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Cucurbiturils Substituted on the Methylene Bridge

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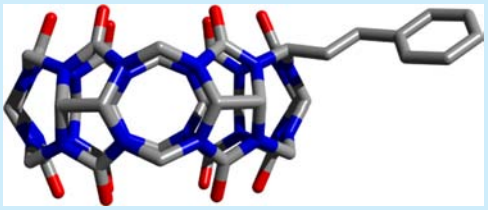
Supporting Information

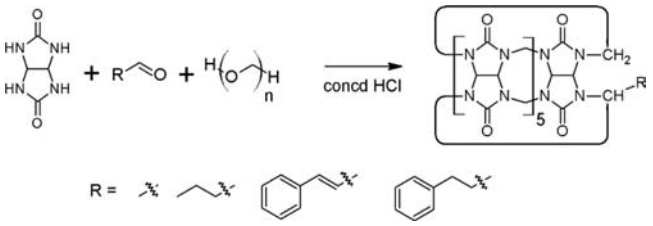
ABSTRACT: Cucurbit[6]uril (CB[6]) with a substituent attached solely to one methylene bridge was prepared for the first time. The monosubstituted CB[6] undergoes self-assembly to form a cyclic tetramer in the solid state. The affinity of the monosubstituted CB[6] to a series of alkylammonium salts was measured revealing a minor effect of the substituent on the binding properties of the macrocycle.



Preparation of substituted cucurbit[n]urils (CB[*n*]) represents one of the greatest challenges in the chemistry of these container molecules.[1] The introduction of the substituent on CB[*n*] is needed to increase their overall low solubility[2] and to allow their further functionalization.[3] The substituents are generally introduced to methine carbon atoms of glycoluril units on the convex face of cucurbiturils; this is achieved by either using substituted glycolurils in the cucurbituril-forming reaction[3c,4] or through direct derivatization of the cucurbituril homologues.[3a,b,5] Contrary to this well-described substitution on the convex face of cucurbiturils, only one successful approach toward cucurbiturils being substituted on methylene bridges has been reported in the literature.[6] The preparation is based on the reaction of the preorganized CB-building block−glycoluril hexamer with *o*-phthalaldehyde or its derivatives.[3d,6,7] The resulting six-membered ring contains two methylene bridges on opposite portals connected by a phenyl-1,2-diyl unit. The reaction of nor-seco-CB[6] with *o*-phthaladehyde leads to the insertion of a dimethyl ether bridge instead of a methylene bridge.[8] In this paper, we report the synthesis of the first cucurbituril bearing a substituent on one methylene bridge position. This compound was prepared simply by the acid-catalyzed condensation of glycoluril and a mixture of paraformaldehyde and 3-phenylpropionaldehyde. We also demonstrate that this approach is universal and can be translated for different aldehydes.

We started to investigate the preparation of cucurbiturils having a substitutent on each methylene bridge of the macrocycle nine years ago. However, all our attempts were based on the reaction of glycoluril and aldehydes/ketones dissimilar to formaldehyde and ultimately failed to produce the anticipated macrocycles. Similar unsuccessful attempts were also reported by other research groups,[1] and the reasons for the failure of the per-substitution on methylene bridge positions were later rationalized.[9] Thus, we decided to test the preparation of cucurbituril with only partial substitution on the methylene-bridged position. We tested the reactions of the desired aldehyde and paraformaldehyde with glycoluril in concentrated hydrochloric acid at elevated temperature (Scheme 1). The raw products were analyzed by MALDI-TOF-MS as the ^{1}H and ^{13}C NMR spectra presented very broad and overlapping signals. Surprisingly, when acetaldehyde, butanal, cinnamic aldehyde, and 3-phenylpropionaldehyde were used in the reaction, the corresponding MS spectra revealed the presence of CB[6], with one or two substituents indicating incorporation of aldehyde into the macrocyclic structure (Supporting Information, Figures S7−10).

