Unsubstituted Bambusurils: Post-Macrocyclization Modification of Versatile Intermediates

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ABSTRACT: A new bambusuril derivative, (H)BU[6], lacking substituents on the ureidic nitrogen atoms, has been isolated and characterized. This macrocycle was prepared by the deprotection of bambusuril (PMB)BU[6]. (H)BU[6] is attractive for use as a starting compound for the preparation of other bambusuril derivatives, which was demonstrated via propargylation and the copper-catalyzed click reaction performed on the macrocycle.

INTRODUCTION

Bambusurils are a family of macrocyclic compounds consisting of n glycoluril units connected by n methylene bridges (where n = 4 and 6).1,2 Four-membered bambusurils (BU[4]) are not able to include any guests inside of their small cavity. On the contrary, six-membered bambusurils (BU[6]) are prized for their excellent affinity for inorganic anions in water and many organic solvents.3−6 The high affinity of six-membered bambusurils toward anions is further shared among other hemicucurbituril derivatives,7−9 including biotinurils.10,11 Recently, bambusuril derivatives, semithio- and semiaza-bambusurils, have been prepared by replacing oxygen atoms on the portals of the bambusurils by sulfur and nitrogen, respectively.12,13 The bambusuril macrocycle has been used as parts of anion recognition systems,14 electromembrane anion extraction,15 photosensitive materials,16 and systems for anion transmembrane transport.17

Both the solubility and binding properties of bambusurils can be influenced by the type of substituents attached to the nitrogen atoms on the opposed macrocycle portals. Until now, there has been only one synthetic approach enabling the synthesis of bambusurils and thus also only one synthetic approach enabling the modification of substituents on their framework. This approach is based on the preparation of desired derivatives of glycoluril (Scheme 1) and its subsequent acid-catalyzed macrocyclization reaction with formaldehyde yielding a desired bambusuril. However, some glycolurils bearing certain types of substituents have proved to be unstable under these conditions, and no macrocycle could be isolated. Herein, we present a new synthetic protocol which allows for the preparation of bambusurils which are not achievable by the traditional synthetic approach.

RESULTS AND DISCUSSION

Our novel synthetic protocol is based on the preparation of a bambusuril bearing protecting groups on the nitrogen atoms of the glycoluril units (Scheme 1). The protecting group would subsequently be removed yielding bambusuril (H)BU[6]/(H)BU[4], with nitrogen atoms on the macrocycle portals available for further reactions. Several protecting groups were tested with this approach. Our first choice, a p-methoxyphenyl substituent (Figure 1), which is removable by oxidizing agents,18 proved to be unsuitable because of the low solubility of the corresponding glycoluril. In addition, steric hindrance by the rigid substituent prevented the glycoluril building blocks from assembling into a macrocyclic structure. We also investigated deprotection of the benzyl substituent on the already available macrocycles (Bn)BU[6] or (Bn)BU[4] (see Figure 1 for the structure). Unfortunately, deprotection of the macrocycles via hydrogenation or their treatment with a solution of sodium metal in liquid ammonia resulted either in...
only partial deprotection (Figure S28) or decomposition of the macrocycle. Finally, we prepared bambusurils (PMB)BU[4] and (PMB)BU[6] bearing a p-methoxybenzyl protecting group (PMB, Scheme 2), which we successfully converted to the bambusurils (H)BU[6] and (H)BU[4]. The synthetic procedure for PMB derivatives started with the quantitative synthesis of the corresponding urea, which can then undergo an acid-catalyzed reaction with 4,5-dihydroxyimidazolidin-2-one to give the glycoluril, with a yield of 81%. The macrocyclization reaction was complicated by the unwanted reaction between formaldehyde and the PMB protecting groups on the glycolurils, which takes place under the acidic conditions required for the reaction.

Thus, moderate formation of the desired macrocycles was only observed when we limited the amount of formaldehyde to an amount equivalent with regard to the monomer unit. Even a slight excess of formaldehyde leads to a complete degradation of the macrocycles formed, and no macrocycle could then be isolated.

