Anion Receptors

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Bambus[6]uril**

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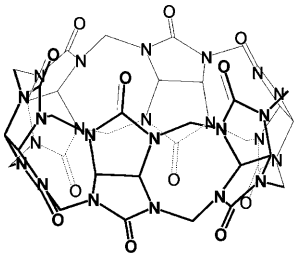
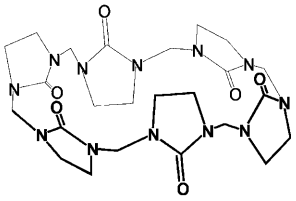
Glycoluril is a rigid bicyclic molecule that has been used as a building block for the assembly of various supramolecular objects. Besides acyclic supramolecular hosts based on glycoluril, such as molecular clips,[1] glycoluril oligomers,[2] and capsules,[3] the family of macrocyclic molecules known as cucurbit[*n*]urils, in which *n* glycoluril units are connected by 2*n* methylene bridges, have received most attention.[4] The ability of cucurbit[*n*]urils to form complexes with organic and inorganic cations as well as neutral organic guests in aqueous media has been investigated extensively.[5] New macrocycles prepared by the acid-catalyzed condensation of ethyleneurea and formaldehyde[6] were named hemicucurbit[*n*]urils ($n = 6$, 12), as their structures resemble the motif obtained when the corresponding cucurbit[*n*]uril is cut in half along the equator. In contrast to cucurbit[*n*]urils, hemicucurbit[*n*]urils are soluble in nonpolar solvents, such as chloroform. Furthermore, hemicucurbit[*n*]urils form complexes with anions, but no interaction with metal cations was observed in an aqueous environment.[7]

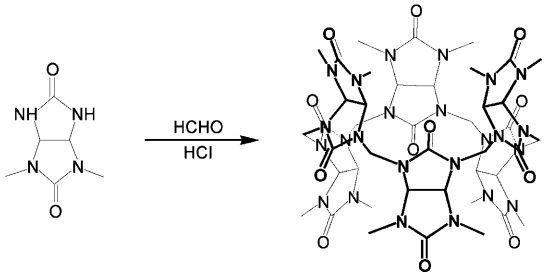


cucurbit[6]uril



hemicucurbit[6]uril

Herein we describe the synthesis of a cyclic hexamer, bambus[6]uril (**BU[6]**),[8] which combines the structural features of both cucurbit[*n*]urils and hemicucurbit[*n*]urils. For the synthesis, we used 2,4-dimethylglycoluril (2,4-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-dione),[9] in which methyl substituents are attached to the two nitrogen atoms in one of the two fused rings. An acid-catalyzed condensation between 2,4-dimethylglycoluril and formaldehyde in HCl resulted in macrocycle **BU[6]**, in which the glycoluril units are connected through methylene bridges (Scheme 1). The macrocycle precipitated from the solution and was isolated as a white powder in a maximum yield of 30% when the reaction was carried out in 5.4 M HCl at room temperature.



Scheme 1. Synthesis of **BU[6]**.

Monocrystals suitable for X-ray analysis were obtained by the slow evaporation of a solution of **BU[6]** in an equimolar mixture of ethanol and chloroform in the presence of tetrabutylammonium chloride (TBA^+Cl^-; Figure 1).[10] In the crystal structure, the chloride anion is included in the center of the macrocycle, whereas TBA^+ is located outside of the macrocycle. The six glycoluril units adopt alternate conformations; the methine hydrogen atoms on the convex face of each unit point into the cavity. The macrocycle can be divided into two identical parts by a plane defined by the carbon atoms of the six methylene bridges and the carbon atoms of six carbonyl groups arranged alternately above and below the plane in a zigzag manner. In this plane, the internal cavity diameter reaches a maximum of 6.4 Å. With a height of 12.7 Å, **BU[6]** has a significantly deeper cavity than that of cucurbit[*n*]urils, which are 9.1 Å high.

