ORGANIC LETTERS

2011
Vol. 13, No. 15
4000–4003

Bambus[*n*]urils: a New Family of Macrocyclic Anion Receptors

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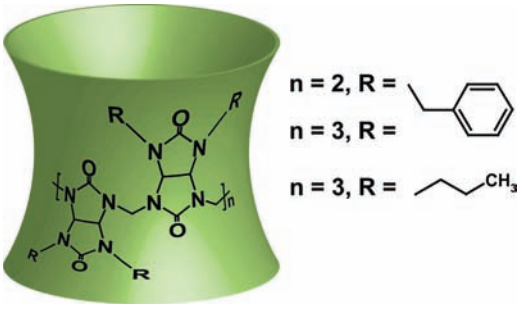
Received June 7, 2011

ABSTRACT



A recently discovered anion receptor is jointed by three related macrocycles differing in the number of glycoluril units and type of substitution. The synthesis is carried out in nonpolar solvents compared to aqueous media used in the case of the original macrocycle. The size of macrocycle is controlled by a template. A hexameric macrocycle with benzyl substitution binds halide anions with an affinity exceeding 10^9 M^{-1} while a tetrameric analog does not bind any of the investigated anions.

Macrocycles are the most important class of supramolecular host molecules.[1] They usually consist of several identical building blocks which are connected forming a cyclic structure with a preorganized shape. In such an arrangement the macrocyclic hosts bear multivalent binding sites which allow the strong and selective binding of the guest. The nature of the binding sites determines if the positively or negatively charged or neutral guests will form supramolecular complexes within a macrocycle. There is a wide range of macrocyclic compounds presented in literature. Only a few of them, however, attract substantial attention. These macrocycles are represented by cation receptors including crown ethers[2] and calixarenes,[3] anion receptors including katapinands[4] and calixpyrroles,[5] and also those receptors in which the hydrophobic effect plays an important role in the complex formation including

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10.1021/ol201515c
Published on Web 06/28/2011

cyclodextrins[6] and cucurbiturils.[7] In all these cases not only a single macrocycle exists, but there are families of macrocycles having the same structural motif but differing in the size or in their substitution. The reasons for the popularity of these receptors are not only their supramolecular properties but also rather simple preparation of at least some of the members within each macrocyclic family.

Recently, we have prepared a new macrocyclic compound, bambus[6]uril (Figure 1), which acts as an anion receptor with high affinity and selectivity for various anions in both organic solvent mixtures and aqueous media.[8]

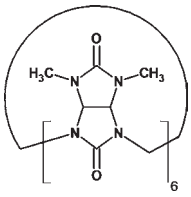
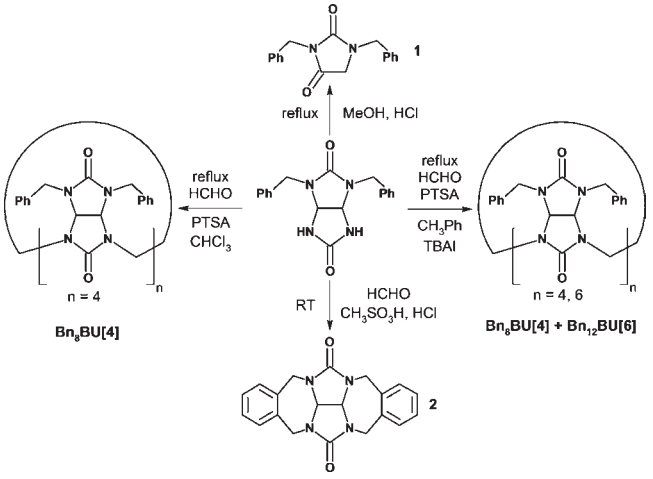


Figure 1. Dodecamethylbambus[6]uril (**Me_{12}BU[6]**).

The starting materials for the synthesis are inexpensive ureas, glyoxal, and formaldehyde. The bambus[6]uril synthesis is simple, as the macrocycle precipitates out from the reaction solution as the only product. Here we show that bambus[6]uril is not the only macrocycle of its kind but there are related molecules consisting of the same building block and differing in their number within the macrocycle as well as in the substitution on the nitrogen atom of glycoluril units. To differentiate the original bambus[6]uril from the new derivatives we will, from now on, name it dodecamethylbambus[6]uril (**Me_{12}BU[6]**). This trivial name reflects the presence of 12 methyl groups and 6 glycoluril units in the macrocycle. New derivatives will be named accordingly.

