How to Cite: Panshina, S.Yu., Bakibaev, A.A., Guslyakov, A.N., & Malkov, V.S. (2022) Synthesis of Cucurbit[6]uril using 1-Hydroxyethylidene-1,1-diphosphonic acid as a "Green catalyst". *Bulletin of the University of Karaganda – Chemistry*. https://doi.org/10.31489/2022Ch4/4-22-3

Article Received: 31 May 2022 | Revised: 26 August 2022 | Accepted: 30 September 2022 | Published online: 8 November 2022

UDC 544.42+519.242.7 https://doi.org/10.31489/2022Ch4/4-22-3

S.Yu. Panshina[1*], A.A. Bakibaev[2], A.N. Guslyakov[2], V.S. Malkov[2]

[1]Karagandy University of the name of academician E.A. Buketov, Karaganda, Kazakhstan;
[2]National Research Tomsk State University, Tomsk, Russian Federation
*(*Corresponding author's e-mail: janim_svetatusik@mail.ru)*

Synthesis of Cucurbit[6]uril Using 1-Hydroxyethylidene-1,1-Diphosphonic Acid as a "Green Catalyst"

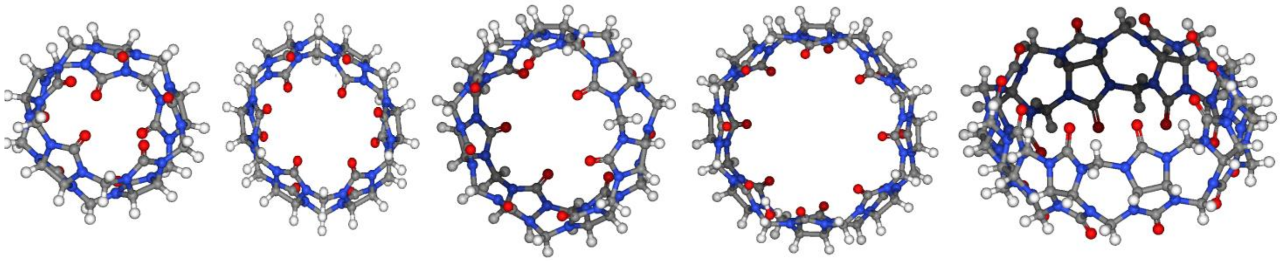
Glycoluril (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione) and its derivatives have a special place in chemistry of heterocyclic compounds. The macrocyclic derivatives of glycoluril, namely cucurbit[n]urils have recently attracted the greatest interest due to their unique properties. Cucurbit[n]urils are usually synthesized by the condensation reaction of glycoluril with paraformaldehyde using strong mineral acids as a catalyst. In this work, 1-hydroxyethylidene-1,1-diphosphonic acid (HEDP) was used for the first time as a catalyst for "Green chemistry" in the synthesis of cucurbit[6]uril in an aqueous medium. The reaction of glycoluril and paraformaldehyde in a ratio of 1: 2 with two equivalents of 1-hydroxyethylidene-1,1-diphosphonic acid as a catalyst was carried out, in which the hexamer of cucurbituril (n = 6) was obtained in 25 % yield. The clathrate of cucurbit[6]uril with acetone was obtained by treating the cucurbituril hexamer with acetone. The reaction of glycoluril with paraformaldehyde in the presence of HEDP can be used as a competitive method for the synthesis of cucurbit[6]uril. The structures of the obtained compounds were proven by NMR and IR spectroscopy methods. The phase composition of isolated crystals of cucurbit[6]uril hydrate was analyzed by the powder X-ray diffraction (XRD).

Keywords: cucurbit[6]uril, 1-hydroxyethylidene-1,1-diphosphonic acid, glycoluril, paraformaldehyde, NMR, "Green" catalyst, oligomer, "guest-host" interactions.

Introduction

2,4,6,8-Tetraazabicyclo[3.3.0.]octane-3,7-dione (glycoluril) **1** (Scheme 1) and its derivatives are the most interesting objects among bicyclic bisureas, which have a special place in the chemistry of heterocyclic compounds [1]. It has been reflected in the creation of valuable substances in various fields of human activity such as disinfectants [2, 3], medicines [4, 5], polymer stabilizers [6], and other important substances and materials based on these compounds. Geometrical features of glycoluril **1** determined the possibility of synthesis and investigation of macromolecular and supramolecular compounds on its basis [7–21]. Cucurbit[n]urils (**CB[n]**) are the main representatives of this type of compounds [9–21]. Macrocycles **CB[n]** have a narrowed hydrophobic cavity, which is outlined by two identical polar portals of carbonyl groups (Fig. 1 [16]). Hexamer cucurbit[6]uril **CB[6]** is the major reaction product due to the favorable deformation and abundance of hydrogen bonds [17–21].

In recent years, cucurbit[n]urils have attracted the significant interest due to their unique properties [11]. It is known [11, 16–21], that cucurbit[n]urils **CB[n]** are usually synthesized by the condensation reaction of glycoluril **1** with formaldehyde or paraformaldehyde in solutions of strong mineral acids at temperatures above 50 °C for a day or more. The use of organic acids in the synthesis of cucurbit[n]urils **CB[n]** is limited only by the use of methanesulfonic acid [21].

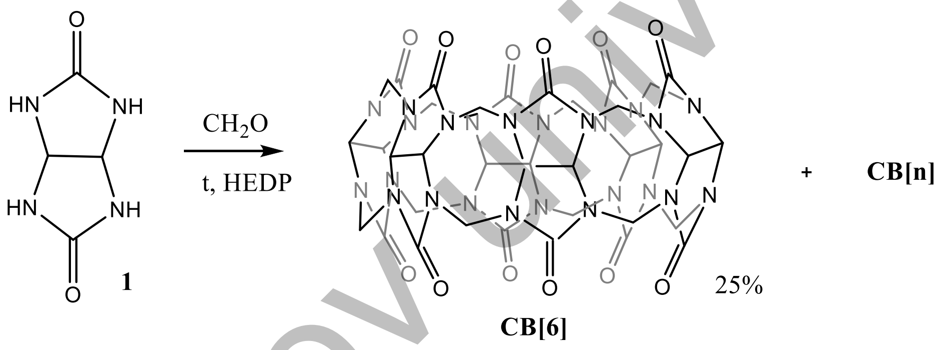


CB[5] CB[6] CB[7] CB[8] CB[10]

Figure 1. Cucurbit[*n*]urils, CB[*n*], *n* = 5, 6, 7, 8, 10.

