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Functionalization of Bambusurils by thiol-ene click reaction and new, facile method for the preparation of anion-free Bambus[6]urils

Djamille Azazna,^[a,b] Marine Lafosse,^[a,b] Julie Rivollier,^[a] Jialan Wang,^[a] Imen Ben Cheikh,^[a] Michel Meyer,^[c] Pierre Thuéry,^[d] Jean-Pierre Dognon,^[d] Gaspard Huber^[d] and Marie-Pierre Heck^{*[a]}

Abstract: New sulfide-functionalized bambus[4]urils ((RS)₈BU[4]) and bambus[6]urils ((RS)₁₂BU[6]) were synthesized through thiol-ene click coupling reactions (TEC) of allylbambus[n]urils. Thiosugars were grafted to BU[4] and BU[6]. Synthesis of BU[6] derivatives always requires the use of a template anion (iodide, chloride or bromide) which is enclosed in the cavity of BU[6]. We show that this anion influences the reactivity of bambus[6]urils. An encapsulated iodide makes allyl functions of allyl₁₂BU[6] less reactive towards TEC and hydrogenation reactions in comparison to the corresponding chloride or bromide inclusion complexes. This is critical for the chemical reactivity of BU[6] and even more to determine their anion-binding properties. We report a new, facile and fast method using AgSbF₆ to prepare anion-free BU[6]. NMR methods were used to estimate association constants of these new empty BU[6] with different anions. Quantum chemistry calculations were employed to rationalize the observed results. These new functionalized bambusuril scaffolds in alternate conformation could find applications as multivalent binders.

Introduction

Bambus[n]urils BU[4] and BU[6] constitute a family of neutral macrocycles formed by n glycoluril units connected by n methylene bridges (n = 4, 6). BU[6] are able to bind anions within their cavity with a high affinity and selectivity, making them very attractive supramolecular receptors.^[1] Since the discovery of the first BU[6] by the group of Sindelar,^[2] the BUs family has expanded both in size and substitution. BU[4] and BU[6] can be substituted on the nitrogen atoms of their glycoluril unit by methyl, benzyl, propyl, or allyl groups and they are named Me₁₂BU[6],^[2] Bn₁₂BU[6],^[3] Bn₈BU[4],^[3] Pr₁₂BU[6],^[3] allyl₈BU[4], and allyl₁₂BU[6], respectively.^[4] They

are generally soluble in organic solvents. Bambus[6]urils bearing benzoate or carboxylate substituents on their portal are known to be water-soluble.^[5,6] Nitrobenzyl bambus[4]urils and bambus[6]urils were recently prepared in the group of Sindelar.^[7] Nitrobenzyl BU[4] derivatives have been successfully reduced into water soluble amino benzyl BU[4] that were further transformed into corresponding urea bambus[4]urils.^[7] Bambus[6]urils containing 12 (ethylene glycol) functions were recently reported to be as soluble in water as in nonpolar solvents.^[8] Although thiobambusurils are still unknown, some heterobambusurils called semithiobambus[4]urils and semithiobambus[6]urils have been prepared from semi-thioglycoluril derivatives,^[9] and used as precursors for semiaza-bambusurils bearing guanidines, which can act as anion channels.^[10] While bambus[6]urils strongly bind anions in their cavity, either in organic or aqueous media,^[3,6,11] the incorporation of sulfur atoms enables additional binding of metal ions at the portals.^[12]

Bambusurils are usually prepared by an acid-catalyzed Mannich-type condensation of disubstituted glycoluril with paraformaldehyde in a solvent at reflux. We have previously improved this synthesis with the use of microwave irradiations that significantly shorten the reaction times and increase the yields of bambusurils.^[4] These microwave conditions have also been successfully used by the groups of Keinan and Sindelar.^[9,7] A templating anion is always required either using reflux or microwaves, to promote the formation of the hexameric BU[6], in preference to the tetrameric BU[4]. Although this methodology has been well established, however BU[6] derivatives are generally isolated as having an anion present inside their cavity and time-consuming steps are necessary to obtain anion-free BU[6].^[3, 8,13]

To our knowledge, only one monofunctionalization reaction on allyl₈BU[4] by a cross metathesis reaction has been reported.^[4] The transformation of semithiobambusurils into semi(methyl)sulfoniumbambusuril and then to semiazabambusurils bearing guanidinium groups at their portal has been detailed by Keinan.^[10]

Interestingly the first nonsymmetrical BU[4] was very recently prepared by Sindelar.^[7] Apart from these few examples, the functionalization and reactivity of BUs are still poorly developed. Therefore, we were interested in preparing new functionalized BU[4] and BU[6] and in studying the reactivity of BU[6] as a function of the enclosed anion.