Scheme 1. Reaction Scheme for Synthesis of Monosubstituted CB[6]



3-Phenylpropionaldehyde was then selected for further detailed studies. The most promising result with this aldehyde was achieved when formaldehyde, 3-phenylpropionaldehyde, and glycoluril were mixed in an equimolar ratio and heated at 90 °C in concd HCl for 24 h. The crude product was precipitated by the addition of water and acetone and was then purified using column chromatography. Only one substituted cucurbituril, mono(2-phenylethyl)cucurbit[6]uril (mPheCB[6]), was successfully isolated (Figure 1). We estimated that 1% of this macrocycle was present in the crude mixture and were able to isolate it at a 0.2% yield. mPheCB[6] was a kinetic product during the reaction as heating of the monosubstituted macrocycle in 35% DCl for 16 h led to the complete conversion to the unsubstituted CB[6]. The ^{1}H and ^{13}C NMR spectra of mPheCB[6] were resolved in the form of an inclusion complex with hexan-1,6-diammonium (HMDA) (Figure 2a).

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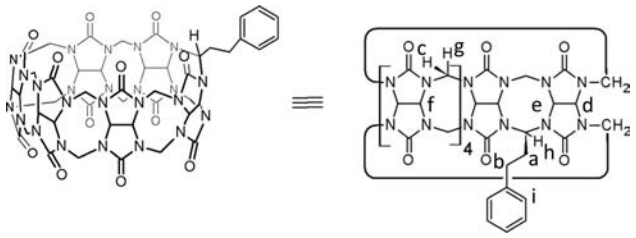

Figure 1. Structure of monosubstituted cucurbituril mPheCB[6].

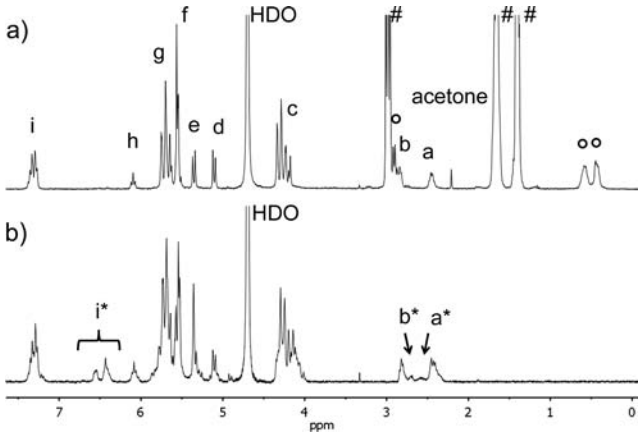

Figure 2. ^{1}H NMR spectra of mPheCB[6] (2.7 mM) in D_2O (a) in the presence of 8 equiv and (b) in the absence of HMDA. #Signal of unbound HMDA. °Signal of bound HMDA.

The signals of the ethylphenyl group were clearly detected in the aliphatic (H_a, H_b) and aromatic (H_i) regions, respectively, with their intensities corresponding to a single substituent on the macrocycle. The postulated structure was further confirmed by the triplet belonging to the proton H_h of the substituted methylene bridge. An important question to be resolved was the position of the substituent on the methylene bridge. Two hydrogen atoms on the methylene bridge of cucurbiturils have very different chemical surroundings: one hydrogen atom points in the same direction as the oxygen atoms on the macrocycle portal, while the second points out from the cavity. The downfield shift of the signal H_h indicates a deshielding influence of the surrounding carbonyl groups on this hydrogen atom. Hence, the ethylphenyl group occupies the position furthest from the oxygen atoms (Figure 1). The position of the substituent was additionally confirmed by ROESY-NMR spectra showing cross-coupling signals between the ethyl H_a and methine protons H_e located at the two glycoluril units surrounding the substituted methylene bridge (Supporting Information, Figure S6).