More recently, in a number of works [22–25] it was shown that 1-hydroxyethylidene-1,1-diphosphonic acid (HEDP) proved to be a convenient "green" catalyst in heterocyclization reactions. 1-Hydroxyethylidene diphosphonic acid (HEDP) is known for its anti-corrosion properties. It is used as a retardant in concrete, scale and corrosion inhibition in circulating cool water system, oil field and low-pressure boilers in fields such as electric power, chemical industry, metallurgy, fertilizer, etc [26]. The HEDP substance decomposes at a temperature of about 250 °C, and decomposes in aqueous solutions at 140 °C [26]. In natural water bodies, HEDP rapidly decomposes under the action of ultraviolet light, and the decomposition products are used as fertilizers [27].

In this work, we first carried out the synthesis of cucurbit[6]uril **CB[6]** in the presence of HEDP as a "green" catalyst (Scheme 1).



Scheme 1. The synthesis of cucurbit[6]uril **CB[6]** in the presence of HEDP

Experimental

NMR spectra were recorded on a Bruker AVANCE III HD spectrometer (Bruker Corporation, Germany) with an operating frequency of 400 and 100 MHz for ^1H and ^{13}C nuclei respectively, in solutions of DMSO-d_6 and F_3CSO_3H. The internal standard was tetramethylsilane (TMS).

IR spectra were recorded on a Nicolet 6700 IR spectrometer, Thermo Fisher Scientific. The samples were studied by the method of disturbed total internal reflection in the spectral range from 400 to 4000 cm^{-1}.

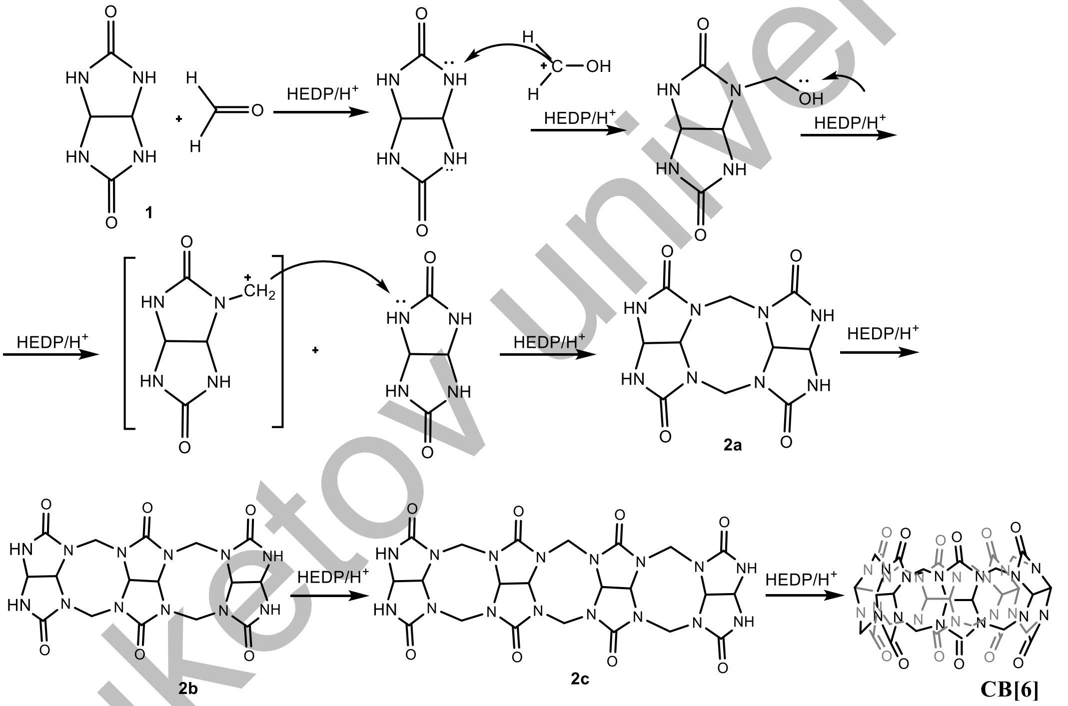
Powder X-ray diffraction for substance **CB[6]** was recorded on a Shimadzu XRD 7000 diffractometer using Cu Kα radiation at λ = 1.54053 Å. Reflections were collected from 5 to 50 in 2Θ with a step of 0.014, a rate of 20 deg / min and a step time of 21.49 s at 17 °C.

Synthesis of cucurbit[6]uril hydrate CB[6] using HEDP. Glycoluril **1** (21.4 g, 0.15 mol), HEDP (61.8 g, 0.30 mol) and 120 ml of water were added to a 250 mL round-bottomed flask equipped with a magnetic stir bar. The mixture was heated to 50 °C and then paraformaldehyde (9 g, 0.30 mol) was slowly added, allowing the solution to stir well. The viscous solution was allowed to stir for 30 min more until the solution set as a gel, which then was heated to 100 °C resulting in a rapid dissolution of the gel. The reaction mass was refluxed for 20 h at 100 °C. Then it was allowed to cool down to room temperature. The resulting precipitate was filtered off and washed with boiling water, after which it was dissolved in boiling 37 % HCl acid. The resulting solution was cooled and left at 0 °C for a week for crystallization. The colorless hexagonal crystals of cucurbit[6]uril hydrate **CB[6]** with high purity were formed on the vessel walls. Substance **CB[6]** is white powder with a yield of **CB[6]** 6.3 g (25 %). T. of decomp. is more than 400 °C. IR spectrum, υ, cm^{-1}: 3441 (H_2O), 2927 (CH), 1712 (C = O). ^1H NMR (400 MHz, F_3CSO_3H/D_2O): δ = 5.82 (s. 12H, CH), 5.58 (d. $J = 16.4$, 12H, CH_2), 4.63 (d. $J = 16.6$, 12H, CH_2). ^{13}C NMR (101 MHz, F_3CSO_3H/D_2O): $\delta = 160.21$ (C=O), 72.71 (CH), 52.04 (CH_2).

