. *Herein, the effects of cationic polyelectrolytes on the properties of solid substrate immobilized acid–base indicators are investigated to predict shifts in their spectral patterns and characteristics.*
Methods. *The properties of the silica gel immobilized indicator dye in a solution of the cationic polyelectrolyte were studied using automatic photometric titration in the visible region and spectrophotometry using a specialized computerized setup.*
Results. *The measured pK_a value of the immobilized dye, which had shifted by three units to the acidic region, was very similar to the pK_a value observed for the indicator in the modifying polymer solution. The observed change in pK_a of the immobilized dye and the influence of the solution's ionic strength were attributed to the local electric potential of the polymer globule. In contrast to the processes associated with covalent immobilization, the effect exerted by the solution's ionic strength on the indicator reaction diminishes, which, in turn, affects the measured values obtained.*
Conclusions. *The creation of a sensor for continuous visualization of pH levels based on Congo Red immobilized on silica gel was described. Here, a color transition was noted between pH 1 and 4. These materials can be used to monitor metal extraction processes from industrial effluents or to optimize the extraction of valuable actinides. The approach demonstrated in this work can be applied to immobilize other indicators for pH level monitoring purposes or the production of sensors for other analytes.*

Keywords: *immobilization of indicators, acid–base indicators, optical pH sensors, Congo Red, organic dyes.*

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Смещение величины р$K_а$ кислотно-основных индикаторов, вызванное иммобилизацией на твердой подложке за счет водорастворимого поликатионного полимера, на примере Конго Красного

А.О. Наумова@, П.В. Мельников, Е.В. Долганова, Н.А. Яштулов, Н.К. Зайцев

МИРЭА – Российский технологический университет (Институт тонких химических технологий имени М.В. Ломоносова), Москва, 119454 Россия
@Автор для переписки, e-mail: alina.nautova.92@bk.ru

Цели. *Целью настоящей работы было изучение влияния катионного полиэлектролита на свойства кислотно-основных индикаторов при их иммобилизации на твёрдой подложке и установление закономерностей сдвига их спектральных и кислотно-основных характеристик.*
Методы. *Свойства индикатора в растворе катионного полиэлектролита и иммобилизованного на поверхности силикагеля изучали методами автоматизированного фотометрического титрования в видимой области, спектрофотометрии и с помощью специализированного компьютеризированного стенда.*
Результаты. *Измеренное значение рK_a красителя при закреплении на силикагеле смещается на 3 единицы в кислую область и близко к значению рK_a для индикатора в растворе модифицирующего полимера. Наблюдаемое изменение величины рK_a при иммобилизации и влияние ионной силы раствора объясняются с точки зрения влияния локального электрического потенциала полимерной глобулы. В отличие от ковалентной иммобилизации, уменьшается влияние ионной силы раствора на индикаторную реакцию, и оно может быть легко учтено при измерениях.*
Выводы. *Показана принципиальная возможность создания датчика для непрерывного визуального контроля рН на основе Конго Красного, иммобилизованного на силикагеле с переходом цвета в интервале 1–4 рН. Такой материал может использоваться для контроля в процессах извлечения металлов из промышленных стоков или для оптимизации извлечения ценных актинидов. Продемонстрированный в настоящей работе подход может быть применен для иммобилизации других индикаторов, как для обеспечения измерения в других диапазонах рН, так и для создания сенсоров на другие аналиты.*

Ключевые слова: *иммобилизация индикаторов, кислотно-основные индикаторы, оптические сенсоры рН, Конго Красный, органические красители.*

Для цитирования: Наумова А.О., Мельников П.В., Долганова Е.В., Яштулов Н.А., Зайцев Н.К. Смещение величины р$K_а$ кислотно-основных индикаторов, вызванное иммобилизацией на твердой подложке за счет водорастворимого поликатионного полимера, на примере Конго Красного. *Тонкие химические технологии.* 2020;15(4):59-70. https://doi.org/10.32362/2410-6593-2020-15-4-59-70

INTRODUCTION

Acid–base indicators enable researchers to quickly and accurately control the composition of liquid or gaseous media, monitor changes related to the progress of a chemical reaction, and convert chemical information about the composition of the reaction medium into an optical signal. They are viable alternatives to electrode based indicator systems. The use of indicators in some cases may be preferable, particularly in high pressure systems or in reactions that exhibit high electrical resistivity where the use of conventional electrode systems results in unreliable readings.

Acid–base indicators usually consist of organic dyes whose molecules contain acidic or basic functional groups. Changes in the pH of the reaction environment lead to the loss or attachment of a proton by the chromophore moiety, and the proton transfer process is accompanied by observable changes in the absorption spectra (or the emission spectra in the case of luminescent systems) associated with the appearance or disappearance of certain electronic transitions in the molecule [1, 2]. These indicators are typically used as aqueous or alcohol based solutions added to the analyte sample. There are also known indicator test systems that include an indicator or a mixture of indicators adsorbed to a substrate, thereby enabling researchers to quickly determine the acid–base properties of analyte solutions [3–6]. Despite the associated benefits, there are significant drawbacks to these measurement systems, namely, the consumption of the indicator, the inability to perform continuous analysis, and the increased risk of contaminating the analyte solution. These shortcomings highlight the need to develop *in situ* reusable dye based sensors that are fixed on solid substrates [6, 7]. Such a system would avoid the issues associated with the consumption of the immobilized indicator during analysis and enable researchers to measure acidity and media composition in living cells [8]. Another potential application of these systems is for nuclear fuel reprocessing purposes, which require real-time monitoring of nitric acid concentrations to optimize the recovery of valuable uranium and plutonium actinides [9]. Furthermore, it is crucial to control the pH when extracting metals from industrial effluents [10, 11].

Although the properties of the acid–base indicator solutions have been extensively studied and documented, the immobilization may alter the observed patterns, in particular, the pK_a of a system [9, 12–14]. In light of this, the study of such regularities is invaluable. Porous microspheres [15, 16] and mesoporous membranes obtained via the sol-gel process [8, 17, 18] were previously proposed as substrates for affixing acid–base indicators as they possess a large inner surface area [16]. Unfortunately, achieving uniformed immobilization of the indicator across the entire surface of the microsphere or mesoporous materials, as well as the even penetration of the analyte [13, 19], is challenging at best. Previously, a procedure was developed to manufacture composite sensors for quantifying molecular oxygen via high-temperature phosphorescence quenching mechanisms [20]. The material consisted of mesoporous microparticles with an indicator affixed in a polymer matrix as a continuous, uniform coating. The success of that experiment prompted us to employ a similar approach to the creation of acid–base indicator systems.

In this paper, the immobilization of the Congo Red indicator in a composite matrix is studied with a particular focus on creating a flow sensor capable of monitoring the composition of the aqueous solutions. The proposed sensor would take the form of a fiber optic probe [14]. The effects of the solution's ionic strength on the pK_a value of unbound and immobilized indicators, as well as the influence exerted on the indicator in a solution of cationic polyelectrolytes used for the sorption of the indicator, were studied.

MATERIALS AND METHODS

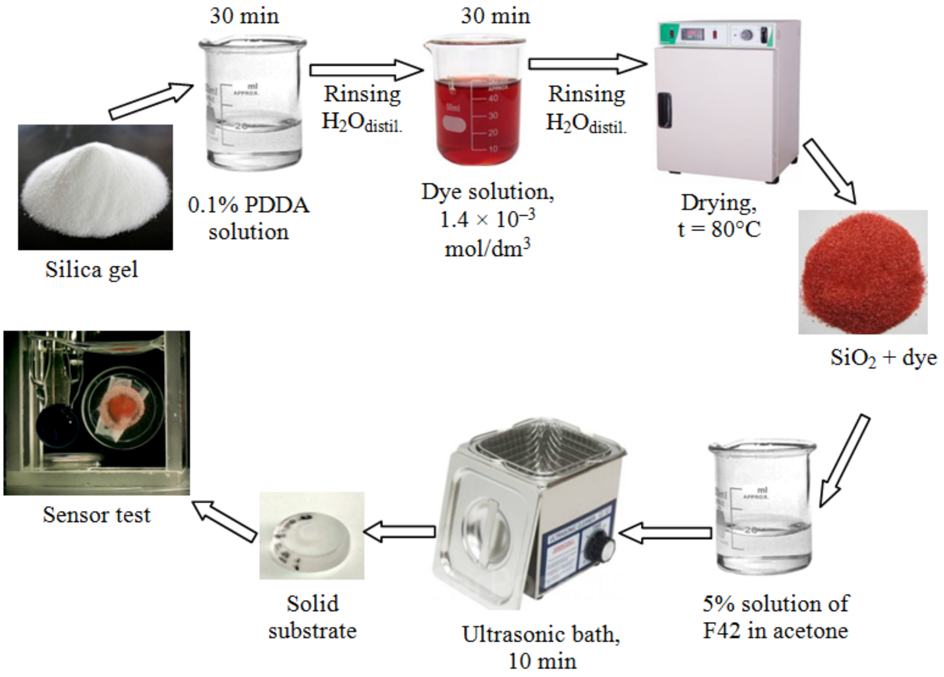
Reagents

The 4,4'-bis-(1-amino-4-sulfo-2-naphthylazo) biphenyl indicator commonly referred to as Congo Red (*LenReaktiv*, Saint Petersburg, Russia) and silica gel LS 5/40 (GOST 8984-75, *NevaReaktiv*, Saint Petersburg, Russia) were used. A solution of polydiallyldimethylammonium chloride (PDDA) with a concentration of 0.1% was obtained by diluting the initial 20% solution (*Sigma–Aldrich*, USA) with distilled water (GOST 6709-72). Fluoroplast 42 (F42, *GaloPolymer*, Moscow, Russia) was used to affix the colored silica gel particles onto the substrate. The ionic strength of the solutions was regulated using sodium chloride and potassium chloride (*LenReaktiv*, Saint Petersburg, Russia). The necessary salt solutions at the required concentrations were prepared from the initial dry reagents via a volumetric method. The appropriate acid solutions were prepared by successive dilutions of the initial solution that had been prepared from the primary standard (*Uralkhiminvest*, Ufa, Russia). All reagents were classified as "pure" or "p.a.", and were used without additional purification. All experiments were performed at a temperature of 25 ± 2°C.