The main focus was on the six-membered bambusuril homologue because this macrocycle, unlike its four-membered homologue, acts as an excellent receptor for a number of anions. The best conversion of the glycoluril to (PMB)BU[6] was achieved when 1,4-dioxane was used as the solvent, and the reaction was carried out with only a catalytic amount of H2SO4 under a longer reaction time (48 h) and at an elevated temperature (Scheme 2). Given the acid lability of the PMB group, we were unable to access an anion-free derivative by the use of a HSO4⁻ template as recently published; instead, an iodide template was employed. (PMB)BU[6] was isolated in the pure form by column chromatography as the TBAI complex, with a 19% yield. The removal of the iodide template by oxidation was not possible because of the instability of PMB groups toward the oxidizing reagents. The (PMB)BU[6] complex with TBAI was used for the deprotection reaction.

The first attempts were made with cerium(IV) ammonium nitrate (CAN) in either a CH3CN/H2O mixture or DMSO/H2O. Unfortunately, because of the low solubility of the partially deprotected macrocycle (in CH3CN/H2O) and difficult separation (in DMSO/H2O), these attempts did not lead to the desired compound. Strong acids, such as CF3COOH, have also been reported in the literature as an alternative for the removal of this protecting group at elevated temperatures. Neat CF3COOH, or its 50% solution in CHCl3, proved to function both as a deprotecting agent and also as a solvent. Complete deprotection was achieved after 1 h at 100 °C in a 50% CF3COOH/CHCl3 mixture or 15 min in neat CF3COOH under microwave irradiation. If a chromatographically purified sample of (PMB)BU[6] was used for the deprotection, it was possible to obtain pure (H)BU[6], with a yield of 58%.

We also investigated if the deprotection of a crude mixture containing (PMB)BU[6] without its chromatography purification could be used to obtain (H)BU[6]. Given the poor solubility of this unprotected macrocycle, we expected that the majority of linear oligomers, and other side products present in the crude material, could be separated because of their better solubilities. Indeed, after deprotection, most of the unwanted oligomers were washed out by MeOH and CH3COOH, and (H)BU[6] was isolated with a purity sufficient for further reactions. Unfortunately, the atom efficiency of the deprotection reactions is low, as the removal of 12 protecting groups radically decreases the molecular weight of the compound. Furthermore, the isolated (PMB)BU[6]-TBAI complex is, in the presence of strong acid, transformed into the (H)BU[6]-HI complex, and the molecular weight of the starting material decreases from 2736 to 1053 g mol⁻¹ in the product. In addition, (PMB)BU[4] was prepared in 1,4-dioxane with p-toluenesulfonic acid (PTSA) used as a catalyst, and in the absence of a template, with the low yield of 6%. Deprotection of (PMB)BU[4] was successfully achieved by its reaction with CAN in a DMSO/MeOH/CH3CN mixture. Given the low amount of the isolated macrocycle as well as its inability to bind anions, its modification was not studied further and (H)BU[4] was only characterized by the ¹H NMR spectrum in DMSO-d₆.

Scheme 2. Preparation of New Bambusuril Derivatives
The addition of an excess of TBAI. as well as compound macrocycle. The propargyl derivative of glycoluril \((\text{H})\text{BU}[6]\) dimethylglycoluril, which is structurally similar to the characteristic signals of product of the NMR signal of the starting alkyne compound; however, this reaction. After the reaction, we observed the disappearance (propargyl)\(\text{BU}[6]\) (Scheme 2) as an alkyne component in catalysis (azide − macrocycle with 11 substituents were present. The inclusion complexe s between six-membered bambusurils and anions are usually observed by \(^1\text{H}\) NMR spectroscopy.

