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S.Yu. Panshina^{1*}, A.A. Bakibaev², A.N. Guslyakov², V.S. Malkov²

¹Karagandy University of the name of academician E.A. Buketov, Karaganda, Kazakhstan;

²National 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”

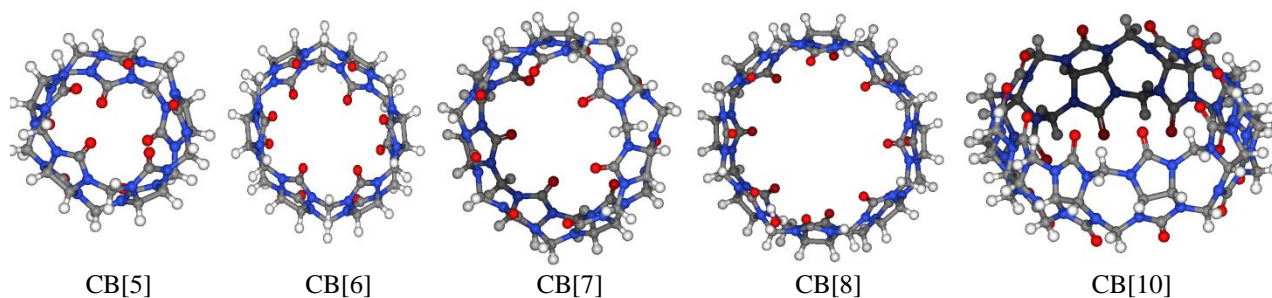
Glycoluril (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione) and its derivatives have a special place in chemistry of heterocyclic compounds. The macrocyclic derivatives of glycoluril, namely cucurbit[n]urils have recently attracted the greatest interest due to their unique properties. Cucurbit[n]urils 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

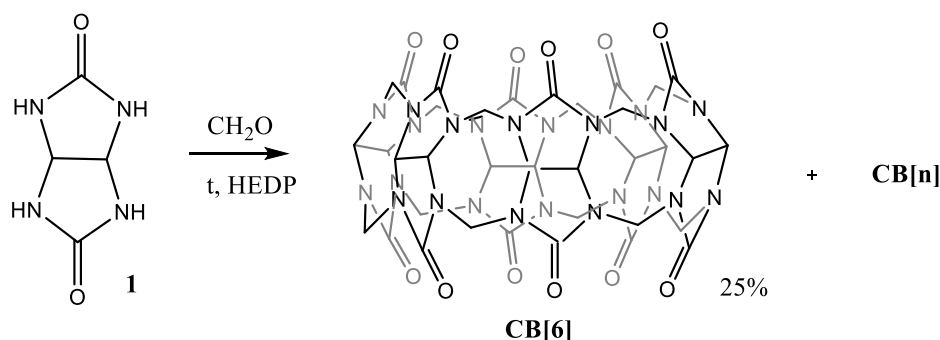
2,4,6,8-Tetraazabicyclo[3.3.0]octane-3,7-dione (glycoluril) **1** (Scheme 1) and its derivatives are the most interesting objects among bicyclic bisureas, which have a special place in the chemistry of heterocyclic compounds [1]. It has been reflected in the creation of valuable substances in various 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].

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 ¹³C nuclei respectively, in solutions of DMSO-*d*₆ and F₃CSO₃H. 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 K α radiation at $\lambda = 1.54053$ Å. Reflections were collected from 5 to 50 in 2 θ with a step of 0.014, a rate of 20 deg / min and a step time of 21.49 s at 17 °C.