The obtained **CB[6]** powder was treated with hot acetone, where the clathrate of hydrate of the cucurbit[6]uril with acetone **CB[6]A** [19] was obtained in a yield of 6.1 g (23 %). The substance **CB[6]A** is practically insoluble in concentrated boiling acids HCl, H_2SO_4 and hardly soluble in F_3CSO_3H. T. of decomp. is more than 400 °C. IR spectrum, υ, cm^{-1}: 3503 (H_2O), 2998 (CH_3), 2933 (CH), 1730 (C=O). ^1H NMR (400 MHz, F_3CSO_3H/D_2O): $\delta = 5.81$ (d. $J = 5.6$, 12H, CH), 5.56 (d. $J = 13.9$, 12H, CH_2), 4.61 (d. $J = 14.5$, 12H, CH_2), 2.67 (s, 3H, CH_3). ^{13}C NMR (101 MHz, F_3CSO_3H/D_2O): $\delta = 198.49$ ($C{=}O_{acetone}$), 160.11 (C=O), 72.68 (CH), 51.87 (CH_2), 29.97 ($CH_{3\ acetone}$).

Results and Discussion

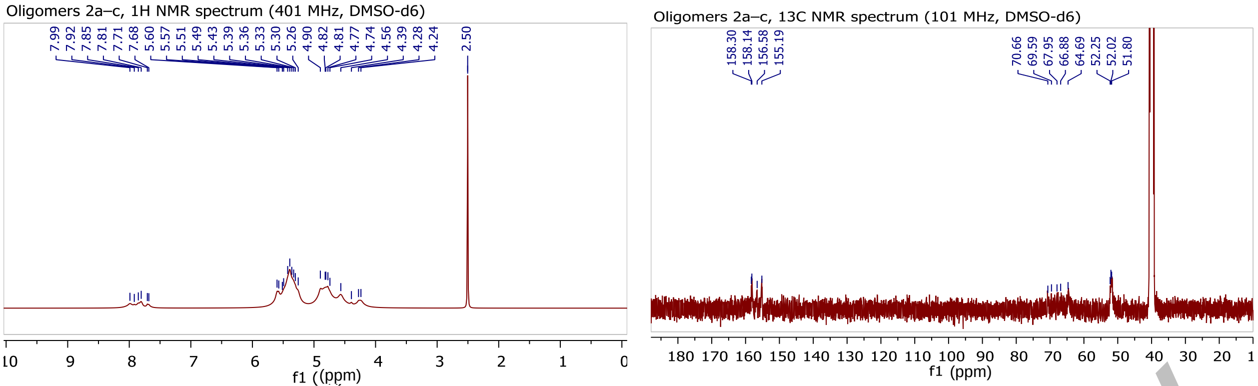
The reaction (Scheme 1) of glycoluril **1** and paraformaldehyde in a ratio of 1:2 was carried out with the traditional procedure [19], but HEDP was used as a catalyst in two equivalents relative to substrate **1**. It was suggested [28] that HEDP promoted more efficient transfer of glycoluril **1** into solution, which significantly accelerated the condensation reaction. In the process of carrying out the synthesis of **CB[6]** upon heating, the reaction mass was homogenized after 5 minutes. Then, after 20 minutes of reaction, a precipitate formed. These are intermediate oligomers **2a–c** of the cucurbit[6]uril **CB[6]** synthesis [18], the proposed structures of which are shown in Scheme 2.



Scheme 2. Formation of cucurbit[6]uril CB[n] by stepwise oligomerization

The reaction mixture was heated for 20 hours and then left to stand in a cold place overnight to crystallize the precipitate, which was isolated and washed with hot water. When the washing solution was cooled, precipitates of intermediate oligomers **2a–c** precipitated. According to the NMR results of the reaction mixture, glycoluril **1** reacted completely.

In the ^1H NMR spectrum (DMSO-d_6) of oligomers **2a–c**, there are multiplets of the main signals of the structure, namely chemical shifts of NH-groups are found at δ 7.68–7.99 ppm, signals of protons of the methine group CH–CH are resonated at δ 5.26–5.60 ppm, and the chemical shifts of the protons of the methylene N-CH_2-N groups are at δ 4.24–4.90 ppm (Fig. 2, *a*).



a) ^{1}H NMR spectrum of oligomers **2a–c** b) ^{13}C NMR spectrum of oligomers **2a–c**

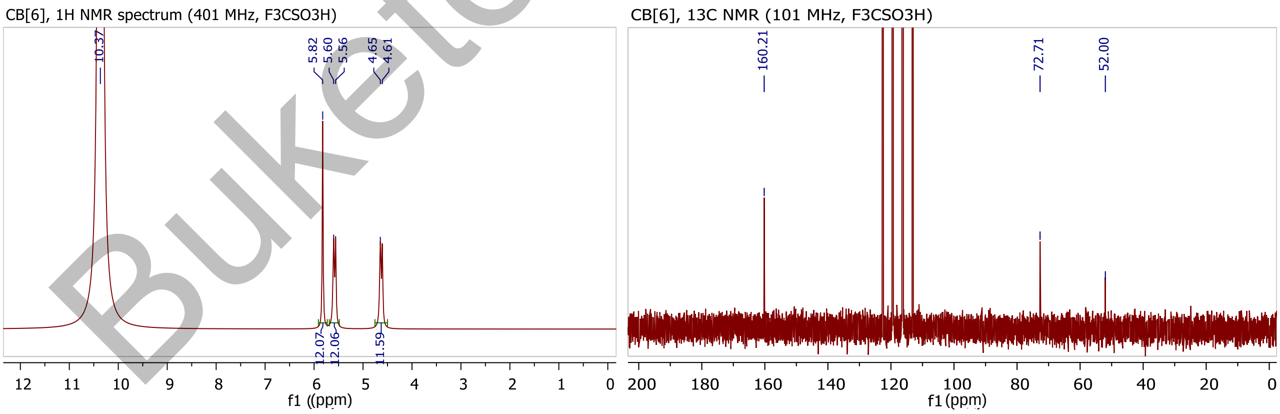
Figure 2. The NMR spectra of oligomers **2a–c** in DMSO-d_6

In the ^{13}C NMR spectrum (DMSO-d_6) of oligomers **2a–c**, chemical shifts are observed at δ 51.8–52.3 ppm, δ 64.7–70.6 ppm and δ 155.2–158.3 ppm, which refer to carbon atoms of N-CH_2-N, CH-CH and C=O, respectively (Fig. 2, *b*). In the IR spectrum of oligomers **2a–c** there are characteristic absorption bands indicating the linearity of the structure of the obtained substances, namely the band at 3231 cm^{-1} corresponds to NH-groups and the band at 1673 cm^{-1} corresponds to amide C=O-groups.