A chemical shift of anion-free bambusuril protons (particularly methine proton \(c\)) differs significantly from that of anion-free macrocycles. We tried to follow the chemical shift of an anion-free \((\text{H})\text{BU}[6]\), generated inside a NMR tube by the addition of an excess of anion-free \((\text{Bn})\text{BU}[6]\) receptor into the solution of the \((\text{H})\text{BU}[6]\) complex with HI. New signals corresponding to an iodide complex with \((\text{Bn})\text{BU}[6]\) indicated that the ion was transferred from \((\text{H})\text{BU}[6]\) to \((\text{Bn})\text{BU}[6]\). Interestingly, we only observed a negligible change in the chemical shift of the NH and CH signals of \((\text{H})\text{BU}[6]\), which would correspond to the removal of \(\Gamma\) from the complex (Figure S11). This unexpected feature is currently under investigation in our laboratory.

We decided to illustrate the use of \((\text{H})\text{BU}[6]\) as a precursor for other bambusuril derivatives. Free NH positions on a bambusuril scaffold can conveniently be alkylated in DMSO in the presence of KOH. As reported, powdered KOH in DMSO acts as a strong base which is just strong enough to deprotonate the ureidic NH groups. \((\text{H})\text{BU}[6]\) prepared from a crude \((\text{PMB})\text{BU}[6]\) mixture was propargylated with an excess of propargyl bromide (Scheme 2). A small amount of insoluble oligomeric impurities were removed after the alkylation. According to MS analysis (Figure S32), the majority of the NH groups on bambusuril reacted and only traces of a deprotected bambusuril represents a versatile bambusuril structures of the novel bambusurils (\((\text{propargyl})\text{BU}[6]\) and 1). Unfortunately, no crystals suitable for X-ray analysis were obtained from any of the novel macrocycles (\((\text{H})\text{BU}[6]\), (propargyl)\(\text{BU}[6]\), or 1). To validate the structure of 1 and to observe the spatial arrangement of its bulky substituents on the glycoluril monomer, we attempted to crystallize compound 2.

This compound was prepared prior to the modification of the macrocycle as a test compound (see the Supporting Information). Slow diffusion of diethyl ether vapors into \(\text{CH}_2\text{Cl}_2\) solution of 1 produced monocrystals suitable for the X-ray diffraction analysis. The crystal structure (Figure 4) showed that the bulky substituents are oriented in such a way that the aromatic ring can possibly engage in π−π stacking interactions.

![Figure 2.](image)

\(\text{H}−\text{C}\) HSQC NMR spectrum (DMSO-\(d_6\), 500/126 MHz, 30 °C) of \((\text{H})\text{BU}[6]\).

![Figure 3.](image)

Glycoluril derivatives used in the optimization of bambusuril derivatization.

![Figure 4.](image)

Front and side views of the crystal structure of glycoluril 2. Color coding: O, red; C, gray; N, blue; and H, white.

- **CONCLUSIONS**

In conclusion, for the first time, four- and six-membered bambusurils lacking substituents on the nitrogen atoms of their portals were synthesized and characterized. This was achieved by careful selection of the protecting group as well as the conditions of macrocyclization and the deprotection reaction. A deprotected bambusuril represents a versatile bambusuril intermediate, which will allow for the preparation of derivatives that are not achievable by classical acid-catalyzed macrocyclization. This post-macrocyclization derivatization of bambusurils was demonstrated by the preparation of the propargyl derivative, which was later used in azide−alkyne cycloaddition.

- **EXPERIMENTAL SECTION**

**General Methods.** NMR spectra were recorded on a Bruker AVANCE III 300 spectrometer with working frequencies of 300.15 MHz for \(^1\text{H}\) and 75.47 MHz for \(^{13}\text{C}\) or...
on a Bruker AVANCE III 500 spectrometer with working frequencies of 500.11 MHz for $^1$H and 125.75 for $^{13}$C. Both spectrometers were equipped with a BBFO probe. All experiments were recorded at 303.15 K and were processed using a MestReNova v. 9.1.0 program. NMR chemical shifts ($\delta$) are reported in parts per million (ppm) using the residual solvent signal as a reference for the measured spectra CDCl$_3$ ($^1$H = 7.26, $^{13}$C = 77.16) and DMSO-$d_6$ ($^1$H = 2.50, $^{13}$C = 39.52). The proton resonances are annotated in text as: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant $[\text{Hz}]$, and integration. In several instances, the position of carbon signal for reported compounds was deduced from HSQC and heteronuclear multiple bond correlation (HMBC) experiments as $^{13}$C NMR produced only weak signals for quaternary groups. The proton resonances are annotated in text as: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant $[\text{Hz}]$, and integration. As $^{13}$C NMR produced only weak signals for quaternary groups.