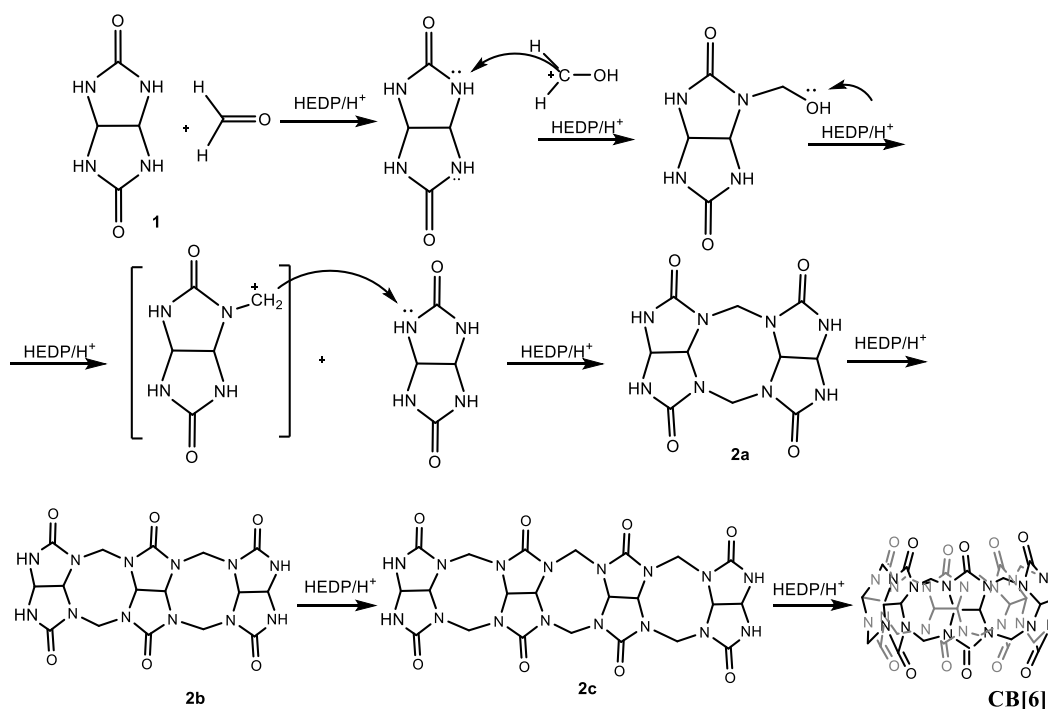
Synthesis of cucurbit[6]uril hydrate **CB[6] using HEDP.** Glycoluril **1** (21.4 g, 0.15 mol), HEDP (61.8 g, 0.30 mol) and 120 ml of water were added to a 250 mL round-bottomed flask equipped with a magnetic stir bar. The mixture was heated to 50 °C and then paraformaldehyde (9 g, 0.30 mol) was slowly 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, ν , cm⁻¹: 3441 (H₂O), 2927 (CH), 1712 (C = O). ¹H NMR (400 MHz, F₃CSO₃H/D₂O): $\delta = 5.82$ (s, 12H, CH),

5.58 (d, $J = 16.4$, 12H, CH₂), 4.63 (d, $J = 16.6$, 12H, CH₂). ¹³C NMR (101 MHz, F₃CSO₃H/D₂O): $\delta = 160.21$ (C=O), 72.71 (CH), 52.04 (CH₂).

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, H₂SO₄ and hardly soluble in F₃CSO₃H. T. of decomp. is more than 400 °C. IR spectrum, ν , cm⁻¹: 3503 (H₂O), 2998 (CH₃), 2933 (CH), 1730 (C=O). ¹H NMR (400 MHz, F₃CSO₃H/D₂O): $\delta = 5.81$ (d, $J = 5.6$, 12H, CH), 5.56 (d, $J = 13.9$, 12H, CH₂), 4.61 (d, $J = 14.5$, 12H, CH₂), 2.67 (s, 3H, CH₃). ¹³C NMR (101 MHz, F₃CSO₃H/D₂O): $\delta = 198.49$ (C=O_{acetone}), 160.11 (C=O), 72.68 (CH), 51.87 (CH₂), 29.97 (CH_{3 acetone}).

Results and Discussion

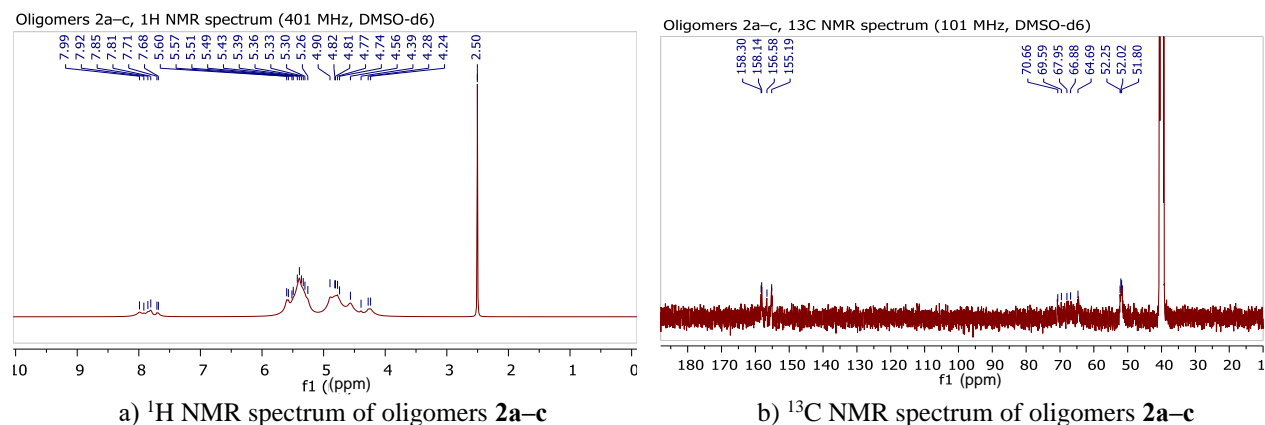
The reaction (Scheme 1) of glycoluril **1** and paraformaldehyde in a ratio of 1:2 was carried out with the traditional procedure [19], but HEDP was used as a catalyst in two equivalents relative to substrate **1**. It was suggested [28] that HEDP promoted more efficient transfer of glycoluril **1** 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-d₆) 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–CH₂–N groups are at δ 4.24–4.90 ppm (Fig. 2, a).