The formation of acyclic structures **2a–c** shows that HEDP acts as a trigger for the formation of a linear platform for further thermodynamically cyclization to cucurbit[n]urils **CB[n]** in an aqueous medium. The obtained cucurbit[6]uril **CB[6]** and non-cyclized oligomers with a high molecular weight are equally insoluble in water, which makes it difficult to isolate **CB[6]** from the aqueous medium. In the IR spectrum of the final precipitate, characteristic absorption bands of C=O-groups of non-cyclized oligomers (1675 cm^{-1}) and C=O-groups of cucurbit[6]uril **CB[6]** (1714 cm^{-1}) are observed. The characteristic absorption band of C=O-groups of cucurbit[6]uril **CB[6]** is shifted to short-wavelength region due to the resonance of the negative charge of the carbamide group of the cavity of cucurbit[6]uril **CB[6]**.

Isolation and purification of cucurbit[6]uril **CB[6]** was carried out in accordance with the procedure [19]. The separated precipitate was dissolved in boiling 37 % acid HCl and left in the cold place. After a week, colorless hexagonal crystals of cucurbit[6]uril **CB[6]** hydrate were obtained.

Due to the low solubility of cucurbit[6]uril **CB[6]**, NMR spectra were recorded in a trifluoromethanesulfonic acid solution (Fig. 3*a*, *b*).



a) ^{1}H NMR spectrum of **CB[6]** **b)** ^{1}H NMR spectrum of **CB[6]**

Figure 3. The NMR spectra of **CB[6]** in F_3CSO_3H

The recorded NMR spectra of the substance **CB[6]** (Fig. 3*a*, *b*), in general, are identical to those previously recorded in the solvent DCl [18, 19].

We additionally analyzed the phase composition of the isolated crystals of cucurbit[6]uril hydrate **CB[6]** by the powder X-ray diffraction (XRD) (Fig. 4). XRD analysis showed that the type of crystal lattice and phase composition of crystals of cucurbit[6]uril hydrate **CB[6]** obtained in the presence of HEDP was identical to crystals of cucurbit[6]uril hydrate **CB[6]*4.66 H_2O** [19], which were synthesized in the presence of HCl acid as a catalyst.

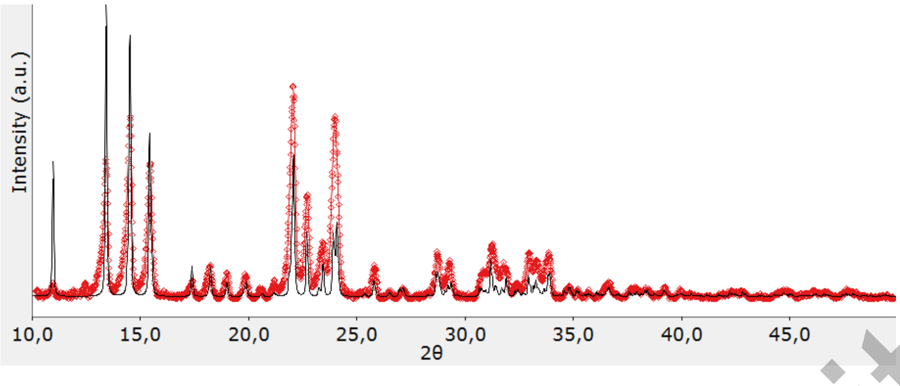
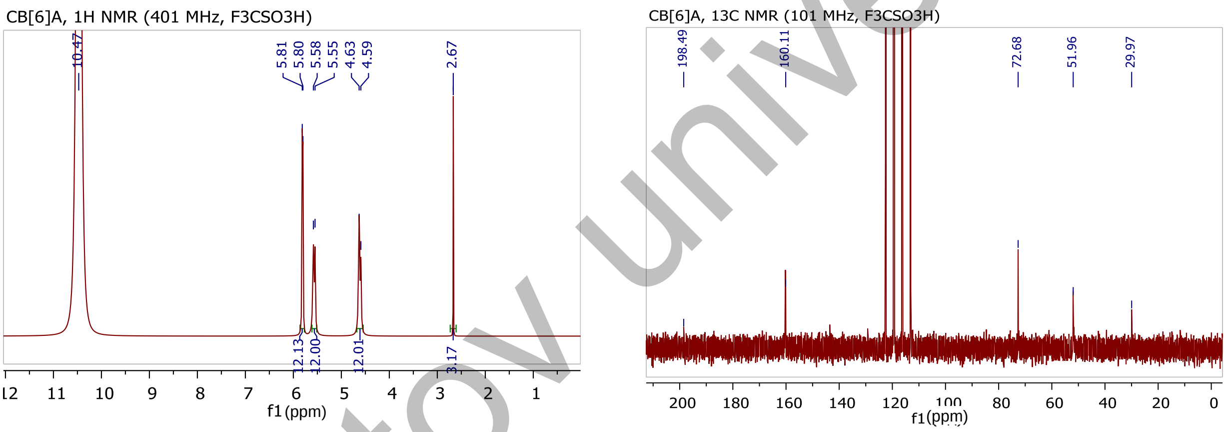


Figure 4. XRD of powder crystals of the isolated hydrate cucurbit[6]uril **CB[6]** structure (red line) and the corresponding theoretical picture of hydrate cucurbit[6]uril, (black line)

The clathrate of cucurbit[6]uril with acetone **CB[6]A** was obtained by treating the substance **CB[6]** with hot acetone. Substance **CB[6]A** is insoluble in concentrated acids HCl, H_2SO_4 and slightly soluble in F_3CSO_3H acid. The structure of **CB[6]A** was investigated by IR- and NMR spectroscopy (Fig. 5*a, b*).



a) ^1H NMR spectrum of **CB[6]A** b) ^1H NMR spectrum of **CB[6]A**

Figure 5. The NMR spectra of **CB[6]A** in F_3CSO_3H

Previously, a similar clathrate [19], was described using X-ray diffraction analysis, the structure of which was a composition of one CB[6] per one acetone and eight water molecules. In our case, according to NMR data, the ratio of CB[6] and acetone molecules was also 1:1 in the clathrate. In the NMR spectra (Fig. 5*a*, *b*) of the clathrate **CB[6]A**, in addition to the main chemical shifts of cucurbit[6]uril **CB[6]**, there are chemical shifts of acetone.

"Guest-host" interactions in cucurbit[n]uril chemistry have been studied in detail [11], and ion-dipole and dipole-dipole interactions are considered as the main driving forces for binding various guests (acetone) with **CB[6]**. Dipole-dipole interactions are shown in NMR spectra, where in the ^{13}C NMR spectrum the peak of the C=O group of acetone is shielding by an average of 8 ppm (Fig. 5*b*), and in the ^1H NMR spectrum the chemical shift of the CH_3-groups of acetone is deshielding by an average of 0.3 ppm (Fig. 5*a*), relative to chemical shifts of a free acetone molecule.