The immobilization of the indicator

The immobilization of Congo Red on the SiO_2 surface using cationic polyelectrolyte was performed according to Scheme 1.

The silica gel was kept in the 0.1% PDDA solution for 30 min with periodic stirring. Next, the sample was washed repeatedly (at least 10 times) with distilled water to remove remnants of any non-adsorbed polymers before being kept for 30 min in a solution containing the indicator at a concentration of C_{CR} at 1.4×10^{-3} mol/dm^3, which had been prepared by dissolving Congo Red (0.1 g) in 100 cm^3 of distilled water. The colored silica gel was repeatedly washed with distilled water, and the completeness of processing was controlled by measuring the optical density of the wash water. Washing was considered completed when an optical density $A \leq 0.001$ was reached. Next, the silica gel was dried at $T = 80°C$ until constant weight readings were obtained. The resulting bright red powder was mixed with a 5% solution of fluoroplast 42 in acetone before being placed in an



Scheme 1. Immobilization of Congo Red on the SiO_2 surface using cationic polyelectrolytes.

ultrasonic bath for 10 min. The mixed product was then applied to substrates such as sandblasted glass or polyethylene terephthalate films using a knife coating device with a gap of 300 μm.

Conducting measurements

Determining the pK_a of the free indicators, i.e., the indicators that had not been immobilized using the above mentioned method, in aqueous solutions containing PDDA was conducted using the Titrion automatic titrator (*Econics-Expert*, Moscow, Russia) equipped with an Expert-001 pH meter combined with an ESK-10601/7 electrode (*Izmeritelnaya Tekhnika*, Moscow. Russia) and an Expert-003 photometer with a photometric cell (*Econics-Expert*, Moscow, Russia). Hydrochloric acid of various concentrations (i.e., from 1×10^{-3} to 2 mol/dm^3) was used as the titrant, and the dye concentration was 7×10^{-6} mol/dm^3. The spectral data of the solutions were measured using the small scale DT-MINI-2-GS combined spectrophotometer (*Ocean Optics*, Rochester, NY, USA). The pK_a value of the immobilized indicator was determined using the setup shown below (Fig. 1).

The color changes noted in the sample were recorded as digital micrographs using an eScope Pro DP-M17 USB microscope (*OiTEZ*, Shatin, New Territories, Hong Kong). The pH value corresponding to a given color range was determined using the Expert-001 pH meter. Data processing was conducted using in house software. The acidity of the medium was adjusted by adding the previously mentioned hydrochloric acid of various concentrations (from 1×10^{-3} to 2 mol/dm^3). Data was automatically acquired after the stabilization of pH meter readings.

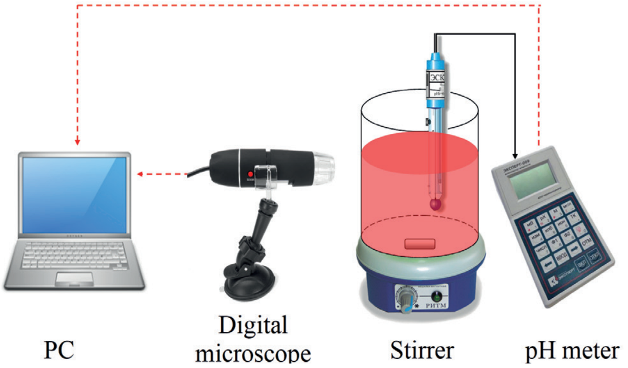
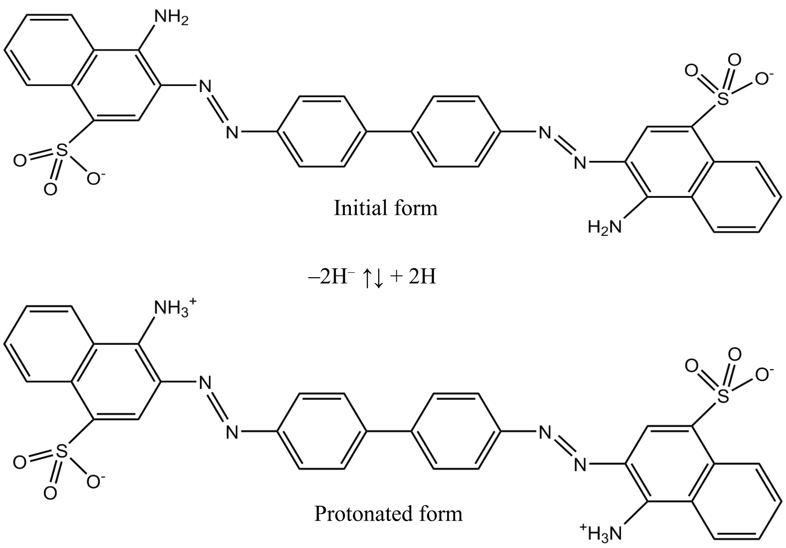


Fig. 1. Setup for determining the pK_a of the immobilized Congo Red indicator.

Generally, each pixel of a digital image represents a set of three basic colors: red, green, and blue. Since the indicator used in this study exhibited a red to blue transition in an increasingly acidic environment, the analytical signal obtained was represented as a ratio of the intensity of the red and blue color channels. Moreover, this assessment was conducted for each pixel of the image independently, making it possible to quantify local changes in pH.

RESULTS AND DISCUSSION

The mechanism governing the indicator’s reaction and the observed color changes is described in Scheme 2 [21].

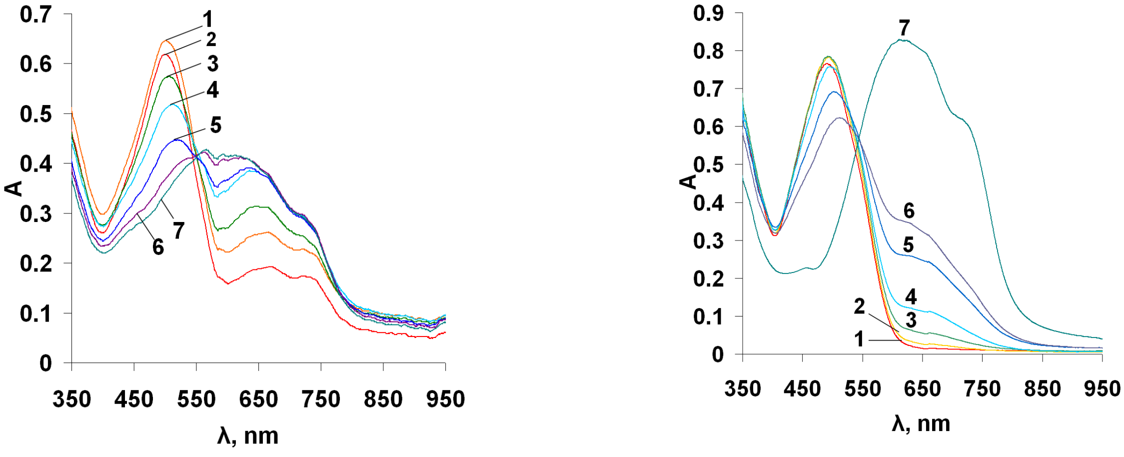


Scheme 2. The mechanism governing the indicator's reaction and the observed color changes.

The formation of an indicator–polyelectrolyte surface salt was the driving force behind the immobilization process. The Congo Red indicator molecule contains negatively charged sulfo groups that, in the presence of the polycationic polymer PDDA, resulted in effective adsorption and immobilization onto the surface of the glass substrate.

It was clear that the polyelectrolyte significantly influenced the optical properties of the indicator. Here, we noted that the optical density (A) at a particular wavelength (λ) was heavily influenced by the pH of the aqueous solution. This was exemplified in the differences observed between the spectral data obtained without and with PDDA (Figs. 2a and 2b, respectively).