**Synthetic Procedures.** 1,3-Bis(4-methoxyphenyl)urea. 4-Methoxybenzaldehyde (1.0 g, 7.7 mmol) and diphenyl carbonate (0.80 g, 3.7 mmol) were mixed in triethylamine (2.7 mL, 19 mmol). The reaction mixture was heated to reflux for 5 h. After cooling down, 1 M NaOH solution (10 mL) was added and the suspension was thoroughly stirred for 30 min. A solid precipitate was collected by filtration and thoroughly washed with water (3 × 5 mL). A white solid product was dried in vacuum (1.1 g, quantitative). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.17 (d, $J$ = 8.6 Hz, 4H), 6.86 (d, $J$ = 8.6 Hz, 4H), 6.28 (t, $J$ = 6.0 Hz, 2H), 4.14 (d, $J$ = 5.9 Hz, 4H), 3.72 (s, 6H), spectral data correspond to the literature.

2,4-Bis(4-methoxybenzyl)glycoluril. 1,3-Bis(4-methoxybenzyl)urea (6.3 g, 21 mmol) and DHI (4.9 g, 42 mmol) were suspended in MeOH (84 mL) and acidiﬁed with 35% HCl (0.42 mL). The mixture was refl ﬂuxed for 8 h during which all starting materials dissolved. The mixture was ﬁltered while hot to remove small amount of unsubstituted glycoluril and after cooling to room temperature (RT), it was left to crystallize in fridge overnight. A colorless crystalline product was collected by ﬁltration and washed with water (2 × 15 mL) and acetone (2 × 10 mL). Yield (6.5 g, 81%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.33 (s, 2H), 7.33 (d, $J$ = 8.2 Hz, 4H), 6.85 (d, $J$ = 8.6 Hz, 4H), 3.71 (s, 6H), spectral data correspond to the literature.

Octakis(4-methoxybenzyl)bambus[4]uril $[(\text{PMB})\text{BU[4]}]$. 2,4-Bis(4-methoxybenzyl) glycoluril (0.5 g, 1.3 mmol), paraformaldehyde (39 mg, 1.3 mmol), and PTSA (0.12 g, 0.65 mmol) were heated in dioxane (2.5 mL) at 80°C for 22 h. After cooling to RT, the solution was diluted with water to a volume of 25 mL. A precipitated solid was collected by ﬁltration and washed with water (2 × 25 mL). The crude material was ﬁltered through silica column (10% acetone in DCM) and later puriﬁed by PTLC (15% acetone in DCM). The solid material (46 mg) was washed with MeOH (1 mL) and collected by centrifugation to obtain pure $[(\text{PMB})\text{BU[4]}]$ as a white solid (33 mg, 6%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$...
Dodecakis(4-methoxybenzyl)bambus[6]uril [(PMB)BU[6]].