Conclusions

Thus, HEDP has been first used in the synthesis of cucurbit[6]uril as a catalyst for "green chemistry" in an aqueous medium. It has been shown that HEDP not only forms linear structures, but also cyclizes oligomers into cucurbit[n]urils, where the most probable and stable hexamer of cucurbituril (n = 6) is obtained in 25 % yield.

The reaction of glycoluril with paraformaldehyde in the presence of HEDP can be used as a competitive method for the synthesis of cucurbit[6]uril. The advantages of using HEDP are in the “green” synthesis conditions and in the rapidity of the formation of the crystal structure of cucurbit[6]uril **CB[6]** hydrate, however, at the purification stage it is necessary to use mineral acids to separate linear products with similar solubility in water.

Acknowledgments

We thank Tomsk State University for financial support to our research groups.

References

1 Bakibaev A. Synthesis of glycolurils and hydantoins by reaction of urea and 1, 2-dicarbonyl compounds using etidronic acid as a “green catalyst” / A. Bakibaev, A. Uhov, V. Malkov, S. Panshina // J. Heterocyclic Chem. — 2020. — Vol. 57. — P. 4262–4270. https://doi.org/10.1002/jhet.4132

2 Patent 102004059041 Germany. Verwendung von Formaldehyd und Formaldehyd freisetzenden Verbindungen in einer Zusammensetzung zur Bekämpfung von Mykobakterien / Beilfuss W., Gradtke R., Krull I., Steinhauer, K. Publication date 08.06.2006.

3 Patent 2354771 Great Britain. Bactericide combinations in detergents / Denk A., Emter A., Moddick C. Publication date 04.04.2001.

4 Bakibaev A.A. 1D and 2D NMR spectroscopy for identification of carbamide-containing biologically active compounds / A.A. Bakibaev, S.Yu. Panshina, O.V. Ponomarenko, V.S. Malkov, O.A. Kotelnikov, A.K. Tashenov // Bulletin of the university of Karaganda–Chemistry. — 2021. — Vol. 101, No 1. — P. 71–81. https://doi.org/10.31489/2021Ch1/71-81

5 Машковский М.Д. Лекарственные средства: пособие для врачей: справочник / М.Д. Машковский. — 15-е изд. — М.: Новая волна, 2005. — 1164 с.

6 Bakibaev A.A. Methods of synthesis of nitrogen-containing heterocycles using ureas and related compounds / A.A. Bakibaev, A.Yu. Yagovkin, S.N. Vostretsov // Russ. Chem. Rev. — 1988. — Vol. 67, No. 4. — P. 295–314. https://doi.org/10.1070/RC1998v067n04ABEH000295

7 Havel V. Modulation of Bambusuril Anion Affinity in Water / V. Havel, M. Babiak, V. Sindelar // Chemistry-A European Journal. — 2017. — Vol. 23, No. 37. — P. 8963–8968. https://doi.org/10.1002/chem.201701316

8 Svec J. Bambus[6]uril / J. Svec, M. Necas, V. Sindelar // Angewandte Chemie International Edition. — 2010. — Vol. 122. — P. 2428−2431. https://doi.org/10.1002/anie.201000420

9 Nandi S. Cucurbit[6]uril-Stabilized Palladium Nanoparticles as a Highly Active Catalyst for Chemoselective Hydrogenation of Various Reducible Groups in Aqueous Media / S. Nandi, P. Patel, A. Jakhar, N.H. Khan, A.V. Biradar, R.I. Kureshy, H.C. Bajaj // ChemistrySelect. — 2017. — Vol. 171, No. 2. — P. 9911–9919. https://doi.org/10.1002/slct.201702196.

10 Kornmuller A. Cucurbituril for water treatment. Part II: Ozonation and oxidative regeneration of cucurbituril / A. Kornmuller, S. Karcher, M. Jekel // Water Res. — 2001. — Vol. 35, No. 14. — P. 3317–3324. https://doi.org/10.1016/S0043-1354(01)00039-2

11 Assaf K.I. Cucurbiturils: from synthesis to high-affinity binding and catalysis / K.I. Assaf, W.M. Nau // Chem. Soc. Rev. — 2015. — Vol. 44. — P. 394–418. https://doi.org/10.1039/C4CS00273C

12 Barrow S.J. Cucurbituril-based molecular recognition / S.J. Barrow, S. Kasera, M.J. Rowland, J.del Barrio, O.A. Scherman // Chem. Rev. — 2015. — Vol. 115. — P. 12320–12406. https://doi.org/10.1021/acs.chemrev.5b00341

13 Isobe H. Ternary Complexes Between DNA, Polyamine, and Cucurbituril: A Modular Approach to DNA-Binding Molecules / H. Isobe, N. Tomita, J.W. Lee, H.-J. Kim, K. Kim, E. Nakamura, // Angew. Chem. Int. Ed. — 2000. — Vol. 39, No. 23. — P. 4257–4260. https://doi.org/10.1002/1521-3773(20001201)39:23 %3C4257:: AID-ANIE4257 %3E3.0.CO;2-6

14 Chen C. Fabrication, characterization and adsorption properties of cucurbit[7]uril-functionalized polycaprolactone electrospun nanofibrous membranes / C. Chen, F. Liu, X. Zhang, Z. Zhao, S. Liu // Beilstein J. Org. Chem. — 2019. — Vol. 15. — P. 992–999. https://doi.org/10.3762/bjoc.15.97

15 Tuncel D. Cucurbituril-based Functional Materials / Eds.: D. Tuncel. — Royal Society of Chemistry. — London, 2019. — 303 p. https://pubs.rsc.org/en/content/ebook/978-1-78801-488-5.

16 Cong H. Synthesis and separation of cucurbit[n]urils and their derivatives / H. Cong, X. Ni, X. Xiao, Y. Huang, Q. Zhu, S. Xue, Z. Tao, L.F. Lindoy, G. Wei // Org. Biomol. Chem. — 2016. — Vol. 14. — P. 4335-4364. https://doi.org/10.1039/C6OB00268D.