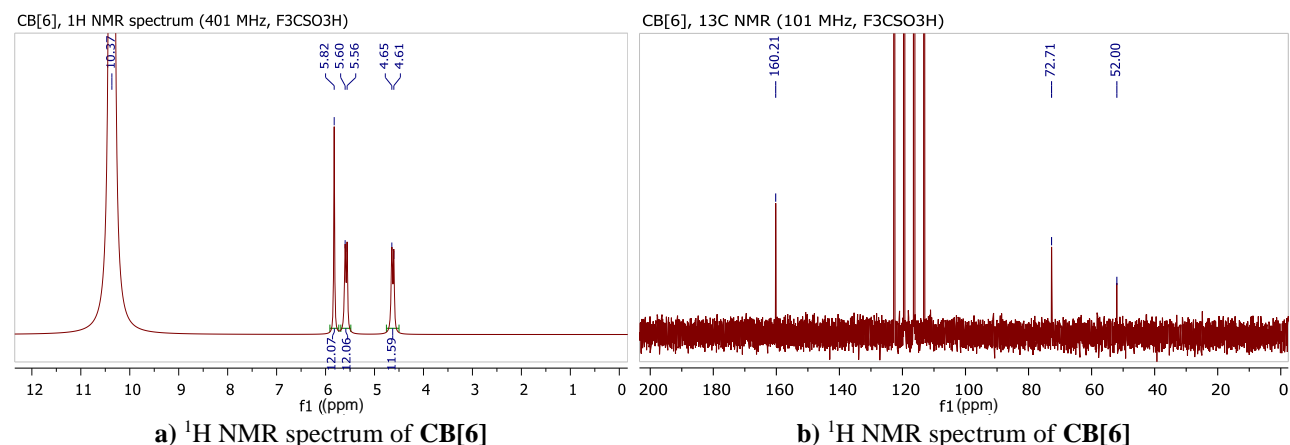
Figure 2. The NMR spectra of oligomers 2a-c in DMSO- d_6

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-CH₂-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. 3a, b).

Figure 3. The NMR spectra of **CB**[6] in F₃CSO₃H

The recorded NMR spectra of the substance **CB**[6] (Fig. 3a, b), in general, are identical to those previously recorded in the solvent DCI [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 $\text{CB}[6] \cdot 4.66 \text{H}_2\text{O}$ [19], which were synthesized in the presence of HCl acid as a catalyst.