We decided to test the preparation of dodecabenzylbambus[6]uril (**Bn_{12}BU[6]**) (see Scheme 1) in which the 12 methyl groups of **Me_{12}BU[6]** are substituted by benzyl groups. We envisioned that the macrocycle should be soluble in single nonpolar solvents compared to the **Me_{12}BU[6]**, which dissolved only in mixtures of solvents when complexed to anions and does not dissolve in any organic solvent in the absence of an anion inside its cavity. Furthermore, benzyl groups would be subsequently deprotected, which would allow further derivatization of the bambusuril skeleton. The starting material, 2,4-dibenzylglycoluril, was prepared by acid catalyzed condensation of 4,5-dihydroxyimidazolidin-2-one[9] with 1,3-dibenzylurea in methanol in 81% yield. The reaction between 2,4-dibenzylglycoluril and formaldehyde, which was expected to give the bambusuril compound, appeared to be very sensitive to the reaction conditions. When the reaction was carried out in the mixture of methanol and 35% HCl_{aq} (1:1), glycoluril selectively rearranged into dibenzylhydantoin **1**.[10] On the other hand, in the mixture of methanesulfonic acid and 35% HCl_{aq} (4:1), the reaction gave clip-shape-like molecule **2** (see Scheme 1) in very good yield (85%). It should be noted that although the crystal structure of this molecule was reported in the literature,[11] the experimental details of its preparation are missing.

Scheme 1. Reaction between 2,4-Dibenzylglycoluril and Formaldehyde under Different Conditions



We then tested the reaction of 2,4-dibenzylglycoluril with paraformaldehyde in chloroform in the presence of a catalytic amount of *p*-toluenesulfonic acid. This reaction finally gave the macrocyclic compound, but it was surprisingly octabenzylbambus[4]uril (**Bn_8BU[4]**) containing four glycoluril units connected by four methylene bridges (Scheme 1). We were able to obtain the crystal structure of **Bn_8BU[4]**. Figure 2A clearly shows that the methine carbon atoms of the glycoluril units point to the center of the macrocycle and the glycoluril units adopt an alternate conformation. Clearly the structural features of **Bn_8BU[4]** are similar to those of previously published **Me_{12}BU[6]**. Thus **Bn_8BU[4]** represents the first bambusuril derivative of its older relative differing in (a) the number of glycoluril units and (b) the 2,4-substituents on glycoluril units.

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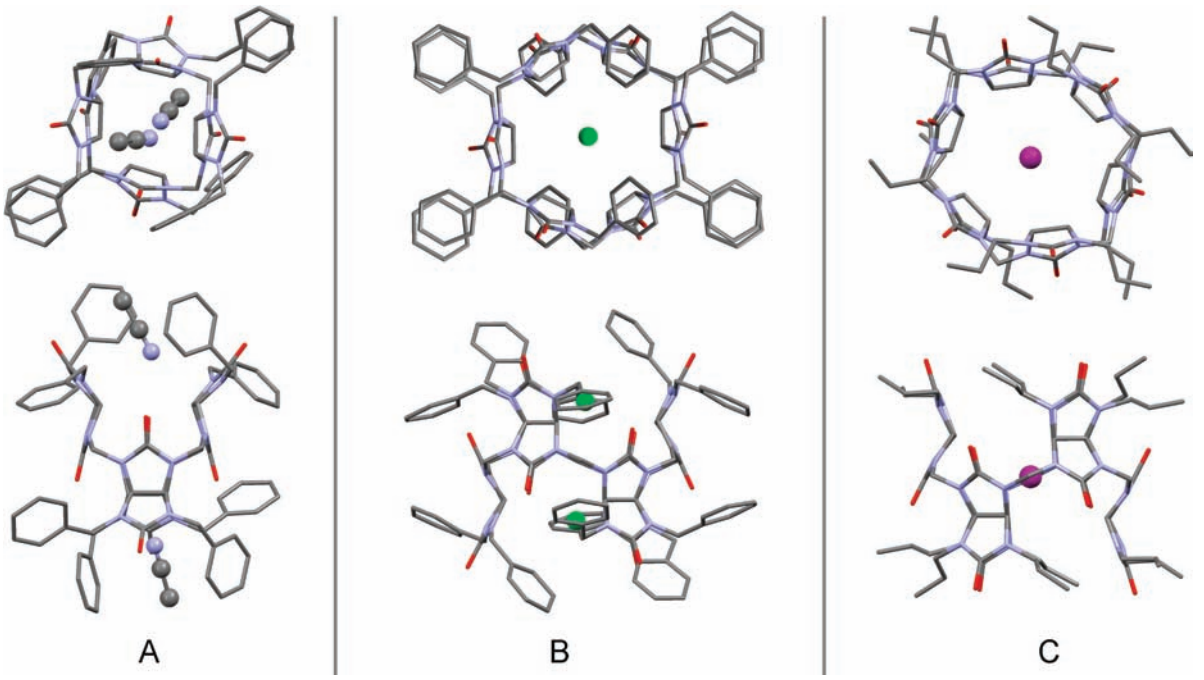