17 Kim J. New Cucurbituril Homologues: Syntheses, Isolation, Characterization, and X-ray Crystal Structures of Cucurbit[n]uril (n = 5, 7, and 8) / J. Kim, I.S. Jung, S.Y. Kim, E. Lee, J.K. Kang, S. Sakamoto, K. Yamaguchi, K. Kim. // J. Am. Chem. Soc. — 2000. — Vol. 122. — P. 540–541. https://doi.org/10.1021/ja993376p

18 Day A. Controlling Factors in the Synthesis of Cucurbituril and Its Homologues / A. Day, A.P. Arnold, R.J. Blanch, B Snushall // The Journal of Organic Chemistry. — 2001. — Vol. 66, No. 24. — P. 8094–8100. https://doi.org/10.1021/jo015897c.

19 Bardelang D. Cucurbit[n]urils (n = 5-8): A Comprehensive Solid State Study / D. Bardelang, K.A. Udachin, D.M. Leek, J.C. Margeson, G. Chan, C.I. Ratcliffe, J.A. Ripmeester // Cryst. Growth. Des. — 2011. — Vol. 11. — P. 5598–5614. https://doi.org/10.1021/cg201173j

20 Huang W.H. Cucurbit[n]uril Formation Proceeds by Step-Growth Cyclo-oligomerization / W.H. Huang, P.Y. Zavalij, L. Isaacs // Journal of the American Chemical Society. — 2008. — Vol. 130, No. 26. — P. 8446–8454. https://doi.org/10.1021/ja8013693

21 Patent WO2000068232A1 Australia. Cucurbiturils and method for synthesis / Day A.I., Arnold A.P., Blanch R.J. Publication date 16.11.2000. https://patents.google.com/patent/WO2000068232A1/en

22 Pansuriya A.M. One-pot synthesis of 5-carboxanilide-dihydropyrimidinones using etidronic Acid / A.M. Pansuriya, M.M. Savant. C.V. Bhuva, J. Singh, Y.T. Naliapara // Arkivoc. — 2009. — No. 7. — P. 79–85. https://doi.org/10.3998/ark.5550190.0010.707

23 Vilapara K.V. Etidronic Acid Promoted Sequential One-Pot Strategy for the Synthesis of 1H-Imidazo[1,2-b]pyrazoles: A Green Catalyst for Groebke-Blackburn-Bienaymé Reaction / K.V. Vilapara, S.P. Gami, Sh.A. Gadara, Y.T. Naliapara // ChemistrySelect. — 2019. — Vol. 4. — P. 11235–11238. https://doi.org/10.1002/slct.201902997

24 Savant M.M. Etidronic Acid: a New and Efficient Catalyst for the Synthesis of Novel 5-Nitro-3,4-Dihydropyrimidin-2(1H)-Ones / M.M. Savant, A.M. Pansuriya, C.V. Bhuva, N.P. Kapuriya, Y.T. Naliapara // Catal. Lett. — 2009. — Vol. 132, No. 1. — P. 281–284. https://doi.org/10.1007/s10562-009-0112-y

25 Panshina S. New Synthesis of 2,4,6,8-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione Using Etidronic Acid as a “Green” Catalyst / S. Panshina, O.V. Ponomarenko. A. Bakibaev, V. Malkov // Russian Journal of Organic Chemistry. — 2020. — Vol. 56, No. 12. — P. 2067–2073. https://doi.org/10.1134/S1070428020120039

26 Кабачник М.И. Оксиэтилендифосфоновая кислота и ее применение / М.И. Кабачник, Н.М. Дятлова, Т.Я. Медведь, Б.И. Бихман и др. // Химическая промышленность. — 1975. — № 4. — С. 254−258.

27 Дятлова Н.М. Комплексоны и комплексонаты металлов / Н.М. Дятлова, В.Я. Темкина, К.И. Попов. — М.: Химия, 1988. — 544 с.

28 Bakibaev A.A. Efficient Synthesis of Tetraacetylglycoluril in the Presence of Phosphorus-Containing Catalysts / A.A. Bakibaev, S.Y. Panshina, N.F. Hoang, D.A. Kurgachev, A.E. Ukhov, V.S. Malkov, K.B. Zhumanov // Russian Journal of Organic Chemistry. — 2021. — Vol. 57, No 1. — P. 58–63. https://doi.org/10.1134/S1070428021010085

С.Ю. Паншина, А.А. Бакибаев, А.Н. Гусляков, В.С. Малков

Кукурбит[6]урилдің синтезі 1-гидроксиэтан-1,1-дифосфон қышқылын «жасыл катализатор» ретінде пайдалану

Гетероциклді қосылыстар химиясында гликолурил (2,4,6,8-тетраааазабицикло[3.3.0]октан-3,7-дион) және оның туындылары ерекше орын алады. Атап айтқанда, гликолурилдің макроциклді туындылары, кукурбит[n]урилдер, өзінің бірегей қасиеттеріне байланысты соңғы уақытта үлкен қызығушылық тудырды. Кукурбит[n]урилдер әдетте катализатор ретінде күшті минералды қышқылдарды пайдалана отырып, гликолурилдің параформальдегидпен конденсациялану реакциясы арқылы синтезделеді. Жақында бірқатар зерттеулер 1-гидроксиэтан-1,1-дифосфон қышқылының (ОЭДФ) гетероциклизация реакцияларында ыңғайлы «жасыл» катализатор екенін дәлелдеді. Бұл жұмыста сулы ортадағы «жасыл химия» катализаторы ретінде кукурбит[6]урил синтезінде 1-гидроксиэтан-1,1-дифосфон қышқылы алғаш рет қолданылған. Гликолурил мен параформальдегидтің катализатор ретінде екі эквивалентті 1-гидроксиэтан-1,1-дифосфон қышқылымен 1:2 қатынасында реакциясы жүргізілді, мұнда 25 % шығымда кукурбитурил гексамер ($n = 6$) алынды. ОЭДФ қатысуымен гликолурилдің параформальдегидпен реакциясы кукурбит[6]урил синтезі үшін бәсекегеқабілетті әдіс ретінде пайдаланылуы мүмкін. Оқшауланған кукурбит[6]урил гексамеры ацетонмен өңделіп, «Қонақ-қожайын» әрекеттесуі арқылы қосылыс алынды. Алынған қосылыстардың құрылымы ЯМР және ИҚ спектроскопиясы арқылы дәлелденді. Кукурбит[6]урил гидратының оқшауланған кристалдарының фазалық құрамы ұнтақ рентгендік дифракциямен (РФТ) сипатталды. РФТ талдауы кристалдық тордың түрі мен 1-гидроксиэтан-1,1-дифосфон қышқы қатысуымен алынған кукурбит[6]урил гидрат кристалдарының фазалық құрамы классикалық әдістермен синтезделген кукурбит[6]урил гидратының кристалдарымен бірдей екенін көрсетті.