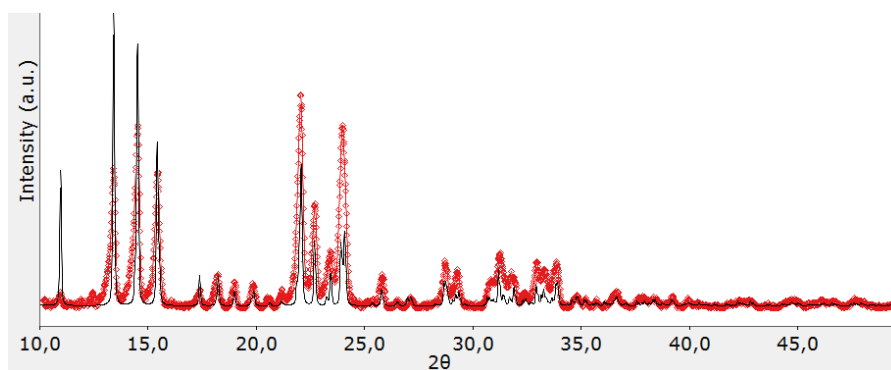
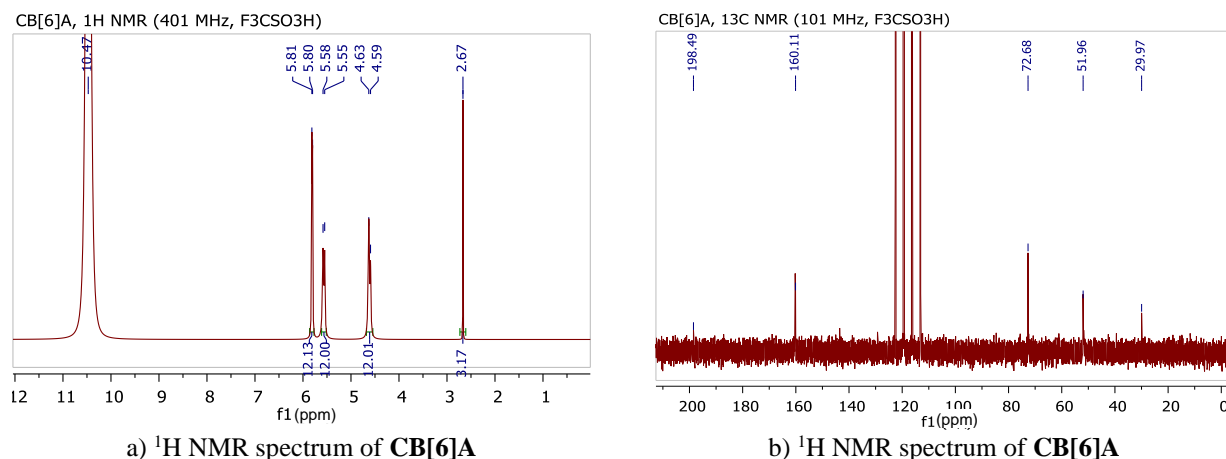


Figure 4. XRD of powder crystals of the isolated hydrate cucurbit[6]uril $\text{CB}[6]$ structure (red line) and the corresponding theoretical picture of hydrate cucurbit[6]uril, (black line)

The clathrate of cucurbit[6]uril with acetone $\text{CB}[6]\text{A}$ was obtained by treating the substance $\text{CB}[6]$ with hot acetone. Substance $\text{CB}[6]\text{A}$ is insoluble in concentrated acids HCl, H_2SO_4 and slightly soluble in $\text{F}_3\text{CSO}_3\text{H}$ acid. The structure of $\text{CB}[6]\text{A}$ was investigated by IR- and NMR spectroscopy (Fig. 5a, b).



a) ^1H NMR spectrum of $\text{CB}[6]\text{A}$

b) ^{13}C NMR spectrum of $\text{CB}[6]\text{A}$

Figure 5. The NMR spectra of $\text{CB}[6]\text{A}$ in $\text{F}_3\text{CSO}_3\text{H}$

Previously, a similar clathrate [19], was described using X-ray diffraction analysis, the structure of which was a composition of one $\text{CB}[6]$ per one acetone and eight water molecules. In our case, according to NMR data, the ratio of $\text{CB}[6]$ and acetone molecules was also 1:1 in the clathrate. In the NMR spectra (Fig. 5a, b) of the clathrate $\text{CB}[6]\text{A}$, in addition to the main chemical shifts of cucurbit[6]uril $\text{CB}[6]$, 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 $\text{CB}[6]$. Dipole-dipole interactions are shown in NMR spectra, where in the ^{13}C NMR spectrum the peak of the $\text{C}=\text{O}$ group of acetone is shielding by an average of 8 ppm (Fig. 5b), 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. 5a), 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.

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С.Ю. Паншина, А.А. Бакибаев, А.Н. Гусяков, 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-тетраазабицикло[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. Жакында 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. Гусяков, В.С. Мальков

Синтез кукурбит[6]урилы 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 гликолурилы — кукурбит[*n*]урилы, что связано с их уникальными свойствами. Кукурбит[*n*]урилы обычно синтезируют реакцией конденсации гликолурилы 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]урилы в качестве катализатора «зеленой» химии в водной среде. Проведена реакция гликолурилы и параформальдегида в соотношении 1:2 с двумя эквивалентами 1-гидроксиэтан-1,1-дифосфоновой кислоты в качестве катализатора, где гексамер кукурбитурилы ($n = 6$) получен с выходом 25 %. Реакцию гликолурилы с параформальдегидом в присутствии ОЭДФ можно использовать как конкурентный метод синтеза кукурбит[6]урилы. Выделенный гексамер кукурбит[6]урилы 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]урилы гидрата охарактеризован методом порошковой рентгенографии (РФА). РФА анализ показал, что тип кристаллической решетки и фазовый состав кристаллов гидрата кукурбит[6]урилы, полученных в присутствии ОЭДФ, идентичны кристаллам гидрата кукурбит[6]урилы, синтезируемым классическими методами.

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

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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*