BU[6] showed a good affinity for halide anions. After its synthesis in HCl, **BU[6]** was isolated as an adduct with one molecule of HCl, **BU[6]**·HCl, which remained intact even after drying under vacuum at 170 °C for 4 h. The presence of the adduct was confirmed by ESI MS through the observation of a major signal at m/z 1127, as well as by the analysis of recrystallized material by X-ray crystallography, which revealed the location of the chloride anion in the center of the cavity. The structure was similar to that in Figure 1C. The adduct of the macrocycle with Cl^- had very low solubility in water (0.02 $g\,L^{-1}$), but was highly soluble in an equimolar mixture of methanol and chloroform (more than 90 $g\,L^{-1}$). **BU[6]**·HCl was further analyzed by ^1H NMR spectroscopy. The presence of singlets at $\delta = 5.36$, 5.15, and 3.11 ppm corresponding to hydrogen atoms c, b, and a, respectively, confirmed that in solution **BU[6]** remains in the conformation in which the glycoluril units have alternate orientations

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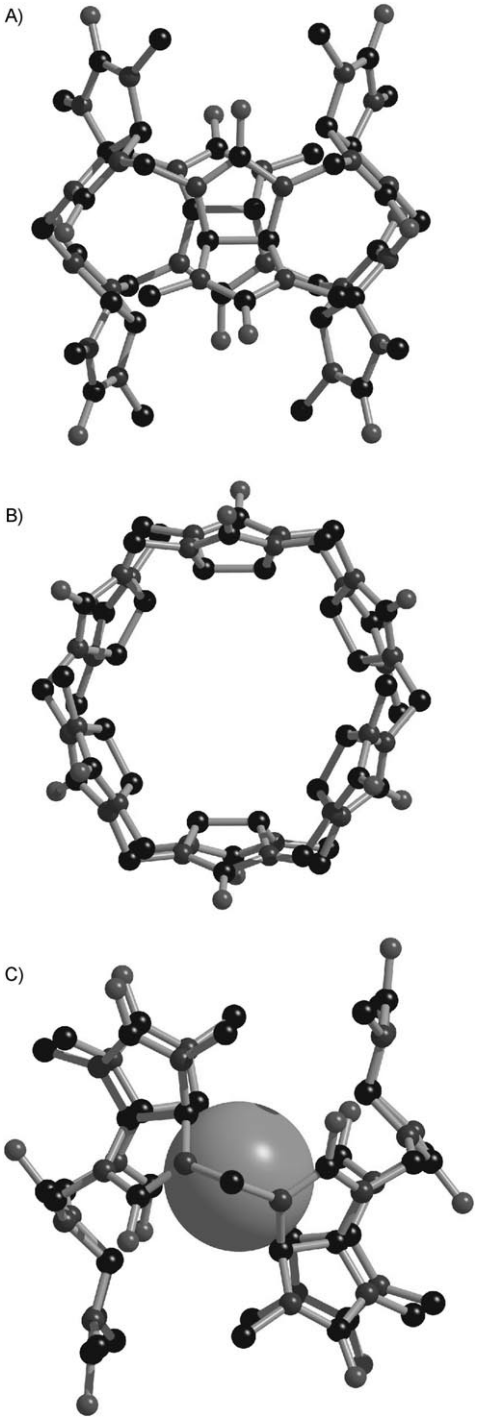

Figure 1. Crystal structure of **BU[6]** without (A,B) and with (C) an included chloride anion.

(Figure 2 A). The assignment of signals in the ^{1}H and ^{13}C NMR spectra was further verified by using 2D NMR methods (see the Supporting Information).

The interaction of **BU[6]** with halide anions in the solution was investigated by ^{1}H NMR titration of the solution of **BU[6]**·HCl with the corresponding tetrabutylammonium salt (Figure 2). After the addition of 1.0 equivalent of $TBA^{+}I^{-}$ to the solution of the macrocycle, signals a and c exhibited

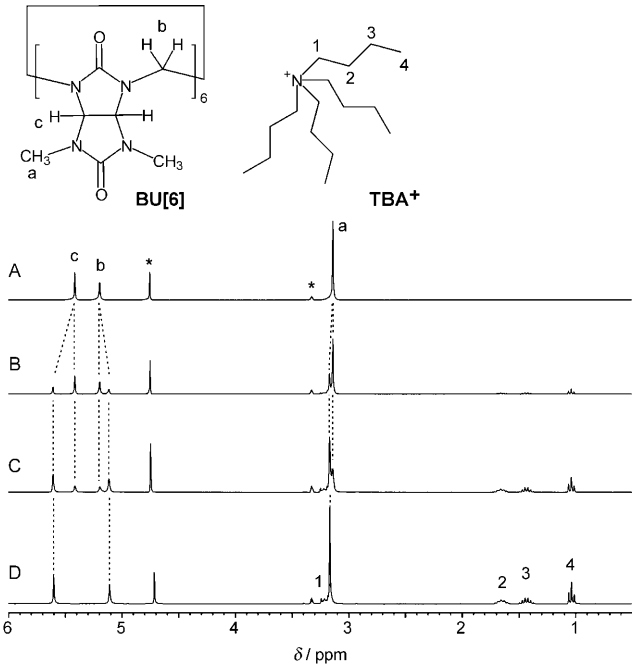

Figure 2. ^{1}H NMR spectra (300 MHz, $CD_3OD/CDCl_3$ (2:1)) of **BU[6]**·HCl in the absence (A) and in the presence of $TBA^{+}I^{-}$ (B) 0.3 equiv, C) 0.6 equiv, and D) 1.0 equiv). *Signals of CH_3OH and H_2O.

downfield shifts of $\delta = 0.02$ and 0.19 ppm, respectively, whereas signal b was shifted upfield by $\delta = 0.09$ ppm. The exchange between free and **BU[6]**-bound anions is slow on the NMR timescale. In the presence of 0.3 equivalents of the iodide salt, two sets of signals corresponding to the macrocycle complexes with chloride and with iodide were observed. We suggest that the chloride anion was also bound in the center of the cavity in the solution. When an iodide salt was added to this solution, the replacement of chloride with iodide inside the cavity was responsible for the observed shift pattern. The formation of a 1:1 complex between **BU[6]** and iodide was further supported by the observation of a major signal corresponding to **BU[6]**·I^{-} at m/z 1219 in the ESI mass spectrum.

We also investigated the interaction between bromide anions and **BU[6]**. The addition of $TBA^{+}Br^{-}$ to the solution of **BU[6]**·HCl was followed by the appearance of a new set of signals similar to those observed after the addition of the iodide salt; however, the bromide-induced shifts were less significant (see the Supporting Information). This result indicated that bromide replaced the chloride anion inside the macrocycle, as confirmed by the observation of a major signal corresponding to **BU[6]**·Br^{-} at m/z 1171 in the ESI mass spectrum. Additional evidence for the proposed complex formation was obtained from the crystal structure of monocrystals obtained by the slow crystallization of a solution of $TBA^{+}Br^{-}$ and **BU[6]**·HCl. In this structure, Br^{-} was again located at the center of the macrocycle (see the Supporting Information).

Additional NMR spectroscopic experiments helped us to evaluate the affinity of the macrocycle for individual halide

anions. When 1.0 equivalent of TBA^+Br^- was added to a solution of **BU[6]**·HCl, Br^- replaced all Cl^- anions from the macrocycle, and only signals corresponding to **BU[6]**·Br^- were observed. The macrocycle is very selective for Br^- over Cl^-: the addition of more than a 100-fold excess of TBA^+Cl^- to the **BU[6]**·Br^- adduct did not affect the chemical shifts of the macrocycle hydrogen atoms. The macrocycle is also very selective for I^- over Br^-: only 1 equivalent of TBA^+I^- was necessary to complete the substitution of I^- for Br^- in the **BU[6]**·Br^- adduct (see the Supporting Information). F^- has an exceedingly low affinity for the macrocycle: no change was observed in the resonances corresponding to the macrocycle in the ^{1}H NMR spectrum when excess TBA^+F^- salt was added to a solution of **BU[6]**·HCl. Thus, **BU[6]** binds halide anions preferentially in the following order: $I^- > Br^- > Cl^- > F^-$.

The reason for the inclusion of anions inside the cavity of **BU[6]** can be seen clearly in a map of the electrostatic surface potential (Figure 3). The cavity interior is significantly

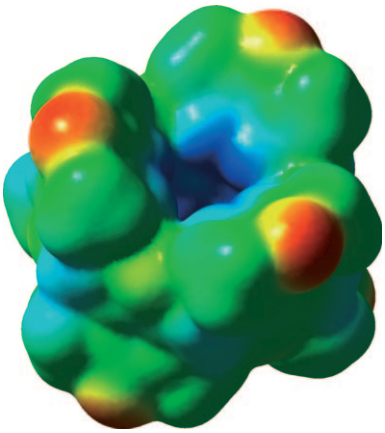

Figure 3. Map of the electrostatic surface potential of **BU[6]** (red → blue: −31 → +36 kcal mol^{-1}).

positively charged, whereas negative charge is located on the oxygen atoms at the portals. The crystal structures of the **BU[6]**·Cl^- and **BU[6]**·Br^- complexes revealed that the halide anion is bound inside the macrocycle through 12 C–H···X^- weak hydrogen bonds between methine carbon atoms on the convex face of glycoluril units and the corresponding anion. Only a few examples of this type of weak hydrogen bonding have been described previously for inclusion complexes.[11] The average C···X^- distance in the C–H···X^- binding system is 3.69 and 3.81 Å in the **BU[6]**·Cl^- and **BU[6]**·Br^- complexes, respectively. The macrocycle is therefore flexible, as its cavity size adapts to the size of the anion. As reported previously, the mean hydrogen-bond distance C···X^- in C–H···X^- binding systems increases as the halide radius increases.[12] For example, the distance between the carbon atom involved in the hydrogen bond and the halide anion in the Cl_2CH_2···X^- pair is 3.57, 3.74, and 3.88 Å for the chloride, bromide, and iodide anion, respectively. The C···X^- distances in the C–H···X^- binding system in the **BU[6]**·Cl^- and **BU[6]**·Br^- complexes also vary with differences in the anion radii. However, the total distances C···X^- in these complexes are higher than the equivalent distances in systems described previously. The methyl groups in the macrocycle probably do not enable the flexible glycoluril units to come close enough to one another to form ideal C···X^- distances upon anion inclusion. The iodide anion, which is the halide with the largest radius, therefore fits best and is bound preferentially inside the large cavity of the macrocycle.

In conclusion, we have reported a novel macrocycle that can be directly prepared by the condensation of 2,4-dimethylglycoluril with formaldehyde. We showed that **BU[6]** is able to bind halide anions through 12 weak C–H···X^- hydrogen bonds with high affinity and selectivity. Further investigations into the synthetic modification of the macrocycle as well as its practical applications are in progress.

Experimental Section

2,4-Dimethylglycoluril (9 g, 53 mmol) and paraformaldehyde (1.6 g, 53 mmol) were heated at 45 °C in HCl (5.4 M, 30 mL) until the starting material had dissolved completely. The solution was then allowed to cool down and was stirred at room temperature for 24 h. The resulting precipitate was collected by filtration, washed with concentrated HCl and water, and dried under vacuum to give **BU[6]** as a white solid in 30 % yield. M.p. > 300 °C (dec.); ^{1}H NMR (500 MHz, [D$_6$]DMSO/$CDCl_3$ (1:1), 30 °C, TMS): $\delta = 5.51$ (s, 12 H, CH), 5.27 (s, 12 H, CH_2), 3.20 ppm (s, 36 H, CH_3); ^{13}C NMR (125 MHz, [D$_6$]DMSO/$CDCl_3$ (1:1), 30 °C, TMS): $\delta = 159.7$, 158.9, 68.3, 49.2, 31.47 ppm; HRMS (ESI−): *m/z* calcd for $[C_{42}H_{60}N_{24}O_{12} + Cl^-]$: 1127.4506; found: 1127.4462.

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[1] a) R. P. Sijbesma, R. J. M. Nolte, *Top. Curr. Chem.* **1995**, *175*, 25–56; b) A. Rowan, J. Elemans, R. Nolte, *Acc. Chem. Res.* **1999**, *32*, 995–1006.

[2] a) W.-H Huang, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2008**, *130*, 8446–8454; b) D. Witt, J. Lagona, F. Damkaci, J. C. Fettinger, L. Isaacs, *Org. Lett.* **2000**, *2*, 755–758; c) A. Wu, A. Chakraborty, D. Witt, J. Lagona, F. Damkaci, M. A. Ofori, J. K. Chiles, J. C. Fettinger, L. Isaacs, *J. Org. Chem.* **2002**, *67*, 5817–5830; d) W.-H. Huang, P. Y. Zavalij, L. Isaacs, *Org. Lett.* **2009**, *11*, 3918–3921.

[3] a) J. Rebek, Jr., *Chem. Soc. Rev.* **1996**, *25*, 255–263; b) J. Rebek, Jr., *Acc. Chem. Res.* **1999**, *32*, 278–286; c) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1668.

[4] a) J. Lee, S. Samal, N. Selvapalam, H. Kim, K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621–630; b) J. Lagona, P. Mukhopadhyay, S. Chakrabarti, L. Isaacs, *Angew. Chem.* **2005**, *117*, 4922–4949; *Angew. Chem. Int. Ed.* **2005**, *44*, 4844–4870.

[5] a) S. Liu, C. Ruspic, P. Mukhopadhyay, S. Chakrabarti, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2005**, *127*, 15959–15967; b) W. L. Mock, N.-Y. Shih, *J. Org. Chem.* **1986**, *51*, 4440–4446; c) M. V. Rekharsky, Y. H. Ko, N. Selvapalam, K. Kim, Y. Inoue, *Supramol. Chem.* **2007**, *19*, 39–46; d) C. Márquez, R. R. Hudgins, W. M. Nau, *J. Am. Chem. Soc.* **2004**, *126*, 5806–5816.

[6] a) Y. Miyahara, K. Goto, M. Oka, T. Inazu, *Angew. Chem.* **2004**, *116*, 5129–5132; *Angew. Chem. Int. Ed.* **2004**, *43*, 5019–5022;

b) Y. Li, L. Li, Y. Zhu, X. Meng, A. Wu, *Cryst. Growth Des.* **2009**, *9*, 4255 – 4257.

[7] a) H.-J. Buschmann, A. Zielesny, E. Schollmeyer, *J. Inclusion Phenom. Macrocyclic Chem.* **2006**, *54*, 181 – 185; b) H.-J. Buschmann, E. Cleve, E. Schollmeyer, *Inorg. Chem. Commun.* **2005**, *8*, 125 – 127.

[8] The structural and binding features of the new macrocycle differ significantly from those of members of the cucurbit[*n*]uril family. Therefore, we proposed the trivial name bambus[6]uril for the macrocycle. The trivial name is derived from the subfamily Bambusoideae, as the macrocycle resembles part of the bamboo-plant stem.

[9] E. Grillon, R. Gallo, M. Pierrot, J. Boileau, E. Wimmer, *Tetrahedron Lett.* **1988**, *29*, 1015 – 1016.

[10] Crystallographic data for **BU[6]**·TBA^+Cl^-·3 $CHCl_3$ ($C_{63}H_{101}Cl_{16}N_{25}O_{12}$): $M_r = 1967.89$, crystal dimensions $0.40 \times 0.40 \times 0.30\ mm^3$, space group $C2/c$, $a = 17.5355(5)$, $b = 16.8649(5)$, $c = 32.2860(10)$ Å, $\beta = 101.917(3)°$, $V = 9342.3(5)$ $Å^3$, $Z = 4$, $\rho_{calcd} = 1.399\ Mg\,m^{-3}$, $\mu = 0.536\ mm^{-1}$. X-ray intensity data were measured at 120 K on a Kuma KM-4 CCD diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), and the structure was solved by using direct methods; 48483 reflections collected, 8218 unique reflections ($R_{int} = 0.0361$), data/restraints/parameters 8218/140/594, final R indices ($I > 2\sigma(I)$): $R1 = 0.0627$ and $wR2 = 0.1862$, $\Delta\rho_{max}/\Delta\rho_{min} = 0.835/-0.394\ e\,Å^{-3}$. CCDC 761932 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) S. S. Zhu, H. Staats, K. Brandhorst, J. Grunenberg, F. Gruppi, E. Dalcanale, A. Luetzen, K. Rissanen, C. A. Schalley, *Angew. Chem.* **2008**, *120*, 800 – 804; *Angew. Chem. Int. Ed.* **2008**, *47*, 788 – 792; b) W. B. Farnham, D. C. Roe, D. A. Dixon, J. C. Calabrese, R. L. Harlow, *J. Am. Chem. Soc.* **1990**, *112*, 7707 – 7718; c) Y. Li, A. M. Flood, *Angew. Chem.* **2008**, *120*, 2689 – 2692; *Angew. Chem. Int. Ed.* **2008**, *47*, 2649 – 2652; d) C. A. Ilioudis, D. A. Tocher, J. W. Steed, *J. Am. Chem. Soc.* **2004**, *126*, 12395 – 12402.

[12] T. Steiner, *Acta Crystallogr. Sect. B* **1998**, *54*, 456 – 463.