Кілт сөздер: кукурбит[6]урил, 1-гидроксиэтан-1,1-дифосфон қышқылы, гликолурил, параформальдегид, ЯМР, «жасыл» катализатор, олигомер, «Қонақ-қожайын» әрекеттесуі.

С.Ю. Паншина, А.А. Бакибаев, А.Н. Гусляков, В.С. Мальков

Синтез кукурбит[6]урила с использованием 1-гидроксиэтан-1,1-дифосфоновой кислоты в качестве «зеленого» катализатора

В химии гетероциклических соединений особое место занимают гликолурил (2,4,6,8-тетраазабицикло[3.3.0]октан-3,7-дион) и его производные. Особенно в последнее время наибольший интерес вызывают макроциклические производные гликолурила — кукурбит[n]урилы, что связано с их уникальными свойствами. Кукурбит[n]урилы обычно синтезируют реакцией конденсации гликолурила с параформальдегидом с использованием сильных минеральных кислот в качестве катализатора. Совсем недавно в ряде работ было показано, что 1-гидроксиэтан-1,1-дифосфоновая кислота (ОЭДФ) оказалась удобным «зеленым» катализатором в реакциях гетероциклизации. В настоящей работе нами впервые была использована 1-гидроксиэтан-1,1-дифосфоновая кислота в синтезе кукурбит[6]урила в качестве катализатора «зеленой» химии в водной среде. Проведена реакция гликолурила и параформальдегида в соотношении 1:2 с двумя эквивалентами 1-гидроксиэтан-1,1-дифосфоновой кислоты в качестве катализатора, где гексамер кукурбитурила (n = 6) получен с выходом 25 %. Реакцию гликолурила с параформальдегидом в присутствии ОЭДФ можно использовать как конкурентный метод синтеза кукурбит[6]урила. Выделенный гексамер кукурбит[6]урила обрабатывали ацетоном, с получением соединения по типу взаимодействия «гость–хозяин». Строение полученных соединений доказано методами ЯМР и ИК-спектроскопии. Фазовый состав выделенных кристаллов кукурбит[6]урилгидрата охарактеризован методом порошковой рентгенографии (РФА). РФА анализ показал, что тип кристаллической решетки и фазовый состав кристаллов гидрата кукурбит[6]урила, полученных в присутствии ОЭДФ, идентичны кристаллам гидрата кукурбит[6]урила, синтезируемым классическими методами.

Ключевые слова: кукурбит[6]урил; 1-гидроксиэтан-1,1-дифосфоновая кислота; гликолурил; параформальдегид; ЯМР; «зеленый» катализатор, олигомер, взаимодействия «гость–хозяин».

References

1 Bakibaev, A. Uhov, A. Malkov, V. & Panshina, S. (2020). Synthesis of glycolurils and hydantoins by reaction of urea and 1,2-dicarbonyl compounds using etidronic acid as a “green catalyst”. *J. Heterocyclic Chem.*, *57*, 4262–4270. https://doi.org/10.1002/jhet.4132

2 Beilfuss, W., Gradtke R., Krull I. & Steinhauer, K. (2006). Verwendung von Formaldehyd und Formaldehyd freisetzenden Verbindungen in einer Zusammensetzung zur Bekämpfung von Mykobakterien. Patent DE No 102004059041(A1). Munich, Germany: DE Deutsches Patent- und Markenamt.

3 Denk, A., Emter, A. & Moddick, C. (2001). Patent UK No. GB2354771(A). London, Great Britain: The Patent Office.

4 Bakibaev, A.A., Panshina, S.Yu., Ponomarenko, O.V., Malkov, V.S., Kotelnikov, O.A. & Tashenov, A.K. (2021). 1D and 2D NMR spectroscopy for identification of carbamide-containing biologically active compounds. *Bulletin of the university of Karaganda-Chemistry*, *101*(1), 71–81. https://doi.org/10.31489/2021Ch1/71-81

5 Mashkovskii, M.D. (2005). Lekarstvennye sredstva: posobie dlia vrachei [Medicines: a manual for doctors]. — 15th ed. — Moscow: Novaia volna [in Russian].

6 Bakibaev, A.A., Yagovkin, A. Yu. & Vostretsov, S. N. (1998). Methods of synthesis of nitrogen-containing heterocycles using ureas and related compounds. *Russian Chemical Reviews*, *67* (4), 295–314. https://doi.org/10.1070/rc1998v067n04abeh000295

7 Havel, V., Babiak, M. & Sindelar, V. (2017). Modulation of Bambusuril Anion Affinity in Water. *Chemistry-A European Journal*, *23*(37), 8963–8968. https://doi.org/10.1002/chem.201701316

8 Svec, J., Necas, M. & Sindelar, V. (2010). Bambus[6]uril. *Angewandte Chemie International Edition*, *122*, 2428–2431. https://doi.org/10.1002/anie.201000420

9 Nandi, S. Patel, P. Jakhar, A. Khan, N.H. Biradar, A.V. Kureshy, R.I. & Bajaj, H. C. (2017). Cuurbit[6]uril-Stabilized Palladium Nanoparticles as a Highly Active Catalyst for Chemoselective Hydrogenation of Various Reducible Groups in Aqueous Media. *ChemistrySelect*, *171* (2), 9911–9919. https://doi.org/10.1002/slct.201702196.

10 Kornmuller, A. Karcher, S. & Jekel M. (2001) Cuurbituril for water treatment. Part II: Ozonation and oxidative regeneration of cucurbituril, *Water Res.*, *35*(14), 3317–3324. https://doi.org/10.1016/S0043-1354(01)00039-2

11 Assaf, K.I., & Nau, W.M. (2015). Cucurbiturils: from synthesis to high–affinity binding and catalysis, *Chemical Society Reviews*, *44*, 394–418. https://doi.org/10.1039/C4CS00273C

12 Barrow, S.J., Kasera, S., Rowland, M.J., del Barrio, J. & Scherman, O.A. (2015). Cucurbitril-Based Molecular Recognition. *Chemical Reviews*, *115*(22), 12320–12406. https://doi.org/10.1021/acs.chemrev.5b00341

13 Isobe, H. Tomita, N., Lee, J.W., Kim, H. -J. Kim, K. & Nakamura, E. (2000) Ternary Complexes Between DNA, Polyamine, and Cucurbituril: A Modular Approach to DNA-Binding Molecules, *Angew. Chem. Int. Ed*, *39*(23), 4257–4260. https://doi.org/10.1002/1521-3773(20001201)39:23<4257:: aid-anie4257>3.0.co;2-6

14 Chen, C., Liu, F., Zhang, X., Zhao, Z. & Liu S. (2019). Fabrication, characterization and adsorption properties of cucurbit[7]uril-functionalized polycaprolactone electrospun nanofibrous membranes, *Beilstein J. Org. Chem*., *15*, 992–999. https://doi.org/10.3762/bjoc.15.97

15 Tuncel, D. (2019) Cucurbituril-based Functional Materials. London: Royal Society of Chemistry. https://pubs.rsc.org/en/content/ebook/978-1-78801-488-5.