In Figure 3, the maxima of the absorption peaks of the protonated (seen in blue, absorption band λ_{max} = 650 nm) and the initial (seen in red, λ_{max} = 505 nm) forms of the indicator did not shift. However, the ratio of the peak intensities of the two forms changed significantly in the presence of PDDA. The maxima of the peaks of both forms of the free indicator are changed in almost equivalent proportions, with a clearly defined isosbestic point. The intensity of the blue band (I_{blue}) in the presence of PDDA was much lower, with no clearly defined boundary between the peaks. The I_{red}/I_{blue} ratio exhibited a sigmoidal relationship with the pH of the medium (Fig. 3), and the pK_a value of the color transition was easily identified via the inflection point [22]. If the ultimate ratio of I_{red}/I_{blue} maxima for the free indicator did not exceed 3.5, then the ultimate ratio of I_{red}/I_{blue} maxima increased by almost an order of magnitude to 29 units in the presence of the polycationic polymer. In the



a

b

Fig. 2. The absorption spectrum of aqueous Congo Red solutions: (a) without polydiallyldimethylammonium chloride (PDDA) (C_{CR} = 1.4 × 10^{-5} mol/dm^3) at pH = (1) 5.55, (2) 5.01, (3) 4.52, (4) 4.23, (5) 4.09, (6) 3.87, and (7) 3.70; (b) in the presence of 0.01% PDDA solution (C_{CR} = 2.8 × 10^{-5} mol/dm^3) at pH = (1) 7.00, (2) 2.48, (3) 1.78, (4) 1.57, (5) 1.44, (6) 0.48, and (7) 0.18.

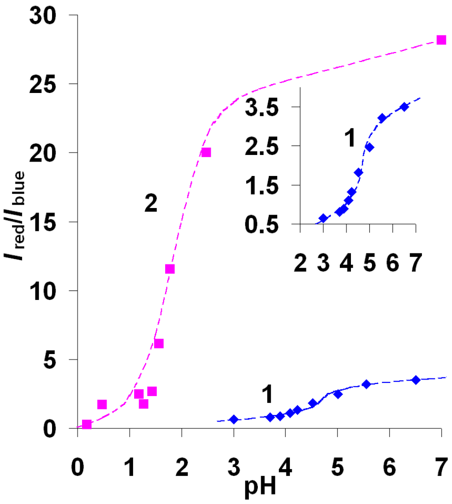


Fig. 3. Variations in the absorption intensity ratios (I_{red}/I_{blue}) of the red and blue forms of the indicator in aqueous solution based on the pH of the medium (1) without PDDA ($C_{CR} = 1.4 \times 10^{-5}$ mol/dm^3) and (2) in the presence of 0.01% PDDA solution ($C_{CR} = 2.8 \times 10^{-5}$ mol/dm^3).

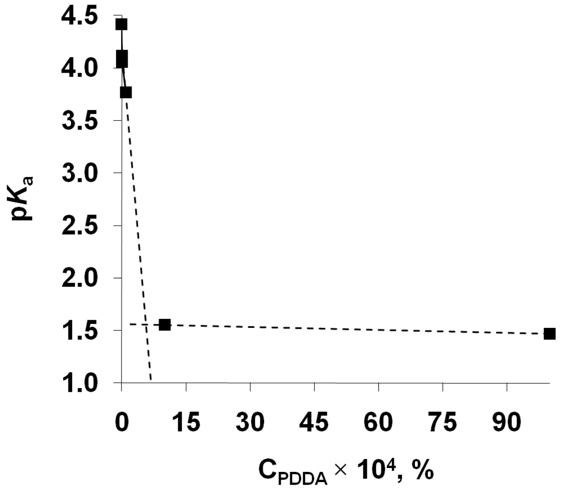


Fig. 4. The influence exerted on the pK_a value by the concentration of PDDA (%) ($C_{CR} = 7 \times 10^{-6}$ mol/dm^3).

latter case, the transition range shifted by 3 units to a more acidic region.

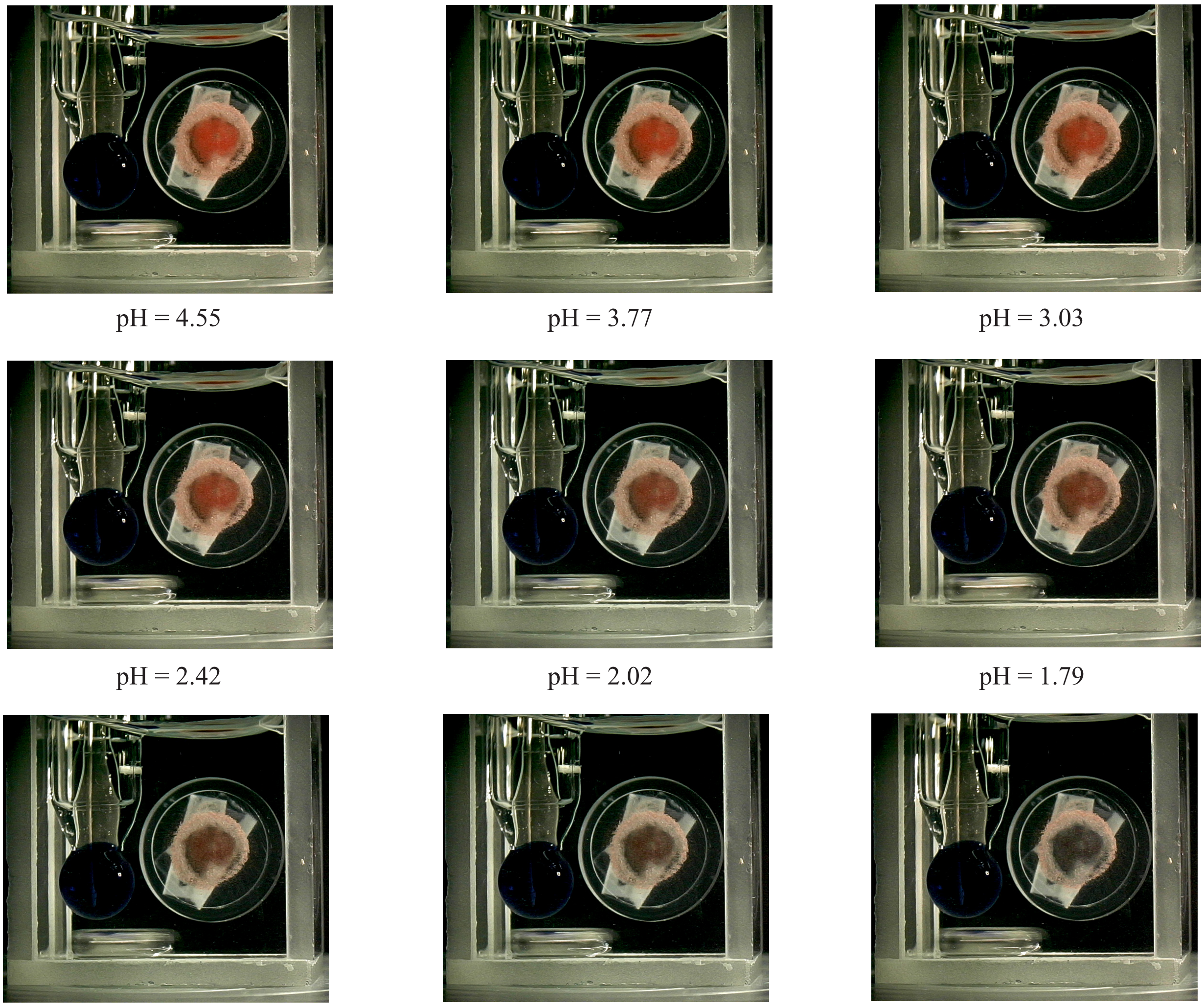
This drastic change in the pK_a value and the spectra obtained was attributed to significant shifts in the reaction equilibrium to the left due to the formation of a positively charged polymer globule around the indicator. This was exemplified by the almost complete absence of the third component (λ_{max} = 733 nm) in the spectrum that corresponded to the cationic form of the dye; this component was revealed in strongly acidic solutions [23]. In the presence of PDDA, traces of this component were visible only in extremely acidic environments at pH ~ 0 (Fig. 2b).

The pK_a values at various PDDA : indicator ratios were determined to assess the effect exerted by the polymer on dye solubilization. Here, we noted that the pK_a value decreased slightly after the addition of small amounts of PDDA. When the polymer content of the solution was 0.001 wt % or higher, the pK_a value shifted to the acidic region and equilibrium was achieved when the value was ~1.5 (Fig. 4); this observation indicated that all active sites on the polymer were occupied by the indicator. The molar ratio, which is indicated as the intersection of linear sections in Fig. 4, shows that the ratio of the structural units of the interacting charged molecules was 1 : 10 when a significant positively charged field was formed by polyelectrolyte; the latter leads to difficulties in the protonation of bound indicator molecules.

Measuring the pK_a of the solid substrate immobilized indicator is demonstrated herein. Photos of the sample at various pH values are shown in Fig. 5. In the current study, we affixed silica gel in a polymer matrix per a previously reported method [20]. Quartz fibers or glass microspheres can also be used as the carrier.

When the pH of the medium decreased, the color transition of the sample was from red to navy blue, which was a transition similar to that observed in the dye solution. The titration curves obtained after digital image processing showed the relationship between the signal intensity (represented in arbitrary units) and the pH of the medium (Fig. 6). A typical S-shaped curve was noted, which allowed us to determine the pK_a of the transition of the immobilized indicator using the inflection point [22]. The curves were reproducible during repeated titration of the sample due to the reusability of the dye; this was because the original form of the dye was firmly bound by PDDA, whereas the protonated neutral form of the dye was insoluble [23], thereby making our dye system ideal for application as a continuous optical pH sensor.

