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Synthesis and study of a novel supramolecular 'host–guest' complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride

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ABSTRACT

A novel supramolecular complex $C_{44}H_{71}Cl_2N_{26}O_{22}$ (CB[6]@Pipa·2HCl) of the "host-guest" type has been synthesized. It is based on cucurbit[6]uril (CB[6]) with dihydrochloride 1,4-bis(2-hydroxyethyl)piperazine (Pipa·2HCl) localized within the portals of the macrocycle. Based on 1H NMR and X-ray crystallography, the host–guest ratio in the complex under the specified conditions was determined to be 1:1. Further evidence of complex formation was observed through IR spectroscopy, where a shift in the absorption band of carbonyl vibrational frequencies of cucurbit[6]uril by 36 cm^{-1} towards the longer wavelength region was detected in CB[6]@Pipa·2HCl compared to the original CB[6]. TGA/DSC analysis results indicated an increase in thermal stability by 55 °C for the obtained CB[6]@Pipa·2HCl complex compared to the initial 1,4-bis(2-hydroxyethyl) piperazine dihydrochloride. The structure of the synthesized CB[6]@Pipa·2HCl complex was confirmed using single-crystal XRD.

1. Introduction

Supramolecular chemistry represents a recognized research field with the potential to make significant contributions to several key applications, including drug delivery, sensing, and catalysis [1–6]. Within the area of supramolecular chemistry, the "host-guest" chemistry focuses on investigating molecular interactions between macrocyclic receptors, known as "hosts," and low-molecular-weight ligands, referred to as "guests," primarily through non-covalent interactions [7,8]. Well-known complexation agents, such as cyclodextrins [9,10], calixarenes [11,12], cucurbiturils [13,14], and pillararenes [15,16] constitute established supramolecular macrocycles capable of encapsulating both organic and inorganic guest molecules within their cavities. Typically, encapsulation of a "guest" within the cavity of a macrocyclic "host" leads to changes in its physicochemical properties [17]. Among the promising "hosts" in this context are cucurbit[n]urils, a class of macrocyclic hosts that exhibit a pumpkin-like shape and consist of five or more glycoluril units connected by pairs of methylene bridges [18–20].

The cavity of **CB[6]**, as depicted in Fig. 1, is classified as a hydrophobic nanospace capable of binding hydrophobic compounds and neutral guest molecules in aqueous environments [21–23]. Furthermore, the negatively charged carbonyl portals promote the binding affinity towards metal ions and cationic compounds [24–27]. Following the interpretation of the structure of the original hexameric homologue of **CB[6]**, Mock and colleagues discovered the strong binding of alkylammonium and alkyl-diammonium ions to **CB[6]** [28,29], opening ways for the synthesis of analogous supramolecular systems.

On the other hand, 1,4-bis(2-hydroxyethyl)piperazine (**Pipa**) (Fig. 2) is a non-planar saturated heterocyclic diol, containing two tertiary amine groups within a six-membered ring and two primary hydroxyethyl groups bound to nitrogen atoms. Consequently, this compound exhibits bifunctionality, both in terms of hydroxyl and amine groups. Owing to these structural attributes, the **Pipa** molecule can act as a ligand and form stable complexes with transition metals [30,31]. The complexation properties of **Pipa** have been used in the synthesis of novel

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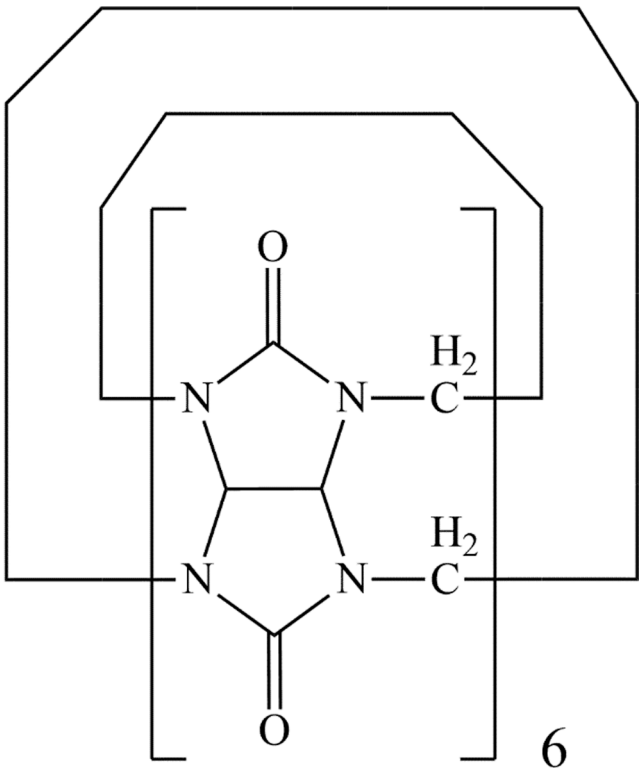

Fig. 1. Molecular Structure of CB.

