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Pressocucurbit[5]uril

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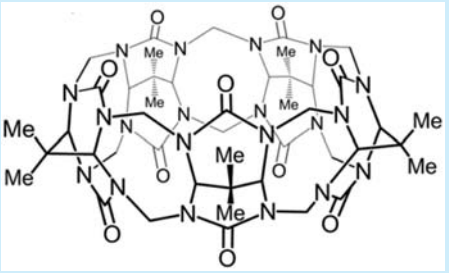
Supporting Information

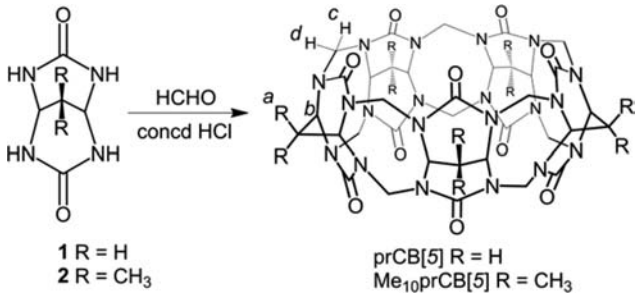
ABSTRACT: A novel macrocycle, decamethylpressocucurbit[5]uril (Me_{10}prCB-[5]), was synthesized by acid-catalyzed condensation of propanediurea and paraformaldehyde. This macrocycle binds methane with higher affinity than cucurbit[5]uril and its permethylated derivative.



Cucurbit[*n*]urils (CB[*n*]) are of increasing interest for their ability to bind inorganic and organic molecules in water with high affinity.[1−3] These macrocycles consist of *n* glycoluril units connected by *2n* methylene bridges. The smallest homologue, CB[5], contains five glycoluril units. Its cavity is too small to form an inclusion complex with any aliphatic chain, but inclusion of small gas molecules was reported.[4,5] On the other hand, the macrocyclic decamer of glycoluril, CB[10], even encapsulates other macrocycles such as porphyrin and CB[5].[6,7] While the diameter of CB[*n*] depends on the number of glycoluril units, their depth is nearly the same. Further, the substitution of hydrogen atoms on the convex face of CB[*n*] by alkyl groups can reduce the depth to a small extent.[8]

Here, we present a new macrocycle, pressocucurbit[5]uril (prCB[5]). This macrocycle is structurally similar to CB[5], except the building blocks are based on propanediurea instead of glycoluril (Scheme 1). As a result, prCB[5] differs from CB[5] not only in diameter but also in depth. We were inspired by the work of Nolte et al., who used propanediurea in the construction of molecular clips.[9,10] The distance between two oxygen atoms in the propanediurea is about 0.57 Å smaller compared to glycoluril.[11−14] It was reported that this rather small difference in the geometry has a pronounced effect on the affinity of molecular clips toward dihydroxybenzenes.[10] Propanediureas resemble the structural features of glycolurils, except for the additional methylene bridge between the two methine carbons. Therefore, we expected that an acid-catalyzed reaction of propanediurea with paraformaldehyde should lead to the formation of cyclic or acyclic oligomers similar to those observed in the cucurbituril-forming reaction. The ability of propanediurea to participate in the cucurbituril-forming reaction was recently confirmed by the synthesis of CB[6], in which one glycoluril unit is replaced by propanediurea.[15]

Scheme 1. Preparation of Pressocucurbit[5]urils



Two propanediureas, **1** and **2** (Scheme 1), differing with substitution on the methylene bridge are mostly used for the construction of supramolecular hosts.[9,10,14] It is known that propanediurea **1** undergoes decomposition under acidic conditions.[14,16] Therefore, its more stable dimethylated derivative **2** was investigated first in a reaction with paraformaldehyde.

The reaction was tested under different conditions including various temperatures, monomer ratios, reaction times, and nature of solvent. In all cases, a transparent solution was obtained that was poured into acetone to precipitate crude products. MALDI TOF MS was used for the initial characterization of the products as the ^{1}H NMR spectra comprised broad overlapping signals. The reactions yielded mixtures of oligomers in which propanediurea moieties were connected by methylene bridges. Macrocycle dodecamethylpressocucurbit[5]uril (Me_{10}prCB[5]) and acyclic propanediurea pentamer were products dominating the crude products. MS spectra indicated that the macrocycle contains five propanediurea units linked with two rows of methylene bridges (Scheme 1).

This structure seems to resemble the structure of CB[5]. The formation of the macrocycle was dependent on the reaction conditions. For instance, the macrocyclization at concentrated HCl took place even at 20 °C, which is in contrast to the

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formation of CB[n] requiring temperatures above 50 °C.[17] On the other hand, when the temperature was raised above 100 °C, massive decomposition of the propanediurea was observed. When the reactions were carried out in methanesulfonic acid, only acyclic oligomers were detected with chain lengths ranging from 4 to 8 and with no apparent dependence on the reaction time in the temperature range from 30 to 100 °C. In these oligomers, several propanediurea units were usually connected just by one instead of two methylene bridges (see the Supporting Information, Figures S11−S13). Our primary goal was to optimize the reaction conditions toward the preparation of the five-membered macrocycle Me_{10}prCB[5]. The best result was achieved when paraformaldehyde and propanediurea in a 3.1:1 ratio were stirred in 35% HCl at 90 °C for 10 h. The MS spectra revealed the presence of five-membered macrocycle accompanied by acyclic oligomers of five propanediurea units. Acyclic oligomers showed higher solubility in acidic media compared to the macrocycle. Thus, the precipitate was washed out repetitively with diluted HCl to remove the oligomers. The macrocycle at this stage contained ammonium chloride, which was formed by partial decomposition of propanediurea during reaction. The salt was removed by passing the solution through ion-exchange resin (Amberlyst A-26 OH) to obtain Me_{10}prCB[5] in a yield of 1%. The resulting macrocycle was unequivocally analyzed by ^{1}H and ^{13}C NMR spectrometry and MS spectrometry. Absence of the salt in the macrocycle was checked using ^{1}H NMR in DMSO-d_6 solution (for details, see Figure S8, Supporting Information). The macrocycle sparingly dissolved in water (40 g L^{-1}). Thus, solubility of Me_{10}prCB[5] is similar to that one for CB[5] (25 g L^{-1} in water).[2] Thermogravimetric analysis revealed a good thermal stability of Me_{10}prCB[5] which is comparable with other five-membered cucurbiturils (Figure S14, Supporting Information). We did not detect any mass loss connected with the decomposition of its sample under air atmosphere up to 300 °C. Despite numerous attempts, we failed to obtain a single crystal for the X-ray structure determination. Therefore, Me_{10}prCB[5] was visualized as a model obtained by quantum chemical calculations (Figure 1). Models of related cucurbiturils, CB[5], and dodecamethylcucurbit[5]uril (Me_{10}CB[5]) were also calculated for comparison. Dimensions of these macrocycles available from X-ray diffraction were not used as they are significantly influenced by the crystal packing and interactions of the macrocycles with other molecules in their proximity.

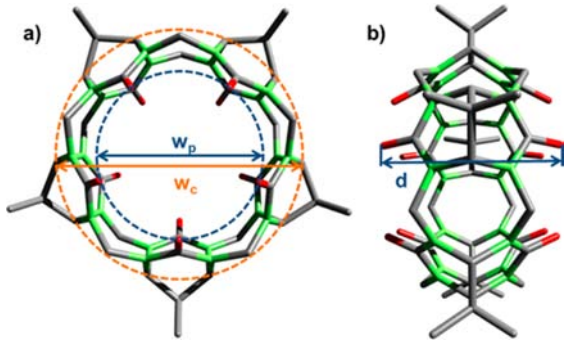

Figure 1. Energy-optimized geometry of Me_{10}prCB[5] with hydrogen atoms omitted for clarity. Top (a) and side (b) views. Color coding: C, gray; O, red; N, green.

The dimensions of the cucurbiturils optimized at the RI-BLYP-d3/def2-TZVPP level of theory are summarized in Table 1 (computational details are provided in the Supporting Information). According to expectations, very similar dimensions for CB[5] and Me_{10}CB[5] were obtained. However, dimensions of glycoluril-based macrocycles and Me_{10}prCB[5] differ significantly. Compared to Me_{10}CB[5], Me_{10}prCB[5] has a smaller common depth (d) of 0.264 Å, a smaller portal diameter (w_p) of 0.020 Å, and a higher cavity diameter (w_c) of 0.516 Å. Thus, Me_{10}prCB[5] can be visualized as the Me_{10}CB[5] macrocycle distorted by pressing the portals of oxygen atoms close to each other. This is why we suggested calling our new macrocycle *presso*cucurbit[5]uril (prCB[5]).

Table 1. Calculated Dimensions of CB[5] Macrocycles

	d (Å)	w_p (Å)	w_c (Å)	volume (Å^3)
Me_{10}prCB[5]	5.951	5.630	9.404	25.1
CB[5]	6.275	5.700	8.768	23.8
Me_{10}CB[5]	6.215	5.650	8.888	24.2

The predicted geometrical changes between Me_{10}prCB[5] and Me_{10}CB[5] have only a minor impact on cavity volume, which is 25.1 and 24.2 Å^3, respectively. The change of 0.9 Å^3 is rather negligible in comparison, for example, to a single water molecule, which has a volume of 11.5 Å^3 (the molecule is approximated as a spherical particle with a radius of 1.4 Å). Further analysis shows that the preservation of the cavity volume is due to the opposite effect of the macrocycle axial size reduction and its radial enlargement and vice versa.

The size differences between the glycoluril-based macrocycles and Me_{10}prCB[5] are clearly due to their structurally different building blocks: glycoluril and propanediurea. For instance, the presence of the methylene bridge significantly alters the distance between the methine carbon atoms from 1.594 Å found in glycoluril, to 2.427 Å found in propanediurea **2**. The presence of the methylene bridge has a more pronounced effect on the skeleton bending (oxygen, center of methine carbon atoms, oxygen angle, see Figure S15, Supporting Information), which is 130.7° and 98.0° for glycoluril and propanediurea, respectively. Skeleton bendings are kept similar when glycoluril is incorporated into the CB[5] macrocycle (from 130.7 to 130.0°) but significantly altered upon the translation of propanediurea **2** into Me_{10}prCB[5] (from 98 to 119.6°). This change indicates an internal stress present in Me_{10}prCB[5] and thus explains the low reaction yield of the macrocycle.

The patterns of ^{1}H NMR spectra in D_2O for Me_{10}prCB[5] and CB[5] are very similar, but the values of chemical shifts differ significantly (Figure 2). Both macrocycles are characterized by two doublets of methylene bridges H(c,d) and a singlet of methine proton H(b); protons H(c) of Me_{10}prCB[5] having a similar direction as the oxygen atoms of the carbonyl groups appear at 6.69 ppm compared to 5.77 ppm for CB[5], while protons H(d) of Me_{10}prCB[5] heading out of the cavity appear at 4.25 ppm compared to 4.43 ppm for CB[5]. This is in agreement with the small portal diameter of Me_{10}prCB[5], in which the influence of the oxygen carbonyl atoms on H(c) protons is more pronounced than in CB[5]. The assignment of protons within the macrocycle was confirmed by NOE cross-peaks of protons H(a) and H(b) with proton H(d) (Figure 3). The reaction of propanediurea **1** with paraformaldehyde in HCl was also tested under different reaction conditions. The main product of the reaction was 2(1*H*)-pyrimidinone, which is a byproduct formed from the propanediurea **1** under the investigated reaction conditions.[14,16] Acyclic and cyclic glycoluril pentamers were also detected in the reaction mixture using MS. Attempts to isolate pure macrocycle failed. The purification only

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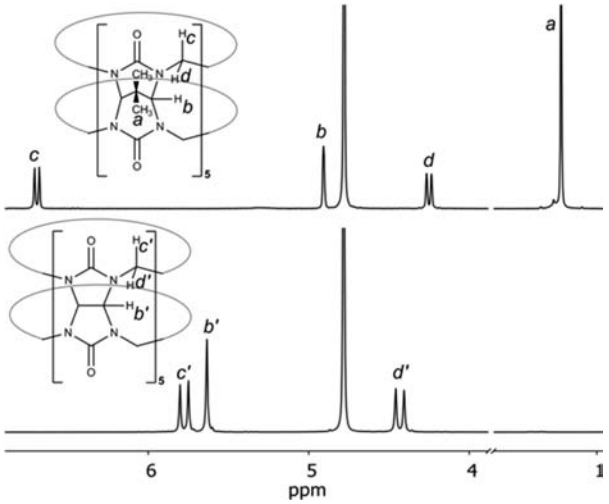

Figure 2. ^{1}H NMR spectra (300 MHz, 30 °C, D_2O) of Me_{10}prCB[5] (top) and CB[5] (bottom).

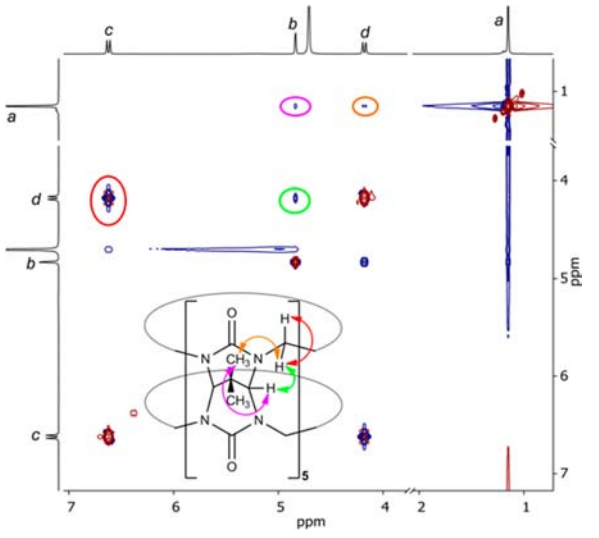

Figure 3. Portion of ^{1}H−^{1}H NOESY spectrum (500 MHz, mixing time 200 ms, 30 °C, D_2O) of Me_{10}prCB[5].

slightly increased the content of the macrocycle to the level that allowed us to identify the signals corresponding to the macrocycle in the ^{1}H NMR spectra (Figure S1, Supporting Information).

Cucurbiturils are known to occur in different sizes depending on the number of glycoluril units within the macrocycle. Therefore, we attempted to prepare related macrocycles with bigger cavity diameters. Despite the large number of reactions performed, we never detected homologues of Me_{10}prCB[5] containing more than five propanediurea units. Quantum chemical calculations provided us with a possible explanation. We calculated the thermodynamical stabilities of CB[n] and prCB[n] homologues for n = 5−8 in water. Since it is rather difficult to express the initial state of the macrocycle formation, the stability was calculated relative to the smallest homologue in each row and expressed as a contribution by one building block (Table 2). Validity of the calculated data can be justified by a correct prediction for CB[n], where the values clearly show that CB[6] and CB[7] are the most stable homologues in the row, which is in accordance with experimental observations.[17]

Table 2. Calculated Relative Reaction Gibbs Free Energies per Building Block in Water[a]

n	prCB[n]	CB[n]
5	0.00	0.00
6	8.99	−7.01
7	26.99	−5.70
8	50.28	−1.06

[a]All values in kcal mol^{-1}.

In contrast, monotonically increasing values found for prCB[5] indicate that the formation of higher homologues is only less favorable. This might be mainly caused by imposed internal stress between the methine hydrogen atoms from adjacent building block. Going from five to eight building blocks, distances in prCB[n] decrease from 2.550 to 1.859 Å, while the same distances in CB[n] are significantly longer spanning the range from 4.279 to 3.579 Å as predicted from DFT calculations.

The ability of CB[5] and Me_{10}CB[5] to include small gas molecules were reported previously. We therefore decided to investigate the potential of Me_{10}prCB[5] for gas binding. We selected methane and studied its interaction with Me_{10}prCB[5] in D_2O/20 mM KBr using ^{1}H NMR spectroscopy (Figure 4a).

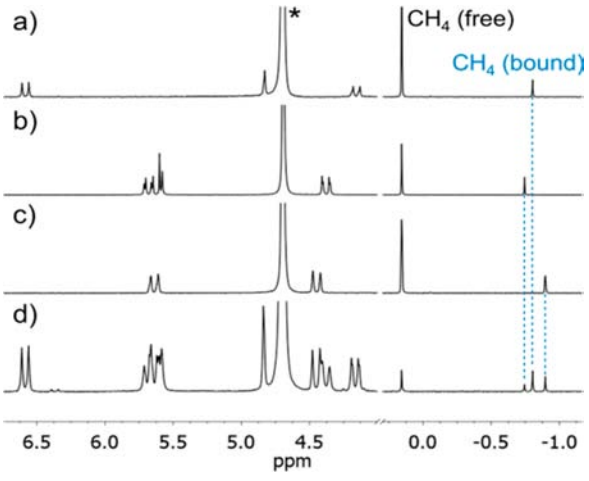

Figure 4. ^{1}H NMR spectra (300 MHz, 30 °C, D_2O/20 mM KBr) of methane in the presence of (a) Me_{10}prCB[5], (b) CB[5], (c) Me_{10}CB[5], and (d) mixture of Me_{10}prCB[5], CB[5], and Me_{10}CB[5].

The inclusion of methane inside the macrocycle were detected by appearance of new signal at −0.804 ppm next to unbound methane at 0.156 ppm; thus, the chemical exchange between free and bound methane molecules is slow on the NMR time scale. This allowed calculation of the association constant (K_a) for the CH_4−Me_{10}prCB[5] complex of 3.1 × 10^3 M^{-1}. Although interaction of CB[5] and Me_{10}CB[5] with methane was previously studied, only estimated values of K_a for this complex on the order of 10^3 M^{-1} were known during our experimental work.[18] Therefore, we also investigated binding of methane in CB[5] and Me_{10}CB[5]. These two macrocycles encapsulate methane in a slow regime on the NMR time scale (Figure 4), which allowed determination of association constants for corresponding complexes. Results summarized in Table 3 show that Me_{10}prCB[5] and methane form the most stable complex, which is about 3 times more stable than the CH_4−CB[5] complex and 1.5 times more stable than the CH_4−Me_{10}CB[5] complex. Very recently, Day and co-workers reported K_a values

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Table 3. Association Constants K_a (M^{-1}) for Complexes of Methane and Three Cucurbiturils Determined by Direct Measurements and Competition

	direct measurement[b]	competition[b]
Me_{10}prCB[5]	$(3.1 \pm 0.2) \times 10^3$	*a*
CB[5]	$(1.0 \pm 0.1) \times 10^3$	$(0.9 \pm 0.1) \times 10^3$
Me_{10}CB[5]	$(2.1 \pm 0.5) \times 10^3$	$(2.0 \pm 0.3) \times 10^3$

[a]Not calculated, value from direct measurement was used to calculate K_a for the remaining two macrocycles. [b]Standard deviations calculated from two independent measurements.

of 1954 and 1304 M^{-1} for the CH_4−CB[5] and CH_4−CyCB[5] complexes in D_2O containing 24.3 mM K^+.[19] Reported data are in a good agreement with those presented in this paper. We also noticed that methane included in each of three macrocycles is characterized by a unique chemical shift on the ^1H NMR spectra (Figure 4). Thus, we were able to perform competition measurements in which two or three macrocycles competed for methane (an example of the competition is presented in Figure 4d). Association constants resulting from the competition measurements were in good agreement with the results from direct NMR measurements (Table 3).

The highest affinity of Me_{10}prCB[5] to methane among three studied macrocycle is probably due to the smallest common depth and largest diameter of its inner cavity. This trend further applies for comparison of CB[5] and Me_{10}CB[5]. Packing coefficient is other criteria usually connected with strength of binding between deep cavitants such as cucurbiturils and organic guests.[20,21] However, cavity volumes of studied macrocycles are rather similar (Table 1), resulting in similar packing coefficient for methane binding. Thus, the influence of packing coefficient is expected to be negligible in this case.

In conclusion, we showed that propanediureas can react with paraformaldehyde in acid-catalyzed polycondensation to yield five-membered macrocycle−pressocucurbiturils (prCB[5]).[22] A new macrocycle, Me_{10}prCB[5], was isolated and characterized. Me_{10}prCB[5] was found to be the most potent host for methane among other five-membered cucurbiturils CB[5] and Me_{10}CB-[5]. Computational study revealed that homologues of prCB[5] consisting of more than five propandiurea units are unlikely to be prepared due to the enormous steric tension between repeating units in the macrocyclic framework. Future work will therefore be concerned with the design and synthesis of macrocycles containing both propanediurea and glycoluril building blocks.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details including synthetic procedures, characterization data, NMR and MALDI TOF MS spectra of Me_{10}prCB-[5], and computational details. 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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