Despite numerous studies on pH sensors with low sensitivity to ionic forces [24, 25], understanding the influence exerted by the ions in the reaction medium is paramount to accurately predicting shifts in the pK_a of the indicator. A comparative study was conducted on the effect of the ionic strength of a solution on the pK_a value in an aqueous solution of the indicator, in a solution of the indicator with the addition of PDDA, and for the indicator that is immobilized on silica gel to understand how the color transition of the indicator is shifted when analyzing various natural objects, predict future color shifts, and to assess incidences of possible distortion in the readings of the sensor with the immobilized dye.



pH = 4.55 pH = 3.77 pH = 3.03

pH = 2.42 pH = 2.02 pH = 1.79

pH = 1.48 pH = 1.21 pH = 0.80

Fig. 5. Color changes in the silica gel-immobilized Congo Red indicator as a result of pH changes.

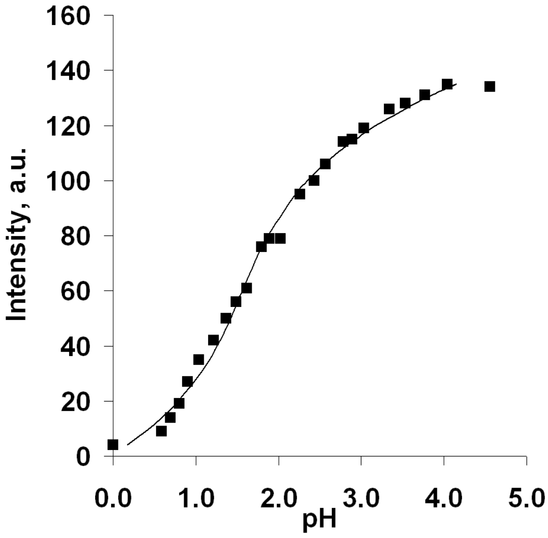


Fig. 6. Titration curve of Congo Red immobilized on silica gel.

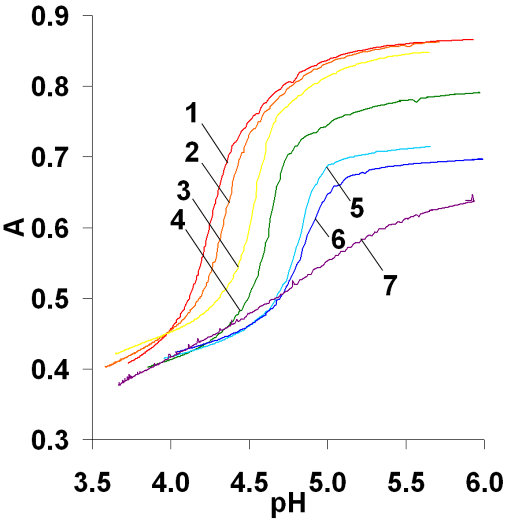


Fig. 7. Titration curves of the indicator solutions ($C_{CR} = 7 \times 10^{-6}$ mol/dm^3) at various ionic strengths, as measured in mol/dm^3, at (1) 0, (2) 0.001, (3) 0.005, (4) 0.01, (5) 0.05, (6) 0.1, and (7) 0.5.

Changes in the shape of the titration curve obtained for the indicator solution as a function of the solution's ionic strength are shown in Fig. 7. Here, we noted that in the absence of other electrolytes, the Congo Red solution underwent a color transition between pH 3.0 and 5.2, with a pK_a value of 4.3. Even though these findings were consistent with published reports [26], the shape of the titration curve changed significantly when the ionic strength of the solution increased. The associated S-shape became less pronounced at high ionic strength values, and the overall color intensity of the solution also decreased. The inflection point corresponding to the observed equilibrium constant (pK) shifted toward a higher pH (Fig. 8a).

As a result of the symmetry of the indicator molecule, its protonation can be schematically depicted as [21, 23]:

$$B^{2-} + 2H^{+} \leftrightarrow H_2B$$

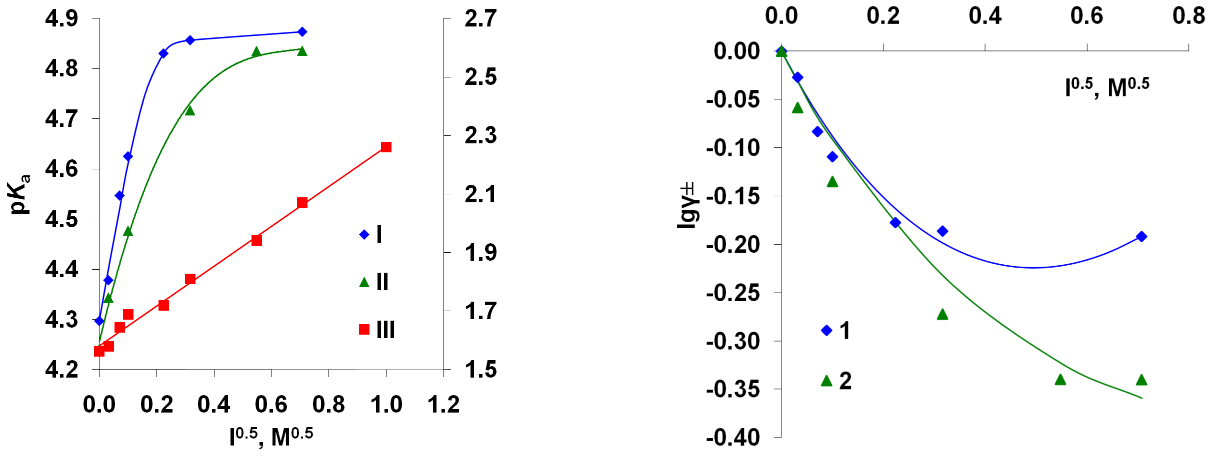
The expression for the equilibrium constant of this reaction is written as:

$$K = \frac{[H_2B]}{[B^{2-}][H^{+}]^2}$$

From the figure, it was clear that an increase in the ionic strength resulted in a decrease in the mean ionic activity coefficient ($\gamma_{\pm}$), leading to an increase in the observed constant $K_{obs} = K \times K_{\gamma}$. The calculated values for lg$\gamma_{\pm}$, which is well define by the Debye-Hückel equation, was noted as $z_1 = 2$, $z_2 = 1$, A = 0.509, B = 1, and C = 0.46 for the respective parameters (Fig. 8b). However, the addition of the polycationic polymer to the solution caused a significant deviation from the theoretical curve. A linear relationship between the shift in the pK value of the substrate immobilized indicator and the square root of the solution's ionic strength was observed even at high salt concentrations (Fig. 8a). This observation was indicative of competition between the anions of the added polyelectrolyte and the Congo Red molecules for active PDDA adsorption sites [27], which, in turn, led to the partial compensation of the polymer globule's positive charge and facilitated the protonation of the dye molecule. In contrast to the results noted for covalently immobilized dyes [28], the influence of the ionic strength of the solution on the color transition of the indicator decreased.

CONCLUSIONS

Herein, the Congo Red indicator was immobilized on a silica gel pre-treated with a cationic polyelectrolyte, PDDA. We noted that the immobilized dye retained its ability to exhibit color transitions based on the prevailing acid–base environment. A significant shift in the pK value of three pH units to a more acidic region was observed



a

b

Fig. 8. (a) The relationship between the pK_a value of the Congo Red indicator and the ionic strength of (I) the aqueous solution of the indicator ($C_{CR} = 7 \times 10^{-6}$ mol/dm^3), (II) the combined 0.01% PDDA–indicator solution ($C_{CR} = 7 \times 10^{-6}$ mol/dm^3), and (III) the solid substrate immobilized indicator. (b) The mean activity coefficient ($\gamma_{\pm}$) of the ionic strength (1) without PDDA and (2) in 0.01% PDDA solution.

in the immobilized indicator due to the influence of the local polyelectrolyte's potential. Given these findings, it was clear that a sensor based on silica gel immobilized Congo Red dye could be produced for continuous visual pH monitoring via an obvious color transition between pH 1 and 4. This sensor system could prove useful during the metal extraction process conducted on industrial effluents or the optimization of the extraction of valuable actinides. The observed reduced effect of the prevailing salt environment must be taken into account since the relationship observed between the pK and the ionic strength of the solution is linear. The method and theories discussed in this paper can also be applied for other immobilized indicators, as a means of expanding the range and applications of these types of sensors.

Acknowledgments

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The authors declare no conflicts of interest.