To complete the family of allylbambus[n]urils starting from allyl₈BU[4] **1** and I@allyl₁₂BU[6].TBA **2**,^[4] we herein report the synthesis of Cl@allyl₁₂BU[6].TBA **3**, and Br@allyl₁₂BU[6].TBA

[a] D. Azazna, M. Lafosse, Dr J. Rivollier, J. Wang, I. Ben Cheikh, Dr. M.-P. Heck, SCBM, CEA, Université Paris-Saclay, 91191 Gif-sur-Yvette, France. E-mail: Marie-Pierre.Heck@cea.fr

[b] D. A and M. L : equal contribution for this study

[c] Dr. M. Meyer, Institut de Chimie Moléculaire de l'Université de Bourgogne, CNRS, Université de Bourgogne-Franche Comté, 9 avenue Alain Savary, BP 47870, 21078 Dijon cedex, France

[d] Dr. P. Thuéry, Dr J.-P. Dognon, Dr G. Huber, NIMBE, CEA, Université Paris-Saclay, 91191 Gif-sur-Yvette, France.

4 and we show that the enclosed halide can alter the reactivity of allyl₁₂BU[6] 2-4. (Figure 1). We synthesized new sulfide-functionalized bambusurils **8-16** through a thiol-ene reaction of allyl₈BU[4] **1** or halide@allyl₁₂BU[6] **2-4**. New R₈BU[4] and R₁₂BU[6] bearing respectively 8 or 12 thioether functions were obtained (Figure 1). We also report a new method using AgSbF₆ to easily prepare anion-free BU[6] **17-21** (Figure 1). The binding properties of **17**, **20** and **21** toward some halides were investigated by ¹H NMR spectroscopy. Quantum chemistry calculations were used to understand our results.

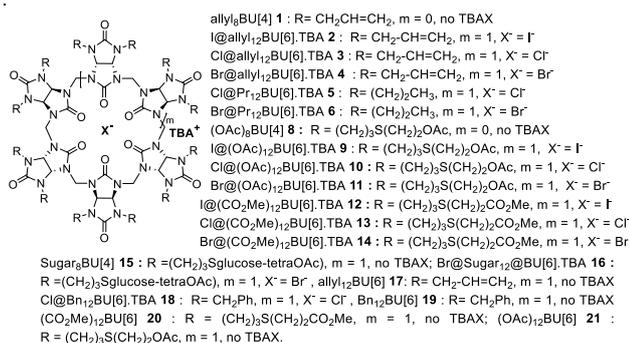
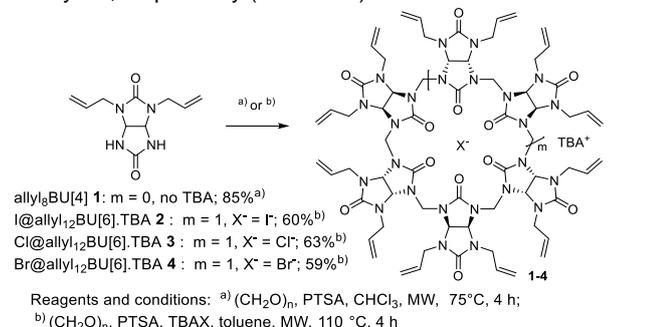


Figure 1: Structures of bambusurils BU[4] and BU[6] studied in this work.