Figure 2. Crystal structures (top and side views) of (A) **Bn_8BU[4]**:2 CH_3CN complex, (B) **Bn_{12}BU[6]**:2 Cl^- complex, and (C) **Pr_{12}BU[6]**: I^- complex. Color coding: C, gray; N, blue; O, red; Cl^-, green; I^-, purple.

The supramolecular properties of **Bn_8BU[4]** were studied in the solid state and in solution. In the crystal, obtained by slow crystallization from acetonitrile solution, each of both portals defined by the benzyl substituents is occupied by one molecule of acetonitrile (Figure 2A). This 2:1 complex is stabilized by van der Waals interactions. On the other hand, we did not observe such a complexation in solution. Furthermore, we investigated the interaction between halide anions and **Bn_8BU[4]** in CD_3Cl using ^{1}H NMR spectroscopy. In contrast with **Me_{12}BU[6]**, which forms very stable complexes with halide anions, **Bn_8BU[4]** did not show any affinity toward anions. The reason is most likely the small cavity of the macrocycle which is not able to include even a fluoride anion.

Bn_8BU[4] did not act as a receptor for anion binding. We therefore continued in our synthetic effort to prepare bambusuril with a larger internal cavity. We found that when 2,4-dibenzylglycoluril reacts with paraformaldehyde in chloroform or toluene in the presence of a template anion, the formation of the cyclic tetramer **Bn_8BU[4]** was suppressed and the hexameric analog **Bn_{12}BU[6]** was detected as the major product (Scheme 1). Among all tested halide templates, the best yield of **Bn_{12}BU[6]** (65%) was achieved when tetrabutylammonium iodide (TBAI) was used. A lower yield of **Bn_{12}BU[6]** (53%) was obtained in the presence of TBACl. This is indeed in agreement with the previously published results,[8] which showed that the affinity of **Me_{12}BU[6]** toward halide anions decreases in the order $I^- > Br^- > Cl^- > F^-$. Good quality monocrystals of **Bn_{12}BU[6]** were obtained by the slow evaporation of the chloroform from the solution of the macrocycle in the presence of TBACl. Figure 2B shows that in the solid state a 2:1 complex is formed in which each of the two portals of **Bn_{12}BU[6]** is occupied by one chloride anion. This is in contrast with the previously obtained 1: 1 complex between **Me_{12}BU[6]** and chloride, in which the anion is located in the center of the cavity.

To evaluate the affinity of **Bn_{12}BU[6]** toward halide anions we first had to isolate the macrocycle without an encapsulated anion. Anion-free **Bn_{12}BU[6]** was obtained by boiling of the complex between **Bn_{12}BU[6]** and a chloride anion in an excess of methanol, filtration of the solid, and drying under vacuum. Compared to anion-free **Me_{12}BU[6]**, which did not dissolve in any of the investigated solvents, **Bn_{12}BU[6]** was readily soluble in chloroform. We, therefore, investigated the affinity of **Bn_{12}BU[6]** toward halide anions in this nonpolar solvent using ^{1}H NMR spectroscopy (Figure 3). For instance, addition of 0.5 equiv of TBACl into **Bn_{12}BU[6]** solution led to the appearance of a new set of signals. In the presence of 1.0 equiv of TBACl the original signals of **Bn_{12}BU[6]** were no longer present and only new signals were detected in the spectra. Further addition of TBA salt no longer influenced the appearance of the **Bn_{12}BU[6]** spectrum. These experiments showed that (a) the complexation between **Bn_{12}BU-[6]** and the chloride anion is slow on the NMR time scale, (b) the formation of the 1:1 complex takes place in the solution instead of the 2:1 complex observed in the solid state, and (c) complex stability is too high which precludes the determination of the association constant (K_a) of the complex using ^{1}H NMR spectroscopy. We further investigated the remaining halide anions and found that all of

them interact with **Bn_{12}BU[6]** in the same manner as the chloride anion. The formation of 1:1 complexes was confirmed by the observation of a major signal corresponding to the m/z value of the complex between **Bn_{12}BU[6]** and each anion in the ESI mass spectrum.