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About the authors:

Alina O. Naumova, Postgraduate Student, Department of Energy Technologies, Systems and Installations, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: alina.naumova.92@bk.ru. Scopus Author ID 57191089401, https://orcid.org/0000-0001-8021-4591

Pavel V. Melnikov, Cand. of Sci. (Physics and Mathematics), Assistant Professor, Department of Physical Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: melnikovsoft@mail.ru. Scopus Author ID 18042368100, ResearcherID D-9773-2014, https://orcid.org/0000-0001-8438-1952

Elena V. Dolganova, Engineer, Department of Energy Technologies, Systems and Installations, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: elcorplus@mail.ru. https://orcid.org/0000-0001-5196-5919

Nikolai A. Yashtulov, Dr. of Sci. (Chemistry), Professor, Department of Energy Technologies, Systems and Installations, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: yashtulovna@mail.ru. Scopus Author ID 6507694451, https://orcid.org/0000-0002-7709-4186

Nikolai K. Zaitsev, Dr. of Sci. (Chemistry), Professor, Head of Department of Energy Technologies, Systems and Installations, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow 119571, Russia). E-mail: nk_zaytsev@mail.ru. Scopus Author ID 57193485921, https://orcid.org/0000-0003-4132-0097

Об авторах:

Наумова Алина Олеговна, аспирантка кафедры энергетических технологий, систем и установок Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО МИРЭА – Российский технологический университет (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: alina.naumova.92@bk.ru. Scopus Author ID 57191089401, https://orcid.org/0000-0001-8021-4591

Мельников Павел Валентинович, кандидат физико-математических наук, доцент кафедры физической химии им. Я.К. Сыркина Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО МИРЭА – Российский Технологический Университет (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: melnikovsoft@mail.ru. Scopus Author ID 18042368100, ResearcherID D-9773-2014, https://orcid.org/0000-0001-8438-1952

Долганова Елена Вячеславовна, инженер кафедры энергетических технологий, систем и установок Института тонких химических технологий им. М.В. Ломоносова ФГБОУ ВО МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: elcorplus@mail.ru. https://orcid.org/0000-0001-5196-5919

Яштулов Николай Андреевич, доктор химических наук, профессор кафедры энергетических технологий, систем и установок Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО МИРЭА – Российский технологический университет (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: yashtulovna@mail.ru. Scopus Author ID 6507694451, https://orcid.org/0000-0002-7709-4186

Зайцев Николай Конкордиевич, доктор химических наук, профессор, заведующий кафедрой энергетических технологий, систем и установок Института тонких химических технологий имени М.В. Ломоносова ФГБОУ ВО МИРЭА – Российский технологический университет (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: nk_zaytsev@mail.ru. Scopus Author ID 57193485921, https://orcid.org/0000-0003-4132-0097

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PAGES OF HISTORY

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HISTORY PAGES

Dedicated to the 90th anniversary of Ivanovo State University of Chemistry and Technology

Scientific activity of Ya.K. Syrkin at the Faculty of Chemistry of the Ivanovo-Voznesensk Polytechnic Institute and in the Ivanovo Institute of Chemistry and Technology (1918–1932)

Alyona S. Malyasova[1,@], Oskar I. Koifman[1,2]

[1]*Ivanovo State University of Chemistry and Technology, Ivanovo, 153000 Russia*
[2]*G.A. Krestov Institute of Solution Chemistry, Russian Academy of Sciences, Ivanovo, 153045 Russia*
[@]*Corresponding author, e-mail: bubnalla@yandex.ru*

Objectives. *Preserving the continuity of scientific schools and increasing scientific motivation is critical for educating new generations of researchers. One way to solve this problem is to promote the historically significant achievements of outstanding scientists working in the field, without which the foundations of modern chemical technologies cannot be imagined. The field of physical chemistry benefited immensely from the contributions made by Professor Yakov Kivovich Syrkin. This article is devoted to the analysis of the growth of Ya.K. Syrkin as a scientist and discusses his main scientific contributions to physical and quantum chemistry.*
Methods. *The article was prepared using archival materials, bibliographic references, original texts of articles, and scientific reports.*
Results. *The article details and documents the main scientific achievements of Ya.K. Syrkin during his work at the Ivanovo-Voznesensk Polytechnic Institute and the Ivanovo Institute of Chemistry and Technology between 1918 and 1932, showing his growth and development as a young scientist through his interactions with teachers and colleagues. Syrkin's research on chemical equilibrium, reaction kinetics, thermodynamics, catalysis, solution theory, solvate effects, and colloidal systems are presented herein.*
Conclusions. *A retrospective analysis of the career of Ya.K. Syrkin shows the scope of his research interests and his ability to build on the foundations provided by great predecessors such as Gibbs, Van't Hoff, Arrhenius, Ostwald, and Nernst. A comprehensive study of fundamental and applied aspects of physical chemistry guided Syrkin's approach to understanding the importance of molecular structure and the nature of chemical bonds in all observed chemical phenomena.*

Keywords: *physical chemistry, equilibrium of heterogeneous systems, chemical kinetics, catalysis, solutions, colloidal systems, separation of liquefied gases, fabric dyeing.*

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ИСТОРИЧЕСКИЙ ОЧЕРК

90-летию Ивановского государственного
химико-технологического университета посвящается

Научная деятельность Я.К. Сыркина на химическом факультете Иваново-Вознесенского политехнического института и в Ивановском химико-технологическом институте (1918–1932 гг.)

А.С. Малясова[1,@], О.И. Койфман[1,2]

[1]*Ивановский государственный химико-технологический университет, Иваново, 153000 Россия*
[2]*Институт химии растворов им. Г.А. Крестова Российской академии наук, Иваново, 153045 Россия*
[@]*Автор для переписки, e-mail: bubnalla@yandex.ru*

Цель. *Сохранение преемственности научных школ, повышение мотивации к научному поиску является актуальной задачей воспитания новых поколений исследователей. Одним из путей решения этой задачи является пропаганда исторически значимых достижений выдающихся ученых, работающих в области, без которой не мыслится развитие фундаментальных основ тонких химических технологий. Такой областью являлась и является сейчас физическая химия, в развитие которой огромный вклад внес профессор Яков Кивович Сыркин. Настоящее исследование посвящено анализу становления Я.К. Сыркина как ученого и обсуждению его основных научных результатов, имеющих принципиальное значение для развития физической и квантовой химии.*

Методы. *При подготовке статьи использованы архивные материалы, библиографические справки, оригинальные тексты статей и научных отчетов.*

Результаты. *В статье подробно рассмотрены и документально подтверждены основные научные достижения Я.К. Сыркина в период его работы на химическом факультете Иваново-Вознесенского политехнического института и в Ивановском химико-технологическом институте (1918–1932 гг.), показано становление молодого ученого, его взаимодействие с учителями и коллегами. Представлены результаты исследований химического равновесия; химической кинетики; установления связи между кинетикой и термодинамикой; катализа; теории растворов; сольватных эффектов; коллоидных систем и др.*

Выводы. *Ретроспективный анализ деятельности Я.К. Сыркина показывает его становление, широту интересов, умение связать, творчески оценить и развить фундаментальные достижения великих предшественников – Гиббса, Вант-Гоффа, Аррениуса, Оствальда, Нернста и других. Разностороннее исследование фундаментальных и прикладных аспектов физической химии привело Я.К. Сыркина к пониманию ключевой роли строения молекул и природы химической связи во всех наблюдаемых химических явлениях.*

Ключевые слова: *физическая химия, равновесие гетерогенных систем, химическая кинетика, катализ, растворы, коллоидные системы, разделение сжиженных газов, крашение тканей.*

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Yakov Kivovich Syrkin was an academician of the USSR Academy of Sciences and a graduate of the Ivanovo-Voznesensk Polytechnic Institute (IVPI), which was the first technical university established in Soviet Russia, from which he graduated in September 1919 with the Diploma No. 1. After receiving a higher education diploma, Ya.K. Syrkin became a Junior Assistant at the Department of General Chemistry. In October 1918, he applied to the rector Mikhail Nikolaevich Berlov with a request for employment at the Laboratory of Inorganic Chemistry at IVPI. The institute's management considered it necessary to attract capable students as employees of the analytical laboratory, particularly one who was as motivated and technically talented as Syrkin. The details surrounding Syrkin's time as a teacher are described in the bibliographic index [1] published for the 120th anniversary of his birth in the series entitled "Golden Fund of Chemtech."

The current publication aims to explore the early scientific activities of this academician and gain insight into the multifaceted scientific interests that enabled him to take advantage of golden opportunities in his field. Syrkin's first steps into science began in the laboratory of Petr Petrovich Budnikov[1] in which their first joint project [2] was on optimizing the conditions for gypsum setting. In this project, Syrkin and Budnikov determined the factors that influenced the rate of high temperature gypsum setting (i.e., above 400°C) in calcium sulfate semi hydrates ($CaSO_4 \cdot ½H_2O$), dihydrates ($CaSO_4 \cdot 2H_2O$), and anhydrous $CaSO_4$ (soluble and insoluble). Here, the features of a previously unreported hydrate were discussed, and the transition points between the various hydrates were established. The researchers were able to slow high temperature gypsum setting by adjusting the growth of insoluble modification, mechanical grinding, and the process of hydration of the insoluble anhydride itself.

Published in 1923, the group's work [3] on the dissociation of $CaSO_4$ would later be used to establish the chemical and physical characteristics of estrichgypsa, a type of gypsum formed when $CaSO_4$ was calcined above 800°C. Several allotropic modifications (i.e., the soluble and insoluble anhydrides) were observed at temperatures as high as 800°C, whereas changes in gypsum's chemical formula were not observed. Further temperature increases led to the formation of CaO- and $CaSO_4$-containing compounds. The purpose of this work was to determine the impact of temperature on the composition of the resulting gypsum.