The ^{1}H NMR spectra of mPheCB[6] with and without HMDA differ significantly (Figure 2). The additional signals H_i*, H_a*, and H_b* were detected in the absence of the guest. Signals H_i* and H_b* are shifted upfield and signal H_a* downfield from their original positions. These signals indicate that some of the ethylphenyl substituents are included inside the mPheCB[6] macrocycle. Intramolecular encapsulation of the ethylphenyl group can be ruled out for sterical reasons. Thus, the observed pattern agrees with the partial self-association of macrocycles by inclusion of the ethylphenyl group of one mPheCB[6] into the cavity of another mPheCB[6] molecule. This interaction was slow on the NMR time scale, which allowed us to determine the diffusion coefficients of the free macrocycle ($(2.693 \pm 0.085) \times 10^{-10}$ m^2 s^{-1}) and its aggregate ($(1.908 \pm 0.083) \times 10^{-10}$ m^2 s^{-1}) using diffusion-ordered spectroscopy (DOSY). The diffusion coefficient for the free macrocyle was approximately 1.41 times higher when compared to its aggregate, which is close to the value of 1.44 theoretically calculated for aggregates containing three molecules of macrocycle.[4k] The self-association can be effectively eliminated through the addition of a guest to the mPheCB[6] solution. For instance, the macrocycle does not self-associate in the presence of 50 mM sodium acetate.

Structural features deriving from the analysis of the macrocycle in the solution were further confirmed by a solid-state study (Figure 3). We were able to solve the crystal structure of monocrystals obtained by the slow evaporation of an mPheCB[6] solution in water. In agreement with our expectations, the substituent is located on the methylene bridge and occupies the position furthest from the oxygen atoms of the portal. The four macrocycles self-assemble into a cyclic tetramer by mutual inclusion of ethylphenyl groups in their cavities. Furthermore, the tetramers are arranged into a honeycomb-like structure with a pore size diameter of approximately 1 nm.[10] It should be noted that the presence of trimers instead of tetramers was detected in the D_2O solution using DOSY, which can be rationalized by the lower solubility of tetramers in comparison to trimers in this media.

The host–guest interaction of mPheCB[6] and a series of alkylammonium salts were investigated using ^{1}H NMR

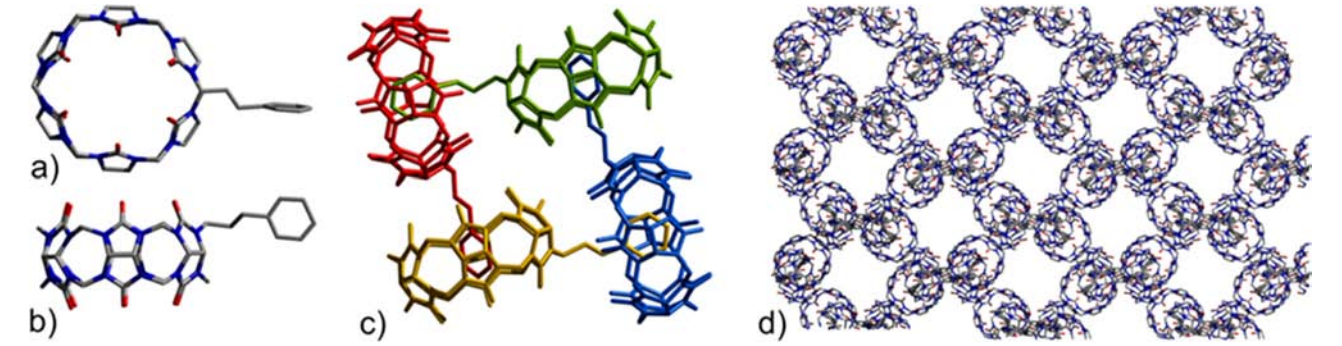

Figure 3. Wireframe representations of the crystal structures of mPheCB[6] (a) top and (b) side views, (c) highlighted self-assembly of the mPheCB[6] macrocycles into tetramer, and (d) packing diagram viewed along the *a*-axis. The hydrogen atoms and water molecules are not shown as their positions could not be determined with sufficient levels of certainty (for details, see the Supporting Information).