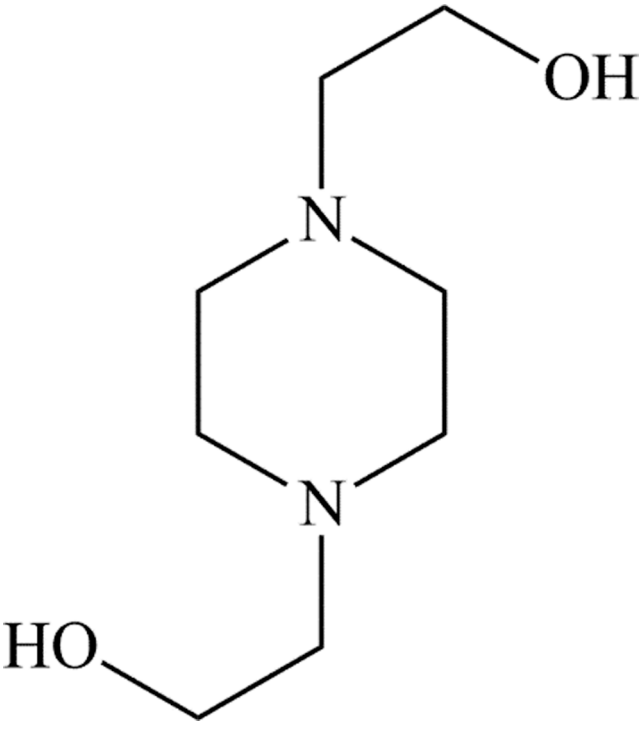

Fig. 2. Molecular Structure of 1,4-bis(2-hydroxyethyl)piperazine.

metal–organic framework structures (MOFs) [32,33] and polyoxometalates (POMs) [34–37]. The piperazine ring serves as a pharmacophore group, a vital structural element in many biologically active compounds. For instance, the antispasmodic drug Nafiverine is a direct diacylated derivative of **Pipa** [38]. In light of this, **Pipa** holds particular interest as a substrate for the synthesis of novel bioactive compounds [39].

It is noteworthy that 1,4-bis(2-hydroxyethyl)piperazine readily undergoes mono- and diprotonation upon exposure to acids, yielding the corresponding salts [40].

Considering the aforementioned, the objective of this study is the synthesis and investigation of a novel supramolecular system based on 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride and cucurbit[6]uril.

The exploration of the obtained complex holds promising potential for its future utilization as a precursor in the synthesis of new metal–organic framework structures and novel bioactive compounds.

2. Materials and methods

Cucurbit[6]uril (CB[6]) was synthesized according to literature [41]. Briefly, glycoluril (21.4 g, 0.15 mol), oxyethylenediphosphonic acid (61.8 g, 0.30 mol), and 120 mL of water were combined in a 250 mL round-bottom flask equipped with a magnetic stirrer. The mixture was heated to 50 °C, and paraformaldehyde (9 g, 0.30 mol) was slowly added, allowing the solution to mix thoroughly. The resulting solution was stirred for an additional 30 min until it solidified into a gel, which was then heated to 100 °C, causing the gel to dissolve rapidly. The reaction mixture was boiled for 20 h at 100 °C. Subsequently, the solution was cooled to room temperature. The obtained precipitate was filtered and washed with hot water, and dissolved in boiling 37 % HCl solution. The resulting solution was cooled and left at 0 °C for a week for crystallization. Colorless hexagonal **CB[6]** crystals of high purity were formed on the vessel walls. **CB[6]** was obtained as a white powder with a yield of 6.3 g (25 %). IR spectrum, ν, cm^{-1}: 3328 (H_2O), 2448 (CH_2), 1684 (C = O). ^{1}H NMR (400 MHz, F_3CSO_3H/D_2O, TMS) δ, ppm: 5.82 (s, 12H, CH); 5.58 (d, 12H, CH_2); 4.63 (d, 12H, CH_2). ^{13}C NMR (101 MHz, F_3CSO_3H/D_2O, TMS) δ, ppm: 160.21 (C = O); 72.71 (CH); 52.04 (CH_2). The structure of the obtained **CB[6]** was confirmed by powder X-ray diffraction (Fig. S1, supplementary material).