Syrkin and Budnikov's research on castelromano potash [4, 5] focused on optimizing the reaction between K_2CO_3 and $Ca(OH)_2$ by determining the optimal temperature and reactant concentrations that were required for maximum product yield. Other aspects of their research included determining the route of synthesis and the conditions under which stable double salts were formed in this process. Here the duo also showed that $Ca(OH)_2$ could be replaced with other caustic agents such as $Sr(OH)_2$ and $Ba(OH)_2$.

In March 1921, Syrkin's first publication as a sole author, entitled "On the question of equilibrium in a heterogeneous system" [6], was sent to the Editorial Office of the *Izvestiya of Ivanovo-Voznesensk Polytechnic Institute*. Based on this work, an Associate Professor of the Department of Analytical Chemistry at IVPI named I.G. Zacks suggested that the then 27-year-old Syrkin, who had become the senior assistant of the Department of General Chemistry of IVPI, should focus on optimizing the reaction between $CaSO_4$ and Na_2CO_3 as this research was pivotal to water treatment processes. Here, Syrkin proved that the reversibility of the aforementioned reaction depended on the concentration of various reagents, and at a low temperature, with dilution of solutions the reversibility increased.

In January 1921, Syrkin presented a scientific report entitled "Kinetic theory and reality of a molecule" at the *Chemical Colloquium of the IPVI Chemical Faculty*, which clearly showed the direction of Syrkin's research interest in reaction kinetics and molecular structure. Between 1921 and 1931, Syrkin was employed at the Ivanovo-Voznesensk Polytechnic Institute (IVPI) and the Ivanovo Institute of Chemistry and Technology (IICT). Here, his research interests included structural elucidation and solvation of molecules, the separation of liquefied gases, and the optimization of fabric dyeing processes as well as the kinetics governing catalysis and gypsum-based reactions.

Syrkin's "On the theory of solvates" article, which was published in the *Izvestiya of Ivanovo-Voznesensk Polytechnic Institute* in 1922 [7], explored

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[1] 

Petr Petrovich Budnikov (1885–1968) was a professor at the Ivanovo-Voznesensk Polytechnic Institute (IVPI) from 1918 to 1926. During this period, he served as the Head of the Department of Mineral Raw Materials of IVPI, and later as the Corresponding Member of the USSR Academy of Sciences and an academician of the Academy of Sciences of the Ukrainian SSR. He was a Doctor of Technical Sciences and held a professorship in the Department for General Technology of Silicates at the prestigious D.I. Mendeleev Moscow Institute of Chemical Technology from 1944 to 1968. Budnikov was awarded three Stalin prizes (in 1942, 1950, and 1952, in addition to ten orders and medals of the USSR. In 1965, he was awarded the title of Hero of Socialist Labor as an honored worker in Science and Technology of the USSR (1943) and the RSFSR (1964).

His research interests included the creation and characterization of anhydrite, alite, and sulfated slag cement binders, chromite–dolomite and corundum–carborundum refractory composites and the development of improved insulation materials and ceramics with special focus on the synthesis and characterization of oxide based refractory materials that possessed melting points above 2000°C. Professor Budnikov also developed state diagrams of composite Li_2O–GeO_2, Al_2O_3–SiO_2, Al_2O_3–SiO_2–ZrO_2, BeO–UO_2, MgO–UO_2, and Sm_2O_3–Al_2O_3 systems in which the physical, chemical, and thermodynamic properties, as well as the kinetic features of transformations in these systems, and the mechanisms governing sintering and recrystallization of their respective solid phases were detailed.

fundamental concepts about solvation and the chemical purity of substances, elements, or hydrate compositions that are still relevant today. This article was groundbreaking as chemists at the time were struggling to precisely define the characteristics and properties of a mixture and a chemical compound. At this time, there was no clear consensus on the applicable science to explain these definitions or account for the recorded observations of these substances in the presence of external stimuli. Should these compounds be defined from a chemical point of view, or are the laws of physics more applicable for explaining the associated phenomena? In this article, Syrkin wrote:

> "*In the field of solvates, the same chemical and physical methods are not applicable. In solvates we have, so to speak, semi-physical, semi-chemical systems*."

Although scientists at the time were aware of the interactions between a solvent and a dissolved substance, many failed to precisely define this interaction and could not understand, let alone account for, the possible mechanisms governing this phenomenon. When asked to explain, Syrkin stated:

> "*It seems to me that purely chemical methods, in the classical sense of the word, do not give precise and definite answers to the questions posed by the fact of solvation.*"

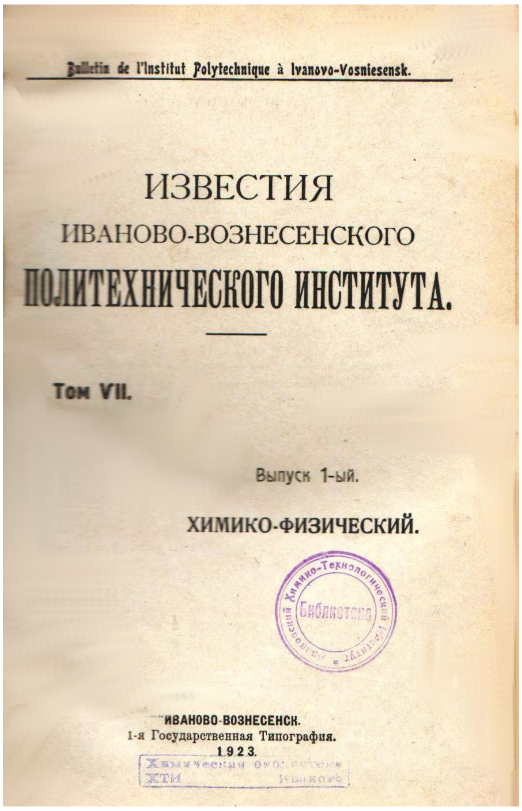
Syrkin realized that the key to answering many of these troubling questions lies in accepting the concept that compounds are capable of existing in various compositions, namely, as solvates in general and hydrates in particular. According to Syrkin, one of the main indicators of hydration was the observed change in internal pressure and the influence of internal forces that governed chemical affinity. The hydrates themselves simply represented a shell of water molecules surrounding the molecules of the dissolved substance.

It is symbolic that this article on the theory of solvates subsequently defined the scientific direction of IICT, which is still in place today. Indeed, this article laid the ground stone in creating the Department of Non-Aqueous Solutions Chemistry of the Academy of Sciences of the Soviet Union in 1980. In 1981, the department was restructured and rebranded as the Institute of Chemistry of Non-Aqueous Solutions of the Academy of Sciences of the Soviet Union (now known as the G.A. Krestov Institute of Chemistry of Solutions of the RAS). Initially, this group's main task was to study the structure of solutions and their applicability in tissue processing technology. The founding fathers of the institute were all winners of the USSR State Prize in Science and Technology (1987), namely, the Corresponding Member of the USSR Academy of Sciences G.A. Krestov, Professor B.D. Berezin, and Professor B.N. Melnikov. These scientists are renowned for their series entitled "Development of theoretical foundations of chemistry of non-aqueous solutions and their practical use," which was published between 1962 and 1985.

In 1923, the *Izvestiya of Ivanovo-Voznesensk Polytechnic Institute* published an article on the topic "Kinetic justification of chemical affinity" [8] (Figs. 1 and 2), in which an attempt was made to quantitatively describe the expression for chemical affinity. In his arguments, Syrkin critically discussed the three most important principles in the concept of chemical affinity, namely, the Berthelot principle, the theory of Guldberg and Voge, and the Nernst theorem. In his groundbreaking equation, the young scientist combined the concepts of chemical statics and kinetics:

$$K = \frac{4}{9r} \frac{\sqrt{4.5\pi R}^{\sigma^{n-1}}}{n_1!n_2} N_0^{n-1} \sqrt{\frac{\frac{n_1}{M_1} + \frac{n_2}{M_2}}{n_1 + n_2}} \sqrt{T} e^{-\frac{q}{RT}} \tag{1}$$

where K is the equilibrium constant of a chemical reaction, r is the radius of the whole sphere, R is the gas constant, n is the stoichiometric coefficient



Bulletin de l'Institut Polytechnique à Ivanovo-Vosniesensk.

ИЗВЕСТИЯ
ИВАНОВО-ВОЗНЕСЕНСКОГО
ПОЛИТЕХНИЧЕСКОГО ИНСТИТУТА.

Том VII.

Выпуск 1-ый.

ХИМИКО-ФИЗИЧЕСКИЙ.