Results and Discussion

We have previously reported the microwave-assisted synthesis of allyl₈BU[4] **1** and I@allyl₁₂BU[6].TBA **2** starting from 2,4-diallylglycoluril and paraformaldehyde with *p*-toluenesulfonic acid.^[4] The 4-membered allyl₈BU[4] **1** was prepared in chloroform (85% yield) in an experiment where no anion has been added, while 6-membered I@allyl₁₂BU[6].TBA **2** (60% yield) was obtained in toluene in the presence of tetrabutylammonium iodide (Scheme 1).^[4] Interested in studying whether the anion enclosed in the cavity of bambus[6]uril would modify its reactivity, we prepared Cl@allyl₁₂BU[6].TBA **3** and Br@allyl₁₂BU[6].TBA **4**. Microwave condensation of diallylglycoluril with paraformaldehyde in toluene in the presence of either tetrabutylammonium chloride or bromide provided Cl@BU[6] **3** and Br@BU[6] **4** in 63% and 59% yield, respectively (Scheme 1).



Scheme 1. Synthesis of allyl₈BU[4] **1** and X@allyl₁₂BU[6].TBA **2-4**, X = I, Cl or Br.

Our results are coherent with Sindelar's work reporting that I@Bn₁₂BU[6].TBA and Cl@Bn₁₂BU[6].TBA were isolated in comparable yields (65% and 53% respectively).^[3]

Crystals of Cl@allyl₁₂BU[6].TBA **3** were obtained by their slow evaporation in CH₂Cl₂/MeOH (9/1 v/v) and Br@allyl₁₂BU[6].TBA **4** was recrystallized in CH₂Cl₂/Et₂O (8/2 v/v). The crystal structures of the isomorphous BU[6] **3** and **4** were determined by single-crystal X-ray diffraction, and confirm that the macrocycles consist in six diallylglycoluril units in an alternate conformation, connected by one row of methylene bridges. As iodide in the isomorphous I@allyl₁₂BU[6].TBA **2**,^[4] the chloride and bromide anions, which are located on an inversion center, are included in the cavity of the centrosymmetric macrocycles **3** and **4** (Figure 2).

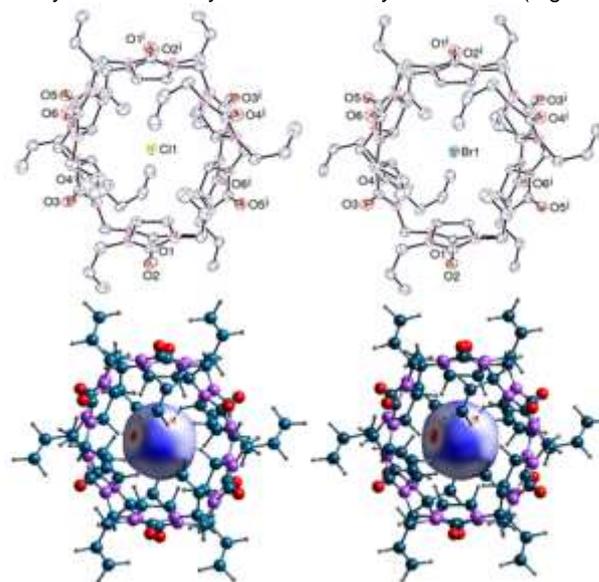


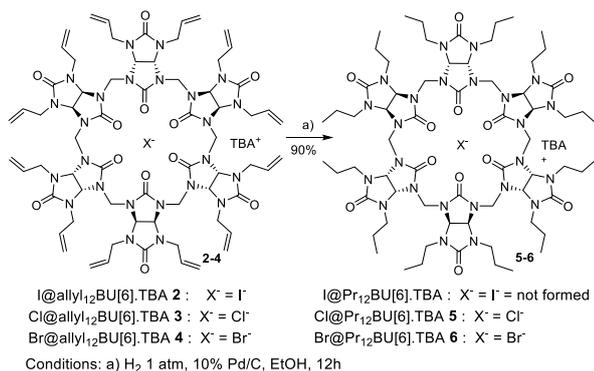
Figure 2. Top row: Crystal structures of Cl@allyl₁₂BU[6] **3** (left) and Br@allyl₁₂BU[6] **4** (right). Displacement ellipsoids are shown at the 30% probability level. Counterions and hydrogen atoms are omitted. Symmetry code: i = 3/2 - x, 1/2 - y, 1 - z. Bottom row: Views of the Hirshfeld surface of the chloride (left) and bromine (right) anions, showing the hydrogen bonding interactions with methine groups of BU[6] (dashed lines).