16 Cong, H., Ni, X., Xiao, X., Huang, Y., Zhu, Q., Xue, S., Tao, Z., Lindoy, L. F. Wei, G. (2016). Synthesis and separation of cucurbit[n]urils and their derivatives, *Org. Biomol. Chem., 14,* 4335-4364. https://doi.org/10.1039/C6OB00268D.

17 Kim, J., Jung, I.S., Kim, S.Y., Lee, E., Kang, J.K., Sakamoto, S., Yamaguchi, K. & Kim, K. J. (2000). New Cucurbituril Homologues: Syntheses, Isolation, Characterization, and X-ray Crystal Structures of Cucurbit[n]uril (n = 5, 7, and 8), *J. Kim, Am. Chem. Soc., 122,* 540–541. https://doi.org/10.1021/ja993376p

18 Day, A., Arnold, A.P., Blanch, R.J. & Snushall, B. (2001). Controlling Factors in the Synthesis of Cucurbituril and Its Homologues. *The Journal of Organic Chemistry, 66*(24), 8094–8100. https://doi.org/10.1021/jo015897c

19 Bardelang, D., Udachin, K.A., Leek, D.M., Margeson, J.C., Chan, G., Ratcliffe, C.I. & Ripmeester, J.A. (2011) Cucurbit[n]urils (n = 5-8): A Comprehensive Solid State Study, *Cryst. Growth. Des.*, *11*, 5598–5614. https://doi.org/10.1021/cg201173j

20 Huang, W.H., Zavalij, P.Y. & Isaacs, L. (2008). Cucurbit[n]uril Formation Proceeds by Step-Growth Cyclo-oligomerization, *Journal of the American Chemical Society*, *130*(26), 8446-8454. https://doi.org/10.1021/ja8013693

21 Day, A.I., Arnold, A.P., Blanch, R.J. (2002). Patent AU No WO2000068232(A1). Sydney, Australia: Freehills Carter Smith & Beadle. https://patents.google.com/patent/WO2000068232A1/en

22 Pansuriya, A.M. Savant, M.M., Bhuva, C.V., Singh, J. & Naliapara У.T. (2009). One-pot synthesis of 5-carboxanilide-dihydropyrimidinones using etidronic Acid, *Arkivoc*, *7*, 79–85. https://doi.org/10.3998/ark.5550190.0010.707

23 Vilapara, K.V., Gami, S.P., Gadara, Sh.A., & Naliapara, Y.T. (2019). Etidronic Acid Promoted Sequential One-Pot Strategy for the Synthesis of 1H-Imidazo[1,2-b]pyrazoles: A Green Catalyst for Groebke-Blackburn-Bienaymé Reaction, *ChemistrySelect*, *4,* 11235-11238. https://doi.org/10.1002/slct.201902997

24 Savant, M.M., Pansuriya, A.M., Bhuva, C.V., Kapuriya, N.P. & Naliapara, Y.T. (2009). Etidronic Acid: a New and Efficient Catalyst for the Synthesis of Novel 5-Nitro-3,4-Dihydropyrimidin-2(1H)-Ones, *Catal. Lett.*, *132*(1), 281−284. https://doi.org/10.1007/s10562-009-0112-y

25 Panshina, S., Ponomarenko, O., Bakibaev, A., Malkov, V. (2020) New Synthesis of 2,4,6,8-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione Using Etidronic Acid as a "Green" Catalyst. Russian *Journal of Organic Chemistry*, *56*(12), 2067–2073. https://doi.org/10.1134/S1070428020120039

26 Kabachnik, M.I., Dyatlova, N.M., Medved, T.Ya, & Bikhman, B.I. et al. (1975). Oksietilendifosfonovaia kislota i ee primenenie [Oxyethylenediphosphonic acid and its application]. *Khimicheskaia promyshlennost — Chemical industry*, 4, 254−258 [in Russian].

27 Dyatlova, N.M., Temkina, V.Ya., & Popov, K.I. (1988). *Kompleksony i kompleksonaty metallov [Complexones and complexonates of metals]*. Moscow: Khimiia [in Russian].

28 Bakibaev, A.A., Ukhov, A.E., Malkov, V.S., Zhumanov, K.B. (2021) Efficient Synthesis of Tetraacetylglycoluril in the Presence of Phosphorus-Containing Catalysts. *Russian Journal of Organic Chemistry,* 57(1), 58–63. https://doi.org/10.1134/S1070428021010085

Information about authors*

Panshina, Svetlana Yur'evna — *(corresponding author)* Postgraduate of chemistry specialty, Department of Organic Chemistry and Polymers, Karagandy University of the name of academician E.A. Buketov, Universitetskaya street, 28, 100024, Karaganda, Kazakhstan; e-mail: janim_svetatusik@mail.ru; https://orcid.org/0000-0001-6824-2645

Bakibaev, Abdigali Abdimanapvich — Doctor of Chemical Sciences, Professor, Leading Researcher of the Laboratory of Organic Synthesis, National Research Tomsk State University, Lenin str., 36, 634050, Tomsk, Russia; e-mail: bakibaev@mail.ru; https://orcid.org/0000-0002-3335-3166

Guslyakov, Alexey Nikolaevich — 1st year PhD student, Laboratory of Organic Synthesis, National Research Tomsk State University, Lenin str., 36, 634050, Tomsk, Russia; e-mail: guslyakov.aleksej@bk.ru; https://orcid.org/0000-0001-8807-8766

Malkov, Victor Sergeevich — Candidate of Chemical Sciences, Head of the Laboratory of Organic Synthesis, National Research Tomsk State University, Lenin str., 36, 634050, Tomsk, Russia; e-mail: malkov.vics@gmail.com; https://orcid.org/0000-0003-4532-2882

---

*The author's name is presented in the order: *Last Name, First and Middle Names*