Ивановский Химико-Технологический Институт
Библиотека

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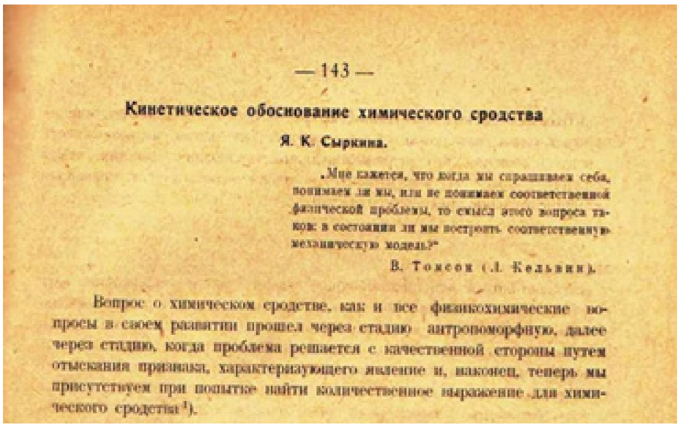
Химическая библиотека
ХТИ Иваново

Fig. 1. Title page of the *Izvestiya of Ivanovo-Voznesensk Polytechnic Institute*.



— 143 —

Кинетическое обоснование химического сродства

Я. К. Сыркина.

„Мне кажется, что когда мы спрашиваем себя, понимаем ли мы, или не понимаем соответственной физической проблемы, то смысл этого вопроса таков: в состоянии ли мы построить соответственную механическую модель?"

В. Томсон (Л. Кельвин).

Вопрос о химическом сродстве, как и все физикохимические вопросы в своем развитии прошел через стадию антропоморфную, далее через стадию, когда проблема решается с качественной стороны путем отыскания признака, характеризующего явление и, наконец, теперь мы присутствуем при попытке найти количественное выражение для химического сродства[1]).

Fig. 2. Ya.K. Syrkin's article entitled "Kinetic justification of chemical affinity."

(i.e., the number of moles), σ is the volume of the reaction sphere gas, N_0 is the Avogadro number, M is the molecular weight of the gas, T is the temperature, and q is the energy of a single molecule. In describing his equation, Syrkin emphasized that:

> "*[the equation] expressed the entire chemical dynamics in the general form for processes of any order.*"

Although Equation (1) appears difficult to understand at first glance, its simplified form (2) can be obtained if we assumed that each individual process in the first part of the equation could be represented by a constant. By denoting this value with the letter ***A***, we obtain:

$$K = A\sqrt{T}e^{-\frac{q}{RT}} \qquad (2)$$

In [9], expressions are given for determining the absolute entropy (3) and the chemical constant of a gas (4), which do not depend on the degree of freedom for a particular gas:

$$S_n = kN\lg\frac{(2\pi mkT)^{\frac{n}{2}} a^{n-3} Ve^{1+\frac{n}{2}}}{Nh^n} \qquad (3)$$

$$C^n = \lg\frac{(2\pi m)^{\frac{n}{2}} k^{1+\frac{n}{2}} a^{n-3}}{h^n} \qquad (4)$$

where k is Boltzmann's constant, N is the Avogadro number, m is the mass of the molecule, T is the absolute temperature, a is the diameter of the atom, V is the volume, h is Planck's constant, and n is the degree of freedom.

The key advantages of the provisions expressed by Syrkin in this revolutionary article can be seen in the definitions of the absolute entropy of a gas and the chemical constant. When expressing the absolute entropy of gases in Syrkin's equation, the equivalence of translational and rotational quanta of energy is taken into account. In addition to universal values, the expression for a chemical constant includes only the mass of the molecule and its diameter. Syrkin noted strong correlations between the calculated and experimentally determined chemical constants of gases, particularly for molecules such as Cl_2, Br_2, and I_2.

The rapid development of industry and agriculture at the time led to chemical and technological innovations. To this end, the development of air rectification processes in 1902 to meet the growing demand for large scale oxygen production came at a fortuitous time. This was followed closely by calls to repurpose this technology for the large scale production of nitrogen to facilitate the downstream manufacturing of ammonia, calcium fertilizers, and nitrides. In response, Syrkin published a study on the large scale acquisition of nitrogen and oxygen from liquid air in the 1925 edition of the *Journal of Chemical Industry* [10]. Here, the optimal conditions under which the output of liquid oxygen was significantly increased (i.e., at a pressure of 325 atm and pre-cooling to −50°C) were detailed (Table 1).

Table 1. Experimental conditions for obtaining liquid oxygen [11]

Specific gravity, kg/m^3	479	445	421	402
Pressure, kg/cm^2	325	356	372	382
Temperature, °C	−50	−20	+2	+20
Concentration of oxygen, kg	15.6	12.4	10.4	9.1

The early period of Syrkin's scientific work on chemical kinetics [12–20] (Fig. 3), which are based on ideas about the structure of molecules, led to the publication of "On the speed of chemical reactions" in 1926 [15], in which he presented expressions for the reaction rate constants of the first, second, and third orders.

Fig. 3. Syrkin in the laboratory of the Chemical Faculty of IVPI.

Therein, an expression for the rate constant of monomolecular reactions containing molecular dimensions could be converted to expressions defining characteristic infrared frequencies (5). Additionally, he noted that bimolecular reactions (i.e., reactions between two colliding molecules) were activated at the moment of collision by a quantum of light (6). As a result, the third-order reaction rate constant was calculated based on the assumption of a three molecule collision (7):

$$k = 7.4ve^{-\frac{q}{kT}} \tag{5}$$

$$k'' = \frac{N_0 \sigma akT}{h} e^{-\frac{hv}{kT}} \tag{6}$$

$$k''' = \frac{N_0^2}{3r}\sqrt{\frac{2m_2 + m_1}{3m_1m_2}} e^{-\frac{q}{kT}}, \frac{\left(\mathrm{sm}^3\right)^2}{\mathrm{mol}^2/\mathrm{s}} \tag{7}$$

where m is the mass, v is the frequency, k is the rate constant, T is the absolute temperature, h is the Planck constant, N_0 is the Avogadro number, q is the heat of activation, σ is the volume of the sphere's collision, and r is the radius of the sphere.

The paper [15] also reported the possibility of rapid reactions caused by "spin-off" reactions produced during each collision. Syrkin concluded that it was impossible to use conventional kinetic methods in these cases. When the interactions were the product of a "triple" collision (i.e., reaction collisions involving three molecules), Syrkin focused on possible correlations between the "double" and "triple" collisions.

In the same year, two articles on catalysis in chemical reactions were published in the *Journal of Chemical Industry* [21, 22] in response to the rising interest in using catalysts for synthesizing dyes, nitrogen binding applications, and in various other chemical processes. Syrkin's work tried to explain the action of catalysts as a function of the reaction time using reaction kinetics:

> *"The catalyst does not introduce anything fundamentally new; it only changes the conditions of the process, it leads in the shortest way to the final goal, i.e., to achieve an equilibrium state of reacting and forming substances. What is achieved with a catalyst can be achieved without it, but in the latter case it will take longer."*

By trying to define the features, characteristics, and regularities of individual catalytic reactions using the decomposition of ethyl acetate as an example, Syrkin showed that three different types of reactions were possible, depending on the nature of the catalyst used (Table 2):

In these publications, Syrkin was able to prove that catalysts accelerated the reaction process and also influenced the type of chemical reaction, which, in turn, affected the outcome. He demonstrated why various catalysts were not always applicable in certain chemical processes by comparing the product yields while transitioning from one catalyst to another [21]. This work sheds light on the influence of external factors such

Table 2. Decomposition of ethyl acetate based on the type of catalyst used

Reaction	Catalyst
$CH_3CO_2C_2H_5 = CH_3CO_2H + C_2H_4$	Oxide of titanium
$CH_3CO_2C_2H_5 = C_3H_8 + CO_2$	Crushed nickel
$2CH_3CO_2C_2H_5 = CH_3COCH_3 + C_2H_5OH + C_2H_4 + CO_2$	Oxide of thorium

as moisture sensitivity, catalytic stability, and production methods on a catalyst's efficiency.

In 1929, widespread recognition for his work on catalysis led to an invitation to publish in the *Technical Encyclopedia* [23] as part of a two part series in collaboration with the academician Vladimir Nikolaevich Ipatiev, a figure who was instrumental in starting the Chemical Faculty of the Ivanovo-Voznesensk Polytechnic Institute. The Encyclopedia's article, entitled "Catalysis," consists of two sections; the first part was written by the future academician Syrkin followed by Ipatiev's "Catalysis in technology."

In his work on chemical kinetics, Syrkin explored not only reactions that occurred in a gas environment. The 1927 article in the *Journal of the Russian Physical and Chemical Society* detailed the equation of chemical kinetics to explain the electron emissions in incandescent bodies [17]. Here, the process of emitting electrons from a metallic surface was equated with similar heterogeneous first order reactions, resulting in an expression for determining the number of electrons *L* emitted per unit of time by a unit of the surface of an incandescent body (8):

$$L = \frac{2\pi m v^3}{kT} e^{-\frac{hv}{kT}}, \tag{8}$$

where m is the mass of the electron, v is the characteristic frequency, k is Boltzmann's constant, T is the absolute temperature, and h is Planck's constant.

Syrkin's scientific contribution to the field of reaction kinetics continued with another publication in the *Technical Encyclopedia* entitled "Chemical Kinetics" in 1930. The concepts presented in this article helped researchers take advantage of the newly offered opportunities in instrumentation and pushed the boundaries of experimental possibilities.