This arrangement is similar to that previously found in Cl@Me₁₂BU[6],^[2] and I@Pr₁₂BU[6].^[3] although complexation of two chloride anions, one at each portal, has been found for Bn₁₂BU[6].^[3] The interactions between the included anion and the macrocycle can be analyzed through calculation of Hirshfeld surfaces (HSs)^[14] with CrystalExplorer.^[15] As shown in Figure 2, the HSs of the anions mapped with *d*_{norm} show only four conspicuous red spots (only two of which are seen in the figure, the others being related to these by inversion) corresponding to contacts shorter than the van der Waals separation with four methine hydrogen atoms (the other methine hydrogen atoms are at distances larger than 3 Å and are not involved in interactions stronger than dispersion). The geometry of these CH...halide hydrogen bonds is similar to that in compound **2**, with distances varying with the halogen ionic radius, thus indicating that the macrocycle retains some flexibility [C...Cl 3.548(3)/3.609(3) Å, H...Cl 2.81/2.76 Å, C-H...Cl 131/143° in **3**; C...Br 3.625(4)/3.601(4) Å, H...Br

2.87/2.76 Å, C–H...Br 133/141° in **4**, and C...I 3.768(6)/3.745(6) Å, H...I 3.02/3.05 Å, C–H...I 134/129° in **2**. Although their existence has long been controversial,^[16] CH...halogen hydrogen bonds are now considered significant, and it is notable that the distances found in the present cases are close to those usually reported.^[17] Although CH...halide bonds are weak, the fact that the anion forms four such bonds in the present species favors their contribution to the stability of the complexes.

Owing to their rapid and efficient synthesis, allyl₈BU[4] **1** and X@allyl₁₂BU[6].TBA **2-4** are valuable molecules for post-functionalization.

First, we studied the reactivity of allylbambus[n]urils in hydrogenation conditions. We have previously shown that the reaction of allyl₈BU[4] **1** with H₂ and Pd/C (10 wt % loading) in ethanol and as catalyst, afforded quantitatively Pr₈BU[4].^[4] However, I@allyl₁₂BU[6].TBA **2** remained unmodified when treated under these hydrogenation conditions, while the use of a larger amount of catalyst resulted in degradation of **2**. On the contrary, the hydrogenation of Cl@allyl₁₂BU[6].TBA **3** and Br@allyl₁₂BU[6].TBA **4** afforded the expected Cl@Pr₁₂BU[6].TBA **5** and Br@Pr₁₂BU[6].TBA **6**, respectively, both in 90% yield (Scheme 2). We suspect that the iodide anion enclosed in the cavity of BU[6] **2** could have poisoned the catalyst, preventing the hydrogenation to proceed.



Scheme 2. Hydrogenation of halides@allyl₁₂BU[6] **2-4**.

Then we decided to transform the allyl arms of allyl₈BU[4] **1** and X@allyl₁₂BU[6].TBA **2-4** with efficient methods able to create highly functionalized materials. Cross-metathesis reaction has already proven to be an effective tool to monofunctionalize allyl₈BU[4] **1**.^[4] We were interested in thiol-ene coupling reaction (TEC), an environmentally friendly click reaction that proceeds in mild conditions and which was successfully applied to the synthesis of bioconjugated polymers, star polymers, dendrimers, disaccharides and to the modification of surfaces.^[18] The AIBN-initiated TEC reaction of tetraallylglycoluril into thioethers was previously reported.^[19] The (allyloxy)₁₂Cucurbit[6]uril, a cavitand bearing twelve allyloxy groups at the equatorial positions, was transformed into Cucurbituril-based carbohydrate thanks to its TEC reaction with thioglycosides.^[20] To the best of our knowledge, apart from these two reports, the thiol-ene reaction has neither

been tested on diallylglycoluril nor on bambusuril scaffolds. Therefore, we investigated TEC of diallylglycoluril as a simple model with a range of thiols using radical conditions initiated either by thermal or photochemical methods, with or without photoinitiator.^[21] As the reaction of diallylglycoluril with 2-mercaptoethanol activated by AIBN in refluxing toluene or CH₂Cl₂ was unsuccessful, we examined UV initiations. The results are reported in Table 1 (method A). TEC reactions of diallylglycoluril under UV irradiation in MeOH, using an excess of six equivalents of mercaptoethanol, methyl 3-mercaptopropionate or NBoc-L-cysteine methyl ester efficiently afforded corresponding dithioether glycolurils **7a**, **7e**, and **7f** in 76%, 40% and 51% yield, respectively (Table 1, entries 1, 5-6, method A).^[22]