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spectroscopy, with the studies performed in 50 mM sodium acetate buffer to enhance the solubility of the macrocycle. The trends in the chemical shifts of the guests upon their inclusion in mPheCB[6] corresponded to those previously described for their inclusion in CB[6]. However, the absolute values of chemical shifts of the guest signals differed. Thus, two separate sets of signals of the guest were observed in the ^{1}H NMR spectrum (Supporting Information, Figures S12 and S13) of the solution containing the guest, mPheCB[6], and CB[6]. These two sets of signals corresponded to the guest included in CB[6] and mPheCB[6]. This allowed us to determine the relative binding constants (K_{rel}) by competition of both macrocycles for the guest and subsequently calculate absolute association constants. The values summarized in Table 1 show that mPheCB[6] binds to monoammonium cations as strong as CB[6]. The relative binding constants of diammonium guests are even slightly higher compared to CB[6], which is probably due to additional stabilizing interactions of the guest with the substituent on the macrocycle.

Table 1. Relative Association Constant K_{rel} of the mPheCB[6] Complex Related to the CB[6] Complex and the Resultant Absolute Association Constants K_a in 50 mM Sodium Acetate Buffer

guest	K_{rel}	K_a[b]/M^{-1}
1-aminobutane·HCl	1.09 ± 0.08	3.38 × 10^6
1-aminopentane·HCl	1.06 ± 0.09	2.34 × 10^6
1-aminohexane·HCl	*a*	
1,4-diaminobutane·2HCl	1.29 ± 0.14	2.58 × 10^7
1,5-diaminopentane·2HCl	1.31 ± 0.08	1.96 × 10^8
1,6-diaminohexane·2HCl	1.17 ± 0.09	3.40 × 10^8

[a]Value could not be determined due to overlapping signals. [b]Calculated using *K* for CB[6] from ref 11.

mPheCB[6] was obtained at a very low yield of 0.2%. Therefore, we investigated different approaches in order to increase the yield. We were unsuccessful in this task for a considerable period of time until the synthesis of glycoluril hexamer and its use in the cucurbituril forming reaction was reported by Isaacs and co-workers.[3c,6] We subsequently performed a reaction of the glycoluril hexamer with 8 equiv of 3-phenylpropionaldehyde in HCl. The ^{1}H NMR spectra of the crude product were easy to read, in contrast to the original synthesis where glycoluril instead of the oligomer was used (Supporting Information, Figure S11). Based on the integration of the relevant signals, we estimated the content of mPheCB[6] in the crude product to be 26%. From this material we obtained the macrocycle in its pure form in 18% yield.

In summary, we showed direct substitution of cucurbiturils on the methylene bridge position by simply mixing glycoluril, paraformaldehyde, and another aldehyde. We were able to isolate the monosubstituted six-membered macrocycle mPheCB[6] and to determine the configuration of the substituent by means of NMR spectroscopy and X-ray diffractometry. In the solid state, the molecules of the macrocycle exhibit self-association into tetrameric aggregates. These aggregates further organize in honeycomb-like structures with pores of 1 nm size. Self-association of the macrocycle in the solution was also observed using NMR techniques. The new macrocycle binds to organic ammonium cations with similar binding constants as CB[6]. With the reported approach enabling access to new substituted cucurbiturils, the scope of cucurbituril applications may therefore be broadened.

■ ASSOCIATED CONTENT

Supporting Information

Description of experimental procedures, ^{1}H and ^{13}C NMR, 2D-NMR spectra, and details of the X-ray structures of mPheCB[6]. Selected ^{1}H NMR spectra from the K_{rel} determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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