The beginning of the 20th century saw a scientific revolution that increasingly drove researchers to expand the existing concepts, laws, and theories governing the world's natural order and to formulate groundbreaking scientific ideas. Access to better instruments and technological advancements enabled scientists to conduct experiments that were previously too difficult or impossible to perform. As a result, there was a shift in how chemists viewed the states of matter, i.e., gases, liquids, and solids, as more researchers were focused on defining these phases and the associated transitions in terms of the intermolecular forces occurring between them. Scientists began to take into account the orientation and polarization forces in definitions for gaseous and liquid molecules. A mismatch in the center of gravity of positive and negative charges led to the concept of an electric dipole. Molecules that possessed higher degrees of electrosymmetry were defined as quadrupoles, octopoles, etc. Syrkin published several reports on these molecules and their interactive forces [24, 25], in which he defined numerous methods for determining their dipole moments:

> "*The dependence of the dielectric constant on temperature, electrostriction, electrostatic rotational fields, the use of viral coefficients from the equation of state, and the dependence of the dielectric constant of solutions on concentration.*"

Since previously reported methods were applicable to a limited number of studied objects and often resulted in different dipole moments for the same molecule, Syrkin proposed an expression for determining the dipole moment ***m*** in a unified manner for all substances based on the orientation forces (9):

$$m = 1.66 \times 10^{-20} \frac{T_{\mathrm{cr}}}{\sqrt{P_{\mathrm{cr}}}} \tag{9}$$

If the electric centers of gravity of positive and negative charges coincided, the dipole moment was defined as zero, and the molecule could no longer be considered as a dipole. Thus, such molecules were classified as quadrupoles, and their associated interactions were determined by the accompanying orientation forces. In [25], a formula for determining the quadrupole moment (10) was reported:

$$m = 10.07 \times 10^{-28} \frac{T_{\mathrm{cr}}^{4/3}}{P_{\mathrm{cr}}^{5/6}}, \tag{10}$$

where T_{cr} is the critical temperature and P_{cr} is the critical pressure.

These equations allowed us to calculate the dipole and quadrupole moments for most substances and, as Syrkin pointed out, were in good agreement with the experimental data obtained by other scientists. Using these results, Syrkin established some regularities in similarly constructed homologous series. For example, he noted a correlation between the dipole/quadrupole moment and the number of CH_2 groups in a molecule. As the number of CH_2 moieties increased, the dipole moment decreased, whereas the quadrupole moment increased.

As a continuation of his research on the properties of dipoles and quadrupoles, another article appeared in the *Journal of Physical Chemistry* in 1930, entitled "On the electrostatics of colloids" [26]. Therein, the stability of colloidal solutions was discussed as a function of the existing electrical forces that were responsible for the emergence, stabilization, and destruction of the colloidal state of a system. Colloidal systems are particularly difficult to study, as minor changes in the external conditions profoundly affect their properties. Syrkin noted:

> "*Of all the fields of physical chemistry, colloids are of the least reproducible experiments.*"

Syrkin's paper presented equations that have allowed us to approximate the electrostatic forces in colloidal systems. He proposed that the conditions governing electrostatic stability of these systems were closely related to the radius and charge density of the interacting molecules (see equations (11) and (12)):

$$r = d\sqrt{\frac{Ad\omega^2}{Ad\omega^2 - \gamma} - 1}\,, \tag{11}$$

$$\omega_{\mathrm{cr}} = 4.48\times10^3\sqrt{\gamma\sqrt{cn^2}} \tag{12}$$

where d is the thickness of the outer layer, $d = \frac{4.3\times10^{-8}}{\sqrt{\Sigma cn^2}}$, ω is the charge density, γ is the energy per unit area, C is the concentration, and n is the charge of the ion. Thus, the transition to true solutions (dispersion) occurred at low values of r, and a decrease in the $d\omega^2$ parameter was associated with coagulation. Here, a high critical charge density was linked with an increasingly unstable solution, high surface tension, increased molecule concentration, and more charged the ions in the solution.

In the same year, Syrkin's research interests turned to determining the frequency of infrared vibrations. At this time, there were no experimental data on the infrared vibrations of simple molecules (i.e., metals) from optical sources. The universality of the Equation (13), as detailed in [27], is defined by the ratio of a substance's density to its atomic mass, whereas the more widely used Lindemann formula (4) includes the melting point:

$$v_{\mathrm{cr}} = 198.8\times10^{12}\,\frac{d^{2/3}}{M^{7/8}} \tag{13}$$

$$v = 2.8\times10^{12}\,T^{1/2}M^{-5/6}d^{1/2}\,, \tag{14}$$

where v_{cr} is the frequency of infrared vibrations, d is the density of the compound, M is the atomic weight, and T is the melting point. In this paper, the oscillation frequency (v) of various metals (i.e., Zn, Ag, Al, Cu, Pb, Hg, and Cd) and various chemical compounds were calculated. However, instead of using the atomic weight of an element or compound, Syrkin's equation featured the average value of the atomic masses of the atoms included in the compound (i.e., $(M_1 + M_2)/2$). The results obtained from Equation (13) were in good agreement with the experimental data.

Syrkin's work in understanding the fabric dyeing process was a direct response to the demands of the local textile industry. In collaboration with the future head of the Department of Chemical Technology of Fibrous Substances, P.V. Moryganov, Syrkin worked in the Laboratory of Colloid Chemistry to produce a publication for the *News of the Cotton and Paper Industry* in 1931 [28]. The reaction kinetics governing the dyeing of cotton fibers with substantial dyes was detailed in this paper. By assuming that the rate of dyeing was directly proportional to the undersaturation of the fiber with the dye, the authors presented a first order equation for calculating the speed constant k of this process (15):

$$k = \frac{1}{t}\ln\frac{A}{A - C}\,, \tag{15}$$

where t is the time measured from the beginning of the experiment, C is the dye concentration in time t, and A is the maximum dye concentration on the fiber (i.e., the equilibrium concentration). In this experiment, orange and oxamine pure blue were chosen as the dyes for the cotton fabric. Syrkin noted that both dyes exhibited a sharp drop in k after 15 min and that the equilibrium state, i.e., the time after which the dye concentration no longer changed, occurred after 1 hour. The paper also detailed the effects of electrolytes in the dye solution using NaCl and $ZnSO_4$. Here, the absorption of both electrolytes by the cotton fibers resulted in a change in the electrical conductivity of the solution, and the associated rate constant of the reaction was almost twice as high as the value obtained when there were no electrolytes in the dye solution.

Syrkin was a very prolific researcher, publishing more than 50 research papers during his time at IVPI–IHTI. After moving to Moscow and joining the Moscow State University of Fine Chemical Technologies in 1931, Syrkin became the Head of the Department of Physical Chemistry, a corresponding member, and then a full member of the Academy of Sciences of the Soviet Union. The Moscow State University of Fine Chemical Technologies was considered to be a real home for Syrkin during the difficult years of "resonance" of persecution.

Throughout this article, we highlighted the main scientific interests of Yakov Kivovich Syrkin. His comprehensive efforts served as the impetus for expansive scientific research at the institute, and the

Fig. 4. Members of the Academy of Sciences of the Ivanovo State University of Chemistry and Technology.

formulation of fundamental concepts in chemistry that lay the groundwork for future advancements in chemical research and technology. The memory of Yakov Syrkin is faithfully preserved by the Ivanovo State University of Chemistry and Technology (Fig. 4).

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About the authors:

Alyona S. Malyasova, Cand. of Sci. (Chemistry), Senior Researcher, Ivanovo State University of Chemistry and Technology (7, Sheremetevskii pr., Ivanovo, 153000, Russia). E-mail: bubnalla@yandex.ru. Scopus Author ID 14021314000, ResearcherID F-4435-2017, https://orcid.org/0000-0002-8539-4998

Oskar I. Koifman, Corresponding Member of the Russian Academy of Sciences, Dr. of Sci. (Chemistry), Professor, President of the Ivanovo State University of Chemistry and Technology (7, Sheremetevskii pr., Ivanovo, 153000, Russia); Main Scientific Employee of the G.A. Krestov Institute of Solution Chemistry of the RAS (1, Akademicheskaya ul., Ivanovo, 153045, Russia). E-mail: oik@isuct.ru. Scopus Author ID 6602070468, ResearcherID R-1020-2016, https://orcid.org/0000-0002-1764-0819

Об авторах:

Малясова Алена Сергеевна, кандидат химических наук, старший научный сотрудник Ивановского химико-технологического университета (Россия, 153000, г. Иваново, Шереметевский пр., д. 7). E-mail: bubnalla@yandex.ru. Scopus Author ID 14021314000, ResearcherID F-4435-2017, https://orcid.org/0000-0002-8539-4998

Койфман Оскар Иосифович, член-корреспондент Российской академии наук, доктор химических наук, профессор, президент Ивановского химико-технологического университета (Россия, 153000, г. Иваново, Шереметевский пр., д. 7); главный научный сотрудник Института химии растворов им. Г.А. Крестова РАН (Россия, 153045, г. Иваново, ул. Академическая, д. 1). E-mail: oik@isuct.ru. Scopus Author ID 6602070468, ResearcherID R-1020-2016, https://orcid.org/0000-0002-1764-0819

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