Table 1. TEC reactions of diallylglycoluril with UV activation (method A) or TBC/Et₃B (method B).

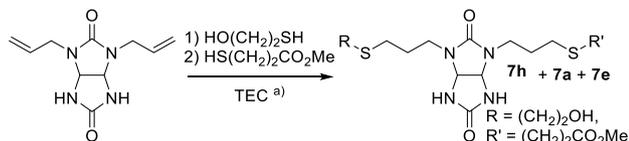
Entry	RSH	Product 7	Yield (%)	
			Method A	Method B
1	HO(CH ₂) ₂ SH	7a	76	82
2	HO(CH ₂) ₃ SH	7b	nd	43
3	CH ₂ CH(OH)-CH(CH ₃)SH	7c	nd	30
4	HOCH ₂ CH(OH)CH ₂ SH	7d	nd	52
5	MeO ₂ C(CH ₂) ₂ SH	7e	40	50
6	HS-CH ₂ -CH(OMe)-NH-Boc	7f	51	77
7	AcO-CH ₂ -CH ₂ -SH AcO-CH ₂ -CH ₂ -SH AcO-CH ₂ -CH ₂ -SH	7g	nd	36

Reagents and conditions. Method A: Diallylglycoluril (1 equiv), RSH (6 equiv), MeOH, UV, 6 h. Method B: Diallylglycoluril (1 equiv), RSH (3 equiv), triethylborane (2.4 equiv), TBC (4-*tert*-butylcatechol, 2.4 equiv), CH₂Cl₂, 12 h at RT. nd = not determined

Then, we tested the hydrothiolation method, reported by the group of Renaud, using triethylborane (Et₃B) as radical initiator and 4-*tert*-butylcatechol (TBC) as co-reagent.^[23] This method, which proceeds without heating or UV activation, was successfully used to link thiols on allyl glycosides as well as thiosugars to maleimide.^[24] Thus, thiol-ene reactions of diallylglycoluril were carried out with a variety of thiols using Et₃B/TBC (Table 1, entries 1-8, method B). As indicated, all symmetric dithioether glycolurils **7a-7g** were isolated in moderate to good yields (entries 1-7, 30%-82% method B). Coupling of diallylglycoluril with 2-mercapto-3-butanol, a secondary thiol, afforded **7c** in the lowest yield of 30% (entry 3, method B). Thioglycerol and methyl 3-mercaptopropionate were successfully linked to diallylglycoluril to generate corresponding dithioether glycolurils **7d-7e** (52 and 50% yields, entries 4-5, method B). *N*-(*tert*-butoxycarbonyl)-L-cysteine methyl ester was grafted on **1** to give thioetherglycoluril **7f** (entry 6, 77% yield, method B). Treatment of diallylglycoluril with 1-thio-β-D-glucose tetraacetate afforded **7g** (entry 7, 36% yield, method B). Renaud's conditions (method B) afforded

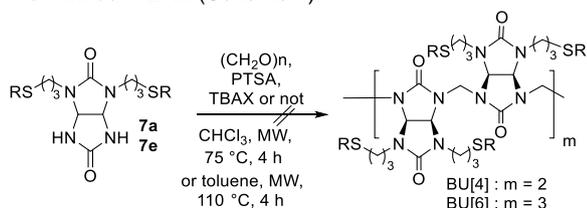
TEC products in higher yields compared to the UV method (method A), and more interestingly method B required a weaker excess of thiol (1.5 vs 6 equivalents by alkene).