1,4-bis(2-hydroxyethyl) dihydrochloridePiperazine (Pipa·2HCl) was obtained by dissolving 1,4-bis(2-hydroxyethyl)piperazine (17.4 g, 0.1 mol) in 20 % HCl. The resulting solution was evaporated to half of its volume and left to crystallize. The obtained crystals were filtered and recrystallized twice from a mixture of methanol/water = 50/50. The yield was 18 g (73 %).

^{1}H NMR (400 MHz, D_2O, TMS) δ, ppm: 3.32 (q, 4H, $–CH_2$-N <); 3.63 (s, 8H, $–CH_2$-N-(cycle)); 3.82 (q, 4H, $–CH_2$-OH).

^{13}C NMR (101 MHz, D_2O, TMS) δ, ppm: 48.48 (CH_2 (cycle)); 54.74 ($–CH_2$-N <); 58.00 ($–CH_2$-OH).

2.1. Encapsulation of 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride in the cavity of cucurbit[6]uril in an aqueous environment

Cucurbit[6]uril (1 g, 0.001 mol) was dissolved in 100 mL of water under constant stirring until complete dissolution. Subsequently, 1,4-bis (2-hydroxyethyl)piperazine dihydrochloride (0.248 g, 0.001 mol) was added, and the mixture was stirred until complete dissolution. The resulting solution was filtered and left in the open air for 14 days for slow solvent evaporation. After 5 days the precipitation of the first **CB[6]@Pipa·2HCl** crystals was observed. After 14 days, the precipitated crystals were filtered and air-dried. The mass of the obtained **CB[6]@Pipa·2HCl** was 0.63 g (50.5 %).

NMR spectra were recorded on a Bruker AVANCE III HD spectrometer (Bruker Corporation, Germany) with an operating frequency of 400 and 100 MHz for ^{1}H and ^{13}C nuclei respectively, in solutions of DMSO-d_6, F_3CSO_3H and D_2O. The internal standard was tetramethylsilane (TMS).

IR spectra of the starting materials and the obtained complex were recorded on a Nicolet 6700 Fourier-transform infrared spectrometer with a diamond crystal attachment at a resolution of 4 cm^{-1}, 64 scans, in the range of 500–3700 cm^{-1}.

2.2. Single crystal X-ray diffraction

Single crystal XRD data were collected on a Bruker D8 Venture diffractometer with a CMOS PHOTON III detector and IμS 3.0 source (mirror optics, λ(MoKα) = 0.71073 Å). The φ- and ω-scan techniques were employed to measure intensities. The crystal structure was solved using the SHELXT [42] and was refined using SHELXL [43], programs with OLEX2 GUI [44]. Atomic displacement parameters for non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed geometrically and refined in the riding model.

Crystal data for **CB [6] @Pipa·2HCl** ($C_{44}H_{71}Cl_2N_{26}O_{22}$) ($M$ = 1387.17 g/mol): monoclinic, space group $P2_1/c$, a = 12.1074(6) Å, b = 20.3920(9) Å, c = 12.6061(5) Å, β = 112.368(2)°, V = 2878.2(2) Å3, Z = 2, T = 150(2) K, μ(CuKα) = 0.22 mm^{-1}, D_{calc} = 1.601 g/cm3, 20,000 reflections measured (3.6° ≤ 2Θ ≤ 52.8°), 5894 unique (R_{int} = 0.0494, R_{sigma} = 0.0602) which were used in all calculations. The final R_1 was 0.093 (I > 2σ(I)) and wR_2 was 0.295 (all data); $\Delta\rho_{max}$ = 1.24 e Å−3, $\Delta\rho_{min}$ = − 0.78 e $Å^{-3}$.

Cambridge Crystallographic DataCentre (CCDC) deposition Number 2295984 contains the supplementary crystallographic data for this paper. These data are provided free of charge from CCDC at https://www.ccdc.cam.ac.uk/structures.

TGA/DSC- were conducted using a Simultaneous Thermal Analyzer (STA) 6000 instrument in a temperature range of 30–800 °C under a nitrogen atmosphere, with a heating rate of 10 °C/min.