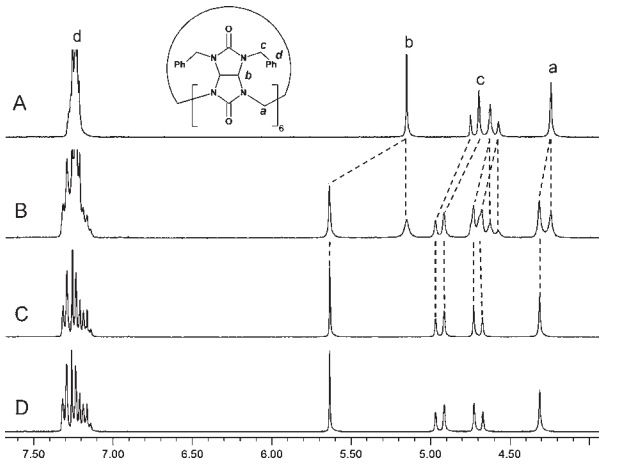

Figure 3. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of **Bn_{12}BU[6]** in the absence (A) and in the presence of 0.5 equiv (B), 1.1 equiv (C), and 2.2 equiv (D) of TBA^+Cl^-.

As direct measurement from ^{1}H NMR spectra was not possible we determined equilibrium association constant (K_a) values of the complexes using isothermal titration calorimetry (ITC). ITC experiments in classical arrangements allowed us to characterize the complexation of F^- and Cl^- with **Bn_{12}BU[6]**. Competitive calorimetric titration was used to measure the binding between Br^- and I^- and the macrocycle because of the high affinity of these complexes. K_a values of 8.6×10^5, 3.0×10^6, 3.0×10^8, and 3.8×10^9 M^{-1} were found for the complexes formed between **Bn_{12}BU[6]** and F^-, Cl^-, Br^-, and I^-. These valeus show that **Bn_{12}BU[6]** is one of the most potent neutral receptors for halide anions. Despite the overall high stability of these complexes, **Bn_{12}BU[6]** exhibits for I^- a high selectivity of about 4400, 1200, and 12 over F^-, Cl^-, and Br^-.

Benzylated bambusurils **Bn_{12}BU[6]** and **Bn_8BU[4]** were prepared in chloroform due to their insolubility in water. On the other hand, **Me_{12}BU[6]** was synthesized in diluted HCl. Therefore, we investigated if some other bambusuril derivatives could be prepared in aqueous media. We selected the reaction between 2,4-dipropylglycoluril and formaldehyde in 5.4 M HCl. MALDI-TOF MS revealed that the reaction at room temperature gave only a mixture of water-soluble acyclic oligomers. However, raising the temperature up to 100 °C resulted in the formation of a precipitate of dodecapropylbambus[6]uril (**Pr_{12}BU[6]**). The binding behaviors of **Pr_{12}BU[6]** were similar to those of **Me_{12}BU[6]**. For instance, the **Pr_{12}BU[6]** formed strong 1:1 complexes with iodide anion in the solution and also in the solid state (see Figure 2C).

In conclusion, we have prepared new bambusuril derivatives **Bn_8BU[4]**, **Bn_{12}BU[6]**, and **Pr_{12}BU[6]**. Thus we have demonstrated that **Me_{12}BU[6]** is not the only macrocycle of its kind, but part of a new family of macrocyclic compounds, the bambusuril family. Bambusuril homologues differ significantly in their supramolecular and physical properties. **Bn_8BU[4]**, with a small internal cavity, did not behave as a receptor of anions. On the other hand, **Bn_{12}BU[6]** was able to bind halide anions with an affinity as high as 3.8×10^9 M^{-1}. In contrast to previously published anion-free **Me_{12}BU[6]**, which does not dissolve in any organic solvent,[8b] **Bn_{12}BU[6]** is soluble in chloroform even in the absence of complexed anions. We are currently exploring the possibility of the bambusuril derivatives with even larger internal cavities as well as the modification of the already reported macrocycles.

Acknowledgment. Support for this work was provided by the Grant Agency of the Czech Republic (P207/10/0695; V.S.), the project "CEITEC - Central European Institute of Technology" (CZ.1.05/1.1.00/02.0068; MW), and the project CETOCOEN (no. CZ.1.05/2.1.00/01.0001; V.S.) from the European Regional Development Fund, and the Ministry of Education, Youth and Sports of the Czech Republic (MSM0021622413; M.W). The crystallographic part was supported by the Institutional research plan No. AVOZ10100521 of the Institute of Physics and the Praemium Academiae project of the AS CR, v. v. i. (M.D.).

Supporting Information Available. Synthetic procedures, full characterization and ^{1}H and ^{13}C NMR spectra of all new compounds, X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.