Moreover, a differently functionalized thioether glycoluril **7h** was prepared via the one-pot TEC reaction of diallylglycoluril with sequential addition of 2-mercaptoethanol and methyl 3-mercaptopropionate in TBC/Et₃B conditions (Scheme 3, **7h** : 42% yield). Symmetrical thioether glycolurils **7a** and **7e** were as well formed in 18 and 12% yields respectively.



Scheme 3. Synthesis of glycoluril **7h**. TEC conditions ^{b)} diallylglycoluril (1 equiv), HO(CH₂)₂SH (1 equiv), HS(CH₂)₂CO₂Me (1 equiv), Et₃B (2.4 equiv), TBC (2.4 equiv), CH₂Cl₂, 12 h, at RT.

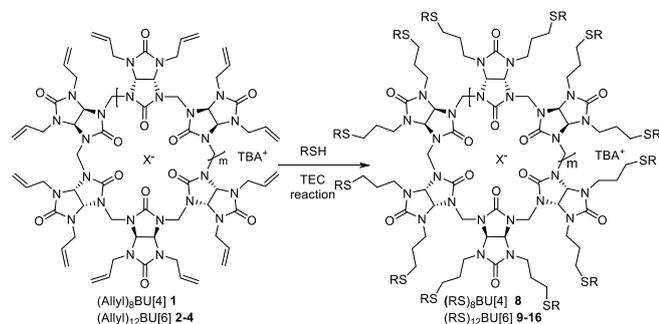
Having thioether glycolurils **7** in hand, we then attempted to prepare the corresponding bambusuril. Thus glycolurils **7a** and **7e** were reacted with paraformaldehyde and *p*-toluenesulfonic acid under MW irradiation, in CHCl₃ or toluene, with or without TBAX (Scheme 4).



Scheme 4. Attempts to prepare bambusurils from dithioglycoluril **7a** and **7e**.

Unfortunately, the expected bambusurils were not obtained, but only a complex mixture of starting products and oligomers was formed.^[25] We supposed that the *N*-substituted urea chains prevented the glycoluril units to closely interact with paraformaldehyde and hence the condensation reaction to proceed.

We then directly set up the hydrothiolation reaction of allyl₈BU[4] **1** and X@allyl₁₂BU[6].TBA **2-4** with various thiols so as to check the influence of the enclosed anion in BU[6] (Scheme 5).



Scheme 5. Hydrothiolation of allyl₈BU[4] **1** and X@allyl₁₂BU[6].TBA **2-4**

The most efficient TEC conditions using Et₃B and TBC (Method B, Table 1) were selected for the hydrothiolation of allylbambusurils **1-4**. The results are summarized in Table 2.

Table 2. TEC reaction of allylbambusurils **1-4**

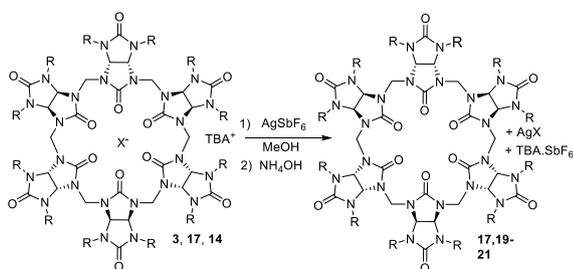
Entry	(Allyl)BU	RS =	(RS)BU	Yield (%)
1 ^[a]	Allyl ₈ BU[4] 1	S(CH ₂) ₂ OAc	8	89
2 ^[a]	I@allyl ₁₂ BU[6] 2	S(CH ₂) ₂ OAc	9	20
3 ^[a]	Cl@allyl ₁₂ BU[6] 3	S(CH ₂) ₂ OAc	10	57
4 ^[a]	Br@allyl ₁₂ BU[6] 4	S(CH ₂) ₂ OAc	11	51
5 ^[b]	I@allyl ₁₂ BU[6] 2	S(CH ₂) ₂ CO ₂ Me	12	49
6 ^[b]	Cl@allyl ₁₂ BU[6] 3	S(CH ₂) ₂ CO ₂ Me	13	55
7 ^[b]	Br@allyl ₁₂ BU[6] 4	S(CH ₂) ₂ CO ₂ Me	14	52
8 ^[b]	Allyl ₈ BU[4] 1	S(CH ₂) ₂ Sugar(OAc) ₄	15	61
9 ^[b]	Br@allyl ₁₂ BU[6] 4	S(CH ₂) ₂ Sugar(OAc) ₄	16	43

Reagents and conditions: ^[a] i) HO(CH₂)₂SH, TBC/Et₃B, CH₂Cl₂, RT, 12 h; ii) Ac₂O, pyridine, RT, 2 h, iii) NaOMe, MeOH, RT, 4 h; ^[b] RSH, TBC/Et₃B, CH₂Cl₂, RT, 12 h.