Elemental analysis CHNS was carried out on an instrument HCNS-O UNICUBE -ORGANIC ELEMENTAL ANALYZER. Standard: sulfanilamide. Detector: Thermal Conductivity Detector (TCD) and Infrared (IR) for sulfur Maximum furnace temperature: 1,200° C.

Elemental analysis CHNS (%) calculated for **CB [6] @Pipa·2HCl**: N – 26.24, C – 38.06, H – 5.12. Found: N – 25.24, C – 38.00, H – 5.15.

3. Results and discussion

3.1. Single crystal X-ray diffraction

The inclusion compound **CB [6] @Pipa·2HCl** crystallizes in a monoclinic crystal system, symmetry space group $P2_1/c$. The asymmetric unit contains half of **CB [6]** host, half of **Pipa·2HCl** guest molecule, one chloride anion and four solvate water molecules. The molecular structure is shown in Fig. 3.

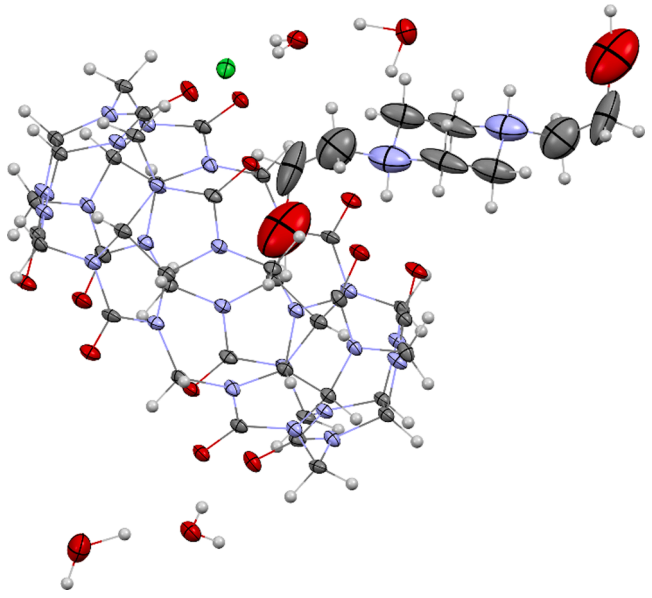

Fig. 3. Molecular structure of CB[6]@Pipa·2HCl according to SCXRD analysis. Thermal ellipsoids are shown at 30 % probability for the guest molecule and at 50 % for the rest of the atoms.

The guest molecules, **Pipa·2HCl,** are located between the portals of the neighboring **CB [6]** molecules. The methylene and NH groups of the guest molecules are involved in multiple C–H···O and N–H···O interactions with five out of six carbonyl groups of **CB [6]** hosts (Fig. 4a). Two distinct types of N–H···O interactions are observed, with H···O internuclear distances of 1.919 Å and 2.524 Å, while the C–H···O interactions are mostly uniform with the average H···O distance of 2.45 Å. Both of the indicated interactions join the **CB [6]** molecules into supramolecular chains oriented along the crystallographic axis c (Fig. 4b, Fig. S2). The chains are linked by C–H···O interactions (d(H···O) = 2.646 Å) involving the methylene and carbonyl groups of **CB [6]** molecules from different chains (Fig. 4b).

3.2. NMR analysis of CB[6]@Pipa·2HCl

The results obtained from single-crystal X-ray diffraction are corroborated by nuclear magnetic resonance (NMR) spectroscopy. NMR spectra of the synthesized material were recorded in D_2O. In the ^1H NMR spectra (Fig. 5), two doublets corresponding to the methylene protons of cucurbit[6]uril were observed at 5.59 and 4.17 ppm, indicative of signals originating from the obtained complex. Additionally, a signal at 5.43 ppm corresponding to the methine protons in cucurbit[6]uril was identified. The signal for the methylene protons in the piperazine ring of 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride appeared as a singlet at 3.73 ppm, with a weak field shift of 0.1 ppm into the weak field area compared to free 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. A substantial field shift of the $–CH_2$-OH group of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, by 0.47 ppm into the weak field area relative to 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, resulted in the methylene protons ($–CH_2$-OH) forming a complex multiplet signal within the 2-hydroxyethyl group. A figure comparing the NMR spectra of ^1H of the initial compounds and the resulting compound is given in the supplementary material (Fig. S3).

In the ^{13}C NMR spectrum of **CB [6] @Pipa·2HCl** (Fig. 6), two distinctive signals at 156.21 and 156.66 ppm correspond to the carbonyl carbon atoms. This signal splitting suggests that one of the portals of cucurbit[6]uril experiences stronger interactions with the guest molecule. Additional signals at 70.23 and 51.29 ppm are attributed to the methine and methylene carbon atoms of cucurbit[6]uril, respectively.

In the case of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride molecule, signals were observed at 54.74 ppm for $–CH_2$-N < and at 48.82 ppm for methylene carbon atoms within the ring. Notably, these signals exhibited chemical shifts of 0.34 ppm and 0.23 ppm, respectively, in a weaker field compared to the free 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. A figure comparing the NMR spectra of ^{13}C of the initial compounds and the resulting compound is given in the supplementary material (Fig. S4).

These NMR spectroscopic findings provide compelling evidence of complex formation and the localization of the guest molecule, 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, at the portals of cucurbit[6]uril.

3.3. IR spectroscopy

The IR spectrum of **CB [6] @Pipa·2HCl** (Fig. 7) exhibits a complex profile, making it challenging to provide a definitive interpretation of the signals. However, a comparative analysis of the IR spectra of the starting materials and the resulting complex shows a splitting of the absorption band corresponding to the valence vibrations of the carbonyl groups of cucurbit[6]uril, as well as their noticeable shift by 36 cm^{-1} and 12 cm^{-1} towards short-wave numbers. Splitting of the absorption band of valence vibrations of carbonyl groups indicates the presence of two groups of nonequivalent carbonyl groups in the supramolecular complex, which is confirmed by the data of single crystal X-ray diffraction. The absorption band at 1684 cm-1 corresponds to five of the

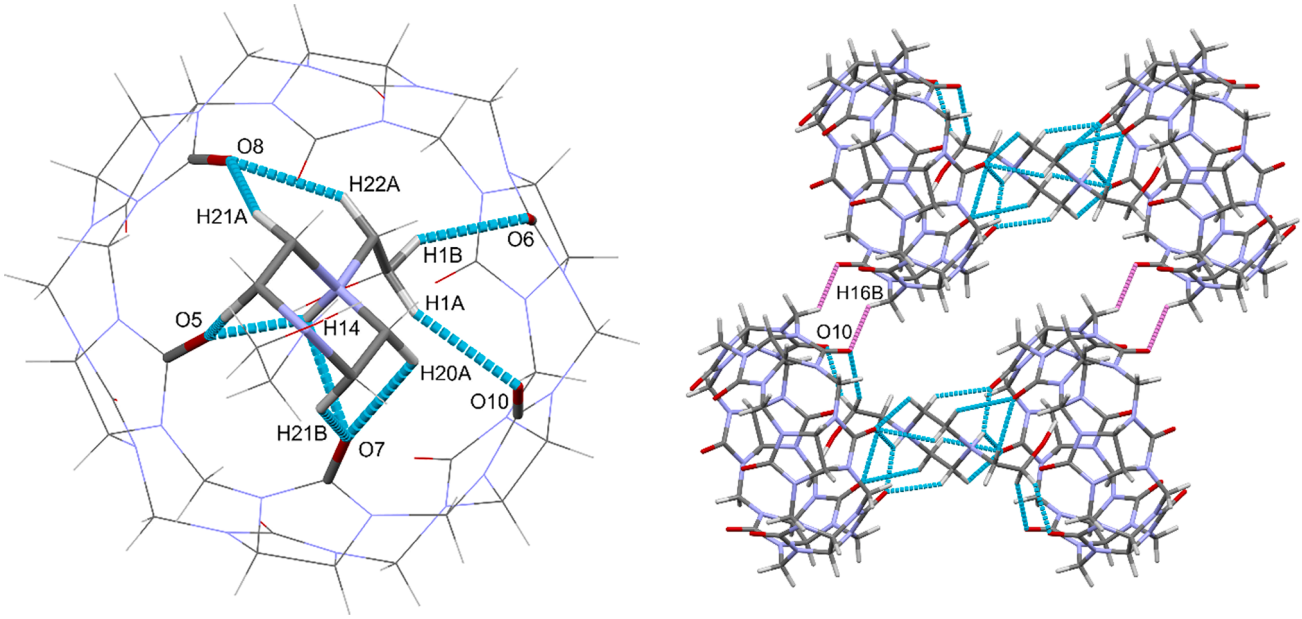

Fig. 4. Supramolecular interactions in the crystal structure of CB[6]@Pipa·2HCl: (a) host–guest C–H···O and N–H···O contacts (shown in blue), view along the crystallographic axis c; (b) C–H···O contacts between the supramolecular chains (shown in purple), view along the crystallographic axis b. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

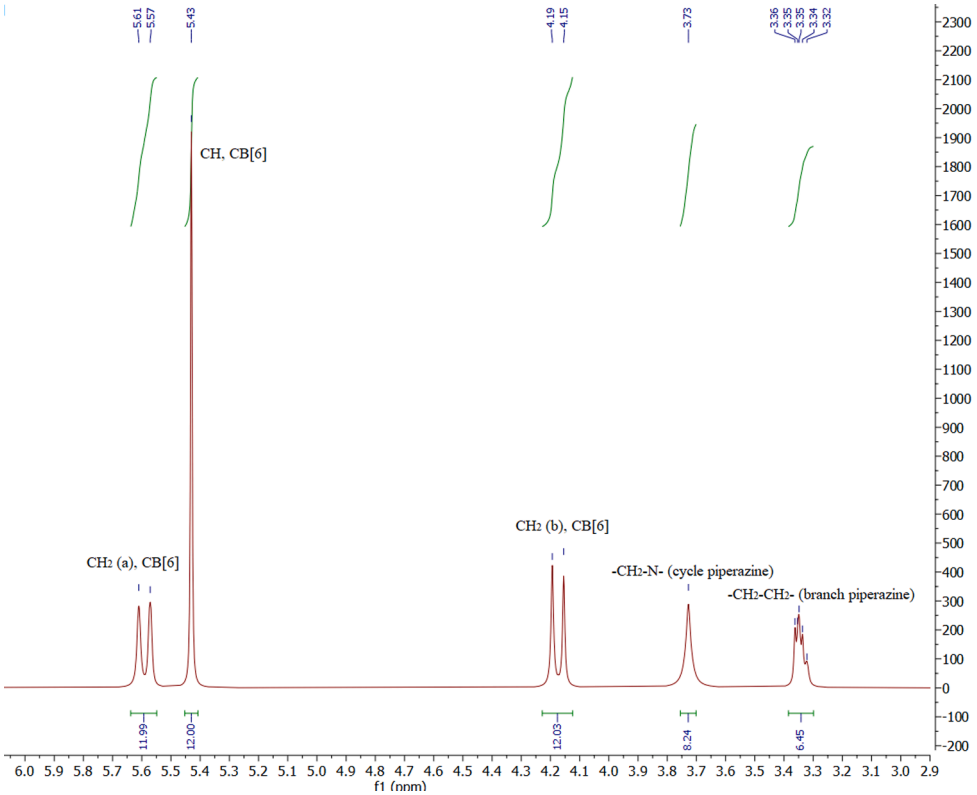

Fig. 5. ^{1}H NMR spectrum of CB[6]@Pipa·2HCl.

six carbonyl groups that are susceptible to interaction with 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. This experimental fact unequivocally confirms the occurrence.

3.4. TGA/DSC

TGA/DSC analyses were performed for the pristine **CB[6]**, **Pipa·2HCl,** and the synthesized **CB[6]@Pipa·2HCl** complex, covering the temperature range of 30–800 °C under an inert nitrogen atmosphere (Figs. 8 and 9). The results revealed that the thermal stability of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride was enhanced by 55 °C compared to the free 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. However, it is noteworthy that the overall TG curve profile of the obtained complex coincides with that of pure

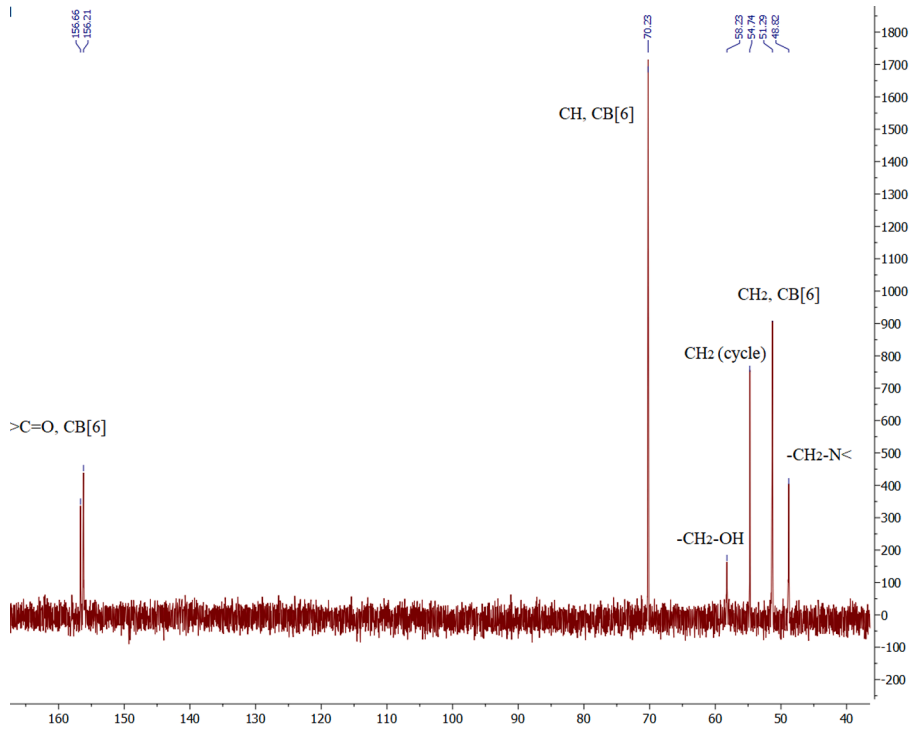

Fig. 6. ^{13}C NMR spectrum of CB[6]@Pipa·2HCl.

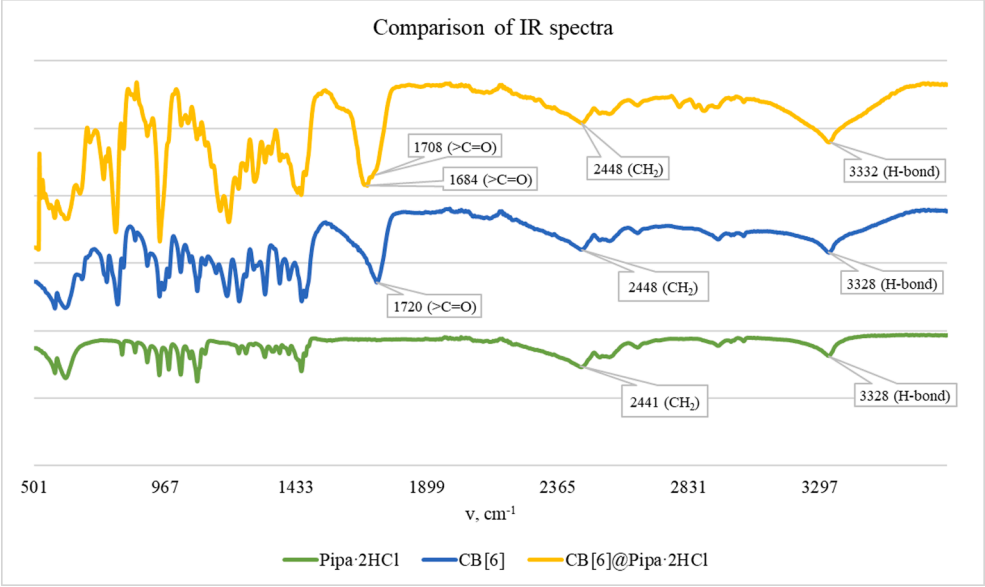

Fig. 7. Comparative analysis of IR spectra of the obtained complex CB[6]@Pipa·2HCl and the starting materials CB[6] and Pipa·2HCl.

cucurbit[6]uril. Although the decomposition of this complex occurs at 473 °C, which is 44 °C lower than the decomposition of free cucurbit[6]uril. A significant increase in the stability of 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride in the complex is due to the fact that it is located in the cavity of cucurbit[6]uril and is retained due to intermolecular non-covalent bonds.

4. Conclusion

In this study successfully synthesized and characterized a novel "host-guest" complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride using various analytical techniques, including NMR, IR spectroscopy, and TGA/DSC analysis. The comparative analysis of the IR spectra of the starting materials and the synthesized complex revealed a shift and splitting of the absorption band of carbonyl vibrations of cucurbit[6]uril by 36 cm^{-1} and 12 cm^{-1} towards smaller wave numbers, which indicates the formation of a complex due to carbonyl oxygen atoms of cucurbit[6]uril. TGA/DSC data suggested an increase in the thermal stability of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride by 55 °C. Additionally, single-crystal XRD confirmed the structure of the obtained complex, showing that the guest molecule, 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, formed complexes through the quaternized nitrogen atoms of the piperazine ring and was localized at the carbonyl portals of cucurbit[6]

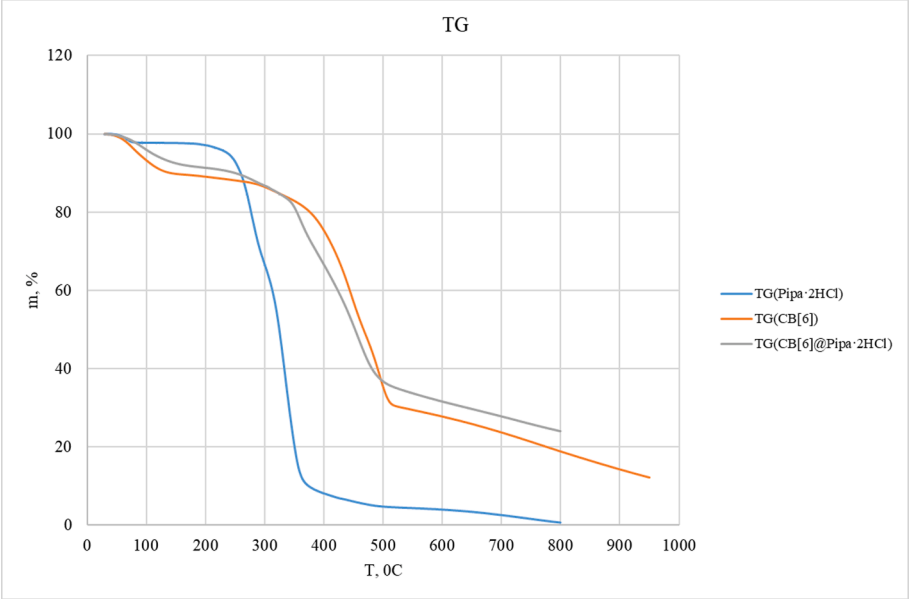

Fig. 8. TGA of Pristine CB[6], Pipa·2HCl, and the synthesized CB[6]@Pipa·2HCl complex.

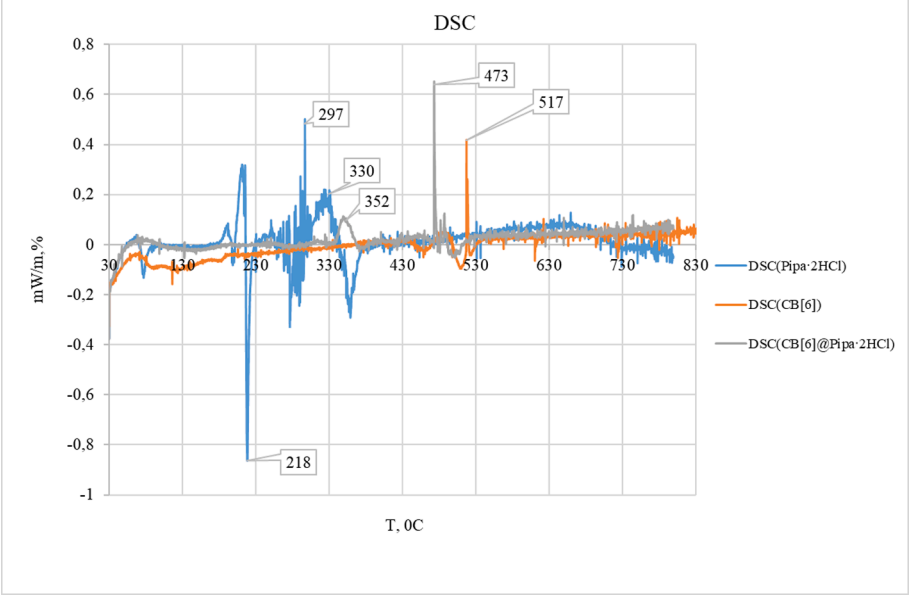

Fig. 9. DSC analysis of pristine CB[6], Pipa·2HCl, and the synthesized CB[6]@Pipa·2HCl complex.

uril.

CRediT authorship contribution statement

Tolkynay Burkhanbayeva: Investigation, Writing – original draft, Validation. **Alexey N. Guslyakov:** Investigation, Writing – original draft. **Farkhad F. Tarikhov:** Validation, Visualization. **Dmitry I. Pavlov:** Conceptualization, Methodology. **Rakhmetulla S. Erkasov:** Project administration, Data curation. **Abdigali A. Bakibaev:** Writing – review & editing. **Andrei S. Potapov:** Software. **Vyacheslav A. Yanovsky:** Formal analysis. **Victor S. Malkov:** Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jscs.2024.101819.

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