2,4-Bis(4-methoxybenzyl)glycoluril (1 g, 2.6 mmol), paraformaldehyde (78.6 mg, 2.62 mmol), and TBAI (0.16 g, 0.44 mmol) were heated in dioxane (4 mL) at 80 °C for 1 h. After cooling to RT, the dark mixture was subjected to microwave irradiation (100 °C, 100 W, 100 °C) for 1 h. After cooling to RT, the dark mixture was precipitated with MeOH (25 mL) and the solid was separated by centrifugation, washed with H2O (5 mL) and dried in vacuum. The residue was added. The mixture was stirred for 20 h; afterward, volatiles were evaporated and the residue was washed with Et2O (5 mL). The crude product was separated by centrifugation, decanted, and mixed with CH2Cl2 (5 mL). The organic phase was washed with H2O (3 × 10 mL), phases were separated by centrifugation, and the aqueous part was discarded. The organic solution was azeotropically dried by coevaporation with CH3CN and dried in vacuum. The residue was purified by column chromatography on silica (15% acetone in DCM, removal of oligomers) and by PTLC [pure EA, separation of (PMB)BU[4] and traces of oligomers from (PMB)BU[6]]. The product was obtained as a complex of TBAI (0.23 g, 19%). 1H NMR (500 MHz, CDCl3): δ 7.25 (d, J = 9.1 Hz, 24H), 6.76 (d, J = 8.7 Hz, 24H), 5.74 (s, 12H), 4.84 (d, J = 15.8 Hz, 12H), 4.57 (d, J = 15.9 Hz, 12H), 4.30 (s, 12H), 3.20−3.02 (m, 8H), 1.58−1.44 (m, 8H), 1.34 (q, J = 7.3 Hz, 8H), 0.96 (t, J = 7.3 Hz, 12H). 13C NMR (126 MHz, CDCl3): δ 160.41, 159.29, 158.70, 131.43, 128.07, 114.00, 70.18, 59.00, 55.33, 47.66, 47.23, 24.12, 19.85, 137.77. HRMS (MALDI-TOF): calcd for [C84H88N16O16 + Na]+, theoretical: 1599.646; experimental: 1599.645 ± 0.003.

Unsubstituted Bambus[6]uril [(H)BU[6]]. (PMB)BU[6]. TBAI (25 mg, 9.1 μmol) was dissolved in CHCl3 (1 mL) and CF3COOH (1 mL) in a 10 mL microwave pressure tube. The reaction mixture was subjected to microwave irradiation (100 W, 100 °C) for 1 h. After cooling to RT, the dark mixture was precipitated with MeOH (25 mL) and the solid was separated by centrifugation. The liquid was decanted, and the crude product was washed with MeOH (2 × 5 mL), CH2Cl2, MeOH 1:1 (5 mL), acetone (5 mL), and H2O (5 mL). In all washing steps, the isolation was done with centrifugation and decantation. After drying in vacuum at 50 °C, the material was obtained as a gray solid (5.6 mg, 58%). After deprotection, the macrocycle was obtained in the form of (H)BU[6]-HI complex. 1H NMR (500 MHz, DMSO-d6): δ 7.66 (s, 1H), 5.32 (s, 1H), 4.52 (s, 1H). 13C NMR (126 MHz, DMSO): δ 160.61, 157.77, 77.96, 46.66. HRMS (MALDI-TOF): calcd for [C84H88N16O16 + H]+, theoretical: 925.3017; experimental: 925.3023 ± 0.0013; calcd for [C84H88N16O16 + Na]+, theoretical: 947.2837; experimental: 947.2825 ± 0.0013.

Dodecapropargylbambus[6]uril [(propargyl)BU[6]]. Crude (H)BU[6]-HI (200 mg) was dissolved in DMSO (dried 4 Å MS, 10 mL) and mixed with powdered KOH (0.58 g, 10 mmol). Afterward, propargyl bromide (1.1 mL, 10 mmol) was added, and the suspension was stirred at RT for 68 h. The product was precipitated with water (40 mL), collected by filtration, and washed with H2O (2 × 15 mL). After drying in vacuum, the solid was washed with small portions of MeOH (total 50 mL). The MeOH solution was evaporated to dryness, and the residue was washed with Et2O (2 × 15 mL). The product was obtained as a dark brown solid (0.18 g). 1H NMR (500 MHz, CDCl3): δ 5.93 (s, 12H), 5.19 (s, 12H), 4.53 (dd, J = 17.9, 2.3 Hz, 12H), 4.46 (dd, J = 17.9, 2.4 Hz, 12H), 2.14 (t, J = 2.3 Hz, 12H). 13C NMR (126 MHz, CDCl3): δ 159.26, 159.10, 80.44, 71.85, 67.93, 59.53, 47.93, 34.21, 24.47, 20.09, 13.93. HRMS (MALDI-TOF): calcd for [C30H36N24O12 + Na]+, theoretical: 1381.490; experimental: 1381.490 ± 0.002.

Dodecakis[3-[[1-[3,5-bis(methoxycarbonyl)phenyl]-1H-1,2,3-triazol-4-yl]methyl]amino]bambus[6]uril (1). (propargyl)BU[6] (10 mg, 6.5 μmol) and dimethyl-5-azidobenzene-1,3-dicarboxylate (23 mg, 97 μmol) and DIPEA (70 μL, 0.40 mmol) were mixed in CH3CN (0.9 mL). The mixture was bubbled with Ar for 10 min, and solid CuI (5.3 mg, 28 μmol) was added. The mixture was stirred for 20 h; afterward, volatiles were evaporated and the residue was washed with Et2O (5 mL). The crude product was separated by centrifugation, decanted, and mixed with CH2Cl2 (5 mL). The organic phase was washed with H2O (3 × 10 mL), phases were separated by centrifugation, and the aqueous part was discarded. The organic solution was azeotropically dried by coevaporation with CH3CN and dried in vacuum. The residue of azide was removed from the product by washing with MeOH and centrifugation. Product 1 was obtained as a brown solid (16 mg, 54%). 1H NMR signals of compound were extremely broad before excess of TBAI was added, even when the reaction was performed already on the I− complex. 1H NMR (500 MHz, CDCl3): δ 8.55 (t, J = 1.6 Hz, 12H), 8.44 (d, J = 1.5 Hz, 24H), 8.18 (s, 12H), 6.45 (s, 12H), 5.31 (s, 16H), 5.12 (d, J = 15.7 Hz, 13H), 4.85 (d, J = 15.7 Hz, 13H), 3.91 (d, 6H). 13C NMR
(126 MHz, CDCl3): δ 165.01, 160.89, 159.72, 146.94, 137.52, 132.34, 130.01, 124.83, 121.37, 70.12, 59.40, 52.83, 47.71, 39.96, 24.36, 19.97, 13.85. MS (MALDI-TOF): calcld for [C16H18N4O2 + H]+, theoretical: 247.1190; experimental: 247.1189. 

1H NMR (500 MHz, CDCl3): δ 8.71 (t, J = 1.4 Hz, 2H), 8.57 (d, J = 1.5 Hz, 4H), 8.18 (s, 2H), 5.28 (s, 2H), 4.91 (d, J = 15.9 Hz, 2H), 4.60 (d, J = 160 Hz, 2H), 3.98 (s, 12H), 3.03 (s, 6H). 13C NMR (126 MHz, CDCl3): δ 159.02, 156.62, 74.08, 69.31, 32.93, 30.65. HRMS (APCI+): calcld for [C12H14N4O2 + H]+, theoretical: 247.1190; experimental: 247.1189.

After drying in vacuum, the product was obtained as brown oil (75%). 

According to NMR, 20% of propargyl groups remained and so the reaction was repeated with the crude mixture and one-half amounts of other reagents. Isolation was repeated, and after evaporation, the residue was washed with Et2O (2 × 5 mL), collected by centrifugation, and dried in vacuum. Product 2 was obtained as beige solid (0.11 g, 53%). 

1H NMR (500 MHz, CDCl3): δ 8.71 (t, J = 1.4 Hz, 2H), 8.57 (d, J = 1.5 Hz, 4H), 8.18 (s, 2H), 5.28 (s, 2H), 4.91 (d, J = 15.9 Hz, 2H), 4.60 (d, J = 160 Hz, 2H), 3.98 (s, 12H), 3.03 (s, 6H). 13C NMR (126 MHz, CDCl3): δ 159.02, 156.62, 74.08, 69.31, 32.93, 30.65. HRMS (APCI+): calcld for [C12H14N4O2 + H]+, theoretical: 247.1190; experimental: 247.1189.

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Detailed synthetic procedures and the spectral characterizations of the new compounds with the included spectra (PDF) 

Crystallographic data for 2 (CIF)

**ASSOCIATED CONTENT**

Supporting Information

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Notes

The authors declare no competing financial interest.

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