To our delight when allyl₈BU[4] **1** was reacted with mercaptoethanol, followed by acetylation to facilitate the purification step, ((CH₂)₃S(CH₂)₂OAc)₈BU[4] **8** containing eight thioether moieties was isolated in good yield (entry 1, 89% yield both steps). TEC performed on I@allyl₁₂BU[6].TBA **2** with mercaptoethanol afforded ((CH₂)₃S(CH₂)₂OAc)₁₂BU[6].TBA **9** in a disappointing 20% yield (entry 2). Hydrothiolation of Cl@allyl₁₂BU[6].TBA **3** or Br@allyl₁₂BU[6].TBA **4** under the same conditions yielded functionalized Cl@thioether)₁₂BU[6].TBA **10** and Br@thioether)₁₂BU[6] **11** in 57 and 51% yield, respectively (entries 3, 4). This result consolidates our hydrogenation study of halide@BU[6], and as above observed, TEC reaction is as well less efficient with I@BU[6].TBA **2**, which encloses an iodide, than with Cl@BU[6].TBA **3** or Br@BU[6].TBA **4** containing a chloride or bromine anion respectively. TEC carried out with methyl 3-mercaptopropionate and I@allyl₁₂BU[6].TBA **2** or Cl@allyl₁₂BU[6].TBA **3** or Br@allyl₁₂BU[6].TBA **4** afforded corresponding BU[6] **12**, **13** or **14**, bearing 12 ester moieties, in 49, 55 and 52% yield respectively (entries 5-7). Again, in that case, a lower yield was observed when iodide was enclosed in BU[6] **2** and the reactivity was similar with chloride@BU[6].TBA **3** or bromine @ BU[6].TBA **4**.

Finally, we succeeded in linking eight (1-thio-β-D-glucose tetraacetate) moieties on allyl₈BU[4] **1** to generate (RS)₈BU[4] **15** in 61% yield (entry 8, Table 2). TEC reaction of Br@allyl₁₂BU[6].TBA **4** with (1-thio-β-D-glucose tetraacetate) provide 12 sugars grafted (RS)₁₂BU[6] **16** (43% yield, entry 9, Table 2). The yield obtained for (RS)₁₂BU[6] **16** is slightly lower than that for (RS)₈BU[4] **15** (43% versus 61%) but it is still a good yield for a one step reaction adding 12 ligands on a skeleton. Indeed, it is the first time that sugars are linked to a bambusuril skeleton to generate an eight- or twelve- thiosugars bearing product. This result is very promising for the preparation of various glycosylated bambusurils and is thus opening the way to new multivalent platforms.^[26] Hence, for further applications, it could be interesting to have access to bambus[6]urils functionalized by biologically active molecules.

Having in hand anion-containing bambus[6]urils functionalized by allyl **2-4**, or thioether groups **9-16**, we were interested in evaluating their association constants with various halide anions. To that end, the corresponding anion-free BU[6] had to be obtained. In the literature, several methods have already been reported to remove anion of the cavity of BU[6]. Typical examples include the exchange of the entrapped bromide by a less-strongly bound chloride anion using a huge excess of salt,^[5] followed by refluxing the Cl@BU[6] complex in methanol.^[3,5,9] Alternatively, oxidation of the encaged iodide of I@BU[6] to iodine, which is unable to interact with the macrocycle has also been proposed.^[13] It was reported that carboxyalkyl bambusurils complexes of HSO₄⁻ can be converted to their corresponding anion-free BU[6] by a treatment with basic water.^[6] More recently (trioxadecyl)₁₂BU[6], bearing polyethylene glