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Extension of the Bambus[*n*]uril Family: Microwave Synthesis and Reactivity of Allylbambus[*n*]urils

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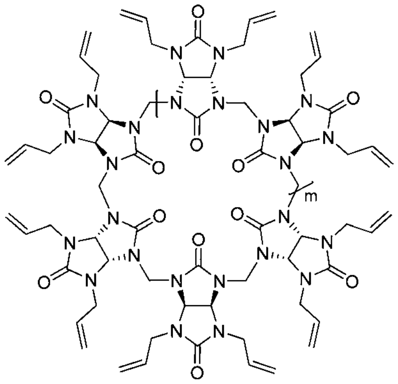
ABSTRACT



Allyl$_8$BU[4] : m = 0
Allyl$_{12}$BU[6] : m = 1

Microwave irradiations allow the preparation of unsaturated bambusurils in 85% yield compared to 20% yield under classical reaction conditions. Five new bambusurils were synthesized including unsaturated derivatives Allyl$_8$BU[4] and Allyl$_{12}$BU[6] bearing diallylglycoluril units. The reactivity of Allyl$_8$BU[4] was tested in a variety of organic reactions showing that this macrocycle acts as a classical double bond-bearing product. The first monofunctionalized bambusuril Allyl$_7$HepBU[4] prepared by a cross metathesis reaction is also reported.

Since the origin of the concept of host–guest interactions, supramolecular chemistry has emerged over the past 20 years with the development of a diversity of host-systems for cations, anions or neutral guests.[1] Numerous macrocycles have been synthesized, including crown ethers, cryptands, cyclodextrins, calixarenes, carcerands, cyclophanes, cryptophanes, calixpyrroles, cyclopeptides and cucurbiturils.[2] All of these host molecules are composed of building blocks with specific structures and reactivity. Among them, glycoluril-based systems are used for the construction of molecular clips and baskets, tennis balls, capsules and cucurbit[*n*]urils.[3] Cucurbit[*n*]urils are constituted of repeated glycoluril units (n = 5–8, 10) doubly bridged by methylene linkers which ensure the rigidity of the

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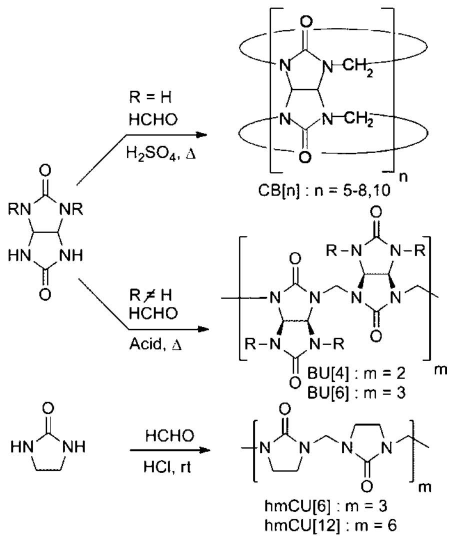
structure around the hydrophobic cavity. They are particularly suitable for the complexation of cations, neutral molecules and gases.[2e,3d,3e,4] Functionalized CB[*n*][5] were added to the family as well as hemicucurbit[n]urils (hmCU[*n*])[6] formed of *n* (*n* = 6, 12) methylene-linked ethyleneurea fragments that have an alternate conformation in solution able to complex anions (Scheme 1).[7]

Scheme 1. Structures of CB[*n*], BU[*n*] and hmCU[*n*]



Recently, a new family of synthetic macrocycles, bambus[n]urils (BU[*n*] with *n* = 4, 6), has been discovered by Sindelar.[8] Their trivial name derives from their resemblance to a bamboo plant stem. They are prepared by an acid-catalyzed condensation of disubstituted glycoluril and formaldehyde, in contrast to the cucurbiturils for which glycoluril (R = H) is the starting product (see Scheme 1 for structures). Bambusurils differ from cucurbiturils by enhanced structural flexibility and good solubility in organic solvents. They bind halide anions with higher affinity and selectivity than the hemicucurbit[*n*]urils.[8,9]

To the best of our knowledge, only four bambusurils, denoted as $Me_{12}BU[6]$, $Bn_{12}BU[6]$, $Bn_8BU[4]$, and $Pr_{12}BU[6]$, have been fully described in the literature by Sindelar (Figure 1).[8,10] A control of the size of the bambusuril cavity was made possible by adding a template anion. Thus, only $Bn_8BU[4]$ was obtained without use of a template (57% yield), whereas $Bn_{12}BU[6]$ was obtained as major product (65% yield) in presence of tetrabutylammonium iodide (TBAI). The resulting $Bn_{12}BU[6]$ entraps an iodide ion inside its cavity, which can be later removed by oxidation.[8c]

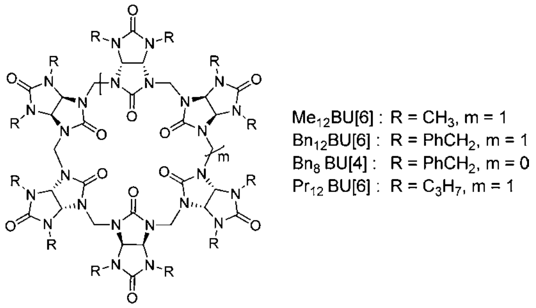


Figure 1. Bambusurils described by Sindelar.[8]

Since our group has been involved in cucurbiturils research,[4b] we were interested in developing new macrocycles, and functionalized bambusurils came to our attention. Herein we report an efficient microwave-mediated synthesis of new bambus[*n*]urils (*n* = 4, 6) (see Figure 2 for the BUs synthesized in this report). Among the various conditions tested, microwave irradiation was found to be the most efficient method to obtain bambusurils in very good yields. We also studied the reactivity of the prepared allylbambusurils in a variety of organic reactions.

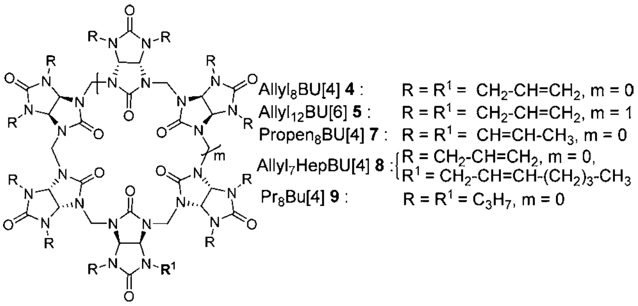


Figure 2. New synthesized bambusurils.

The synthesis of allylbambusurils starts with the preliminary preparation of diallylglycoluril **1**, the essential molecular brick. Compound **1** was synthesized by acidic condensation of 4,5-dihydroxyimidazolidin-2-one **2**[8c,11] and diallylurea **3** using Sindelar's conditions[8c] (91% yield, Scheme 2).

Then **1** was reacted with formaldehyde under various conditions to test the feasibility of preparing the corresponding

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[10] $Me_{24}BU[12]$, $Et_{12}BU[6]$ and $Bn_8thioBU[4]$ are known compounds but their data are not fully reported, see ref 8d.

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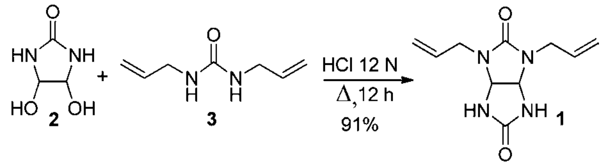
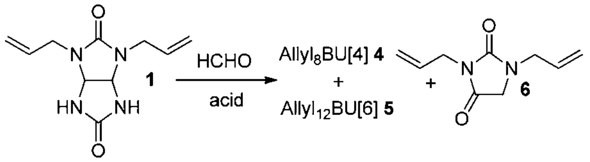
Scheme 2. Preparation of Diallyl Glycoluril **1**



bambusurils. We explored the effects of the nature of the acid, the solvent, the concentration, the temperature and the reaction time (Table 1).

When glycoluril **1** was submitted to formaldehyde in aqueous HCl following Sindelar's original conditions,[8a] the condensation gave BUs **4** and **5** in very low yields, and mostly degradation products (entry 1). To our delight, when we performed the reaction with *p*-toluenesulfonic acid (PTSA) in boiling chloroform for 24 h, under the conditions reported for the synthesis of $Bn_8BU[4]$,[8b] $Allyl_8BU[4]$ **4** was isolated in 20% yield (entry 2). By heating at reflux of acetonitrile, the reaction only afforded hydantoin **6** (90% yield, entry 3). Use of camphorsulfonic acid (CSA) in chloroform provided **4** and **5** in very low yields (3%, entry 4).

Table 1. Optimization of the Synthesis of $Allyl_8$bambus[4]uril **4** and $Allyl_{12}$bambus[6]uril **5**



entry	conditions	temp, time	**4** (%)[a]	**5** (%)[a]	**6** (%)[a]
1	HCl 5.4 M	rt[b], 24 h	3	1	
2	PTSA, $CHCl_3$	reflux, 24 h	20	0	
3	PTSA, CH_3CN	reflux, 24 h			90
4	CSA, $CHCl_3$	reflux, 24 h	3	3	
5	PTSA, toluene, TBAI[c]	reflux, 24 h	5	15	
6	PTSA, $CHCl_3$,0.4 M, MW[d]	75 °C, 2 h	3		
7	PTSA, $CHCl_3$, 0.04 M, MW	75 °C, 2 h	85		
8	PTSA, toluene, 0.01 M, MW, TBAI	110 °C, 4 h	10	60	

[a] Isolated yields. [b] 45 °C for 20 min until dissolution of **1** and then rt for 24 h. [c] TBAI (0.16 equiv). [d] MW: Power = Pmax = 200 W.

In toluene and addition of TBAI, the reaction allowed the formation of **4** and **5** in 5 and 15% yields, respectively (entry 5). As observed by Sindelar, TBAI acted as a template, promoting the formation of bambusuril **5**.

We finally examined the use of microwave irradiations in the synthesis of allylbambusurils (entries 6–8). This technique, which is able to greatly increase the rate of many reactions, is now routinely used in organic synthesis and has already shown its efficiency in cucurbituril synthesis.[12] We first tested the reaction of diallylglycoluril **1** and HCHO with PTSA in $CHCl_3$ in a microwave synthetizer (0.4 M, 75 °C, 2 h, maximum power 200 W, entry 6). Disappointingly, BU **4** was formed in very low yield and degradation products and insoluble oligomers were mainly obtained (entry 6). To avoid oligomerization, we performed the reaction in diluted chloroform (0.04 M) and, as expected, $Allyl_8BU[4]$ **4** was isolated in very good yield (85% yield, entry 7). The reaction run in the presence of TBAI in diluted conditions (0.01 M) afforded BU **5** as a major product, as well as BU **4** (60 and 10% yields, respectively, entry 8).

To generalize the efficiency of microwaves, we performed the synthesis of known BUs.[8] MW method improved the yield of $Bn_{12}BU[6]$ to 90% compared to 65% yield in classical conditions, and reduced the reaction time to 4 h compared to 22 h.[8b] Similarly, the synthesis of known $Pr_{12}BU[6]$ was achieved in 60% yield using MW, compared to prior 15% yield.[8b] (see structures of $Bn_{12}BU[6]$ and $Pr_{12}BU[6]$ in Figure 1).

We obtained single crystals of $Allyl_8BU[4]$ **4** and $Allyl_{12}BU[6]$ **5** by slow evaporation of CH_2Cl_2 and of a 95/5 mixture of CH_2Cl_2/MeOH respectively. X-ray structure determinations of **4** and **5** were carried out and the results are shown in Figure 3. They confirm the expected bambusuril structures **4** and **5** that consist in 4 or 6 diallylglycoluril units in an alternate conformation and connected by one row of methylene bridges. An iodide anion inside the cavity of $Allyl_{12}BU[6]$ **5** is also present as expected when TBAI was used in the synthesis.[8b] When comparing the structure of $Allyl_8BU[4]$ **4** to that of the only one previously described $Bn_8BU[4]$,[8b] it appears that the ureido rings not bound to the methylene bridges are more tilted toward the mean plane defined by the four methylene carbon atoms in BU **4**, with dihedral angles in the range 30.62(9)–39.91(10)° (versus 48.5–53.5° in $Bn_8BU[4]$). As a result, the distance between the barycenter of atoms O2 and O6 and that of atoms O4 and O8 amounts to 7.87 Å, while the analogous distance in the previously reported $Bn_8BU[4]$[8b] is 9.19 Å. The conformation of the centrosymmetric $Allyl_{12}BU[6]$ **5** is very close to that in the previously reported structures,[8] with in particular a maximum deviation of 0.3 Å only for the atoms in the BU[6] **5** skeleton with respect to their counterparts in the previously described iodide complex of $Me_{12}BU[6]$.[8a] As a consequence, the distance between the two planes containing the outermost oxygen atoms, 9.65 Å, is identical to those previously reported (9.61–9.64 Å). As usual,[8b,c] the iodide anion sits at the center of the macrocycle (on the inversion center), where it is held by CH···I hydrogen bonds involving the methine groups pointing inward (C···I distances in the range 3.75–4.00 Å).

At this stage, we were interested in disposing of bambusurils with a closed and less flexible shape, therefore we

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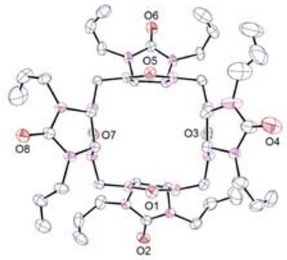
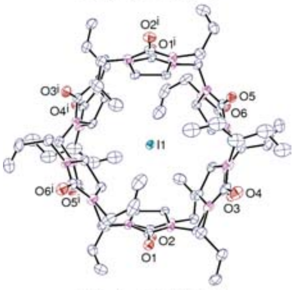
(12) (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. and *Chem. Soc. Rev.* **2008**, *37*, 1127. (b) Wheate, N. J.; Patel, N.; Sutcliffe, O. B. *Future Med. Chem.* **2010**, *2*, 231.

(13) Studies were performed on BU **4** that was at our disposal in higher amount than BU **5**. A preliminary RCM tested on **5** did not proceed presumably because of the presence of iodide inside the cavity of **5**.



Allyl$_8$BU[4] **4**



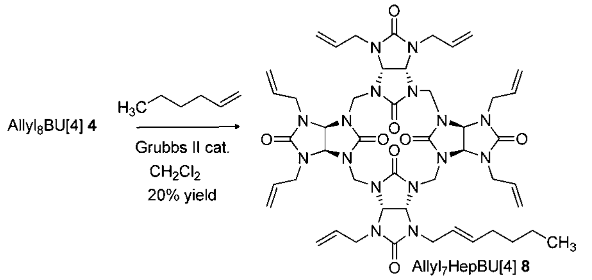
Allyl$_{12}$BU[6] **5**

Figure 3. Crystal structures of Allyl$_8$BU[4] **4** and Allyl$_{12}$BU[6] **5**.

submitted Allyl$_8$BU[4] **4**[13] to ring closing metathesis reactions (RCM). When BU **4** was reacted with Grubbs I, II or Hoveyda-Grubbs I catalysts in CH_2Cl_2 or toluene (room temperature or reflux), no RCM reaction occurred and the starting BU **4** was recovered. Surprisingly, Hoveyda-Grubbs II catalyst at reflux of toluene allowed the isomerization of the diallylureas of BU **4**, yielding quantitatively (1-propenyl)$_8$-BU[4] **7** (see structure **7** in Figure 2). Such isomerization was never described with Hoveyda-Grubbs II, although Grubbs ruthenium carbene is known to deprotect tertiary allylic amines and *N*-allylic amide-like moieties through isomerization followed by an oxidation step.[14] It was reported that such unwanted isomerization can be suppressed by use of acidic additives.[15] In our case, phosphoric acid allowed the desired RCM reaction of BU **4** to proceed with Hoveyda-Grubbs II catalyst. Unfortunately, the expected RCM-closed bambusuril bearing four disubstituted double-bonds was detected only as traces by mass spectra analysis.

Then we studied the cross metathesis reaction (CM) of BU **4** with 1-hexene as olefin partner using various catalysts. Grubbs II was the catalyst of choice, giving the expected monofunctionalized Allyl$_7$HepBU[4] **8** in 20% yield, (use of 2 equivalents of hexene, Scheme 3).[16]

Scheme 3. Cross Metathesis Reaction of Bambusuril **4**



Allyl$_7$HepBU[4] **8**

Finally, we examined the hydrogenation reaction of Allyl$_8$BU **4** with H_2 (1 atm) over 10% Pd/C in EtOH. The corresponding new Pr$_8$BU[4] **9** was obtained in a quantitative yield (see structure **9** in Figure 2).

In conclusion, microwave-assisted synthesis is the method of choice to prepare bambusurils in good yields and rapidly. Two new unsaturated bambusurils, Allyl$_8$BU[4] **4** and Allyl$_{12}$BU[6] **5**, were synthesized. BU **4** represents the second bambusuril bearing four glycoluril units discovered so far. Allylbambusurils act as macrocycles bearing olefins able to undergo metathesis and hydrogenation reactions. Allyl$_7$HepBU[4] **8** was obtained by a cross metathesis reaction of BU **4** with hexene and is the first monofunctionalized bambusuril to be reported. Such cross metathesis methodology using appropriate olefin partners can allow the preparation of useful bambusurils that should find interesting recognition applications. The five new bambusurils **4**, **5**, **7**, **8** and **9** prepared in this report extend the BUs family discovered by Sindelar. Studies concerning their complexation properties and the synthesis of other derivatives are in progress in our laboratory.

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Supporting Information Available. Experimental procedure and full characterization for compounds **1**, **4**–**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Yield was not further optimized. Excess of hexene (10 equiv) afforded a complex mixture of CM products that was not separated.

The authors declare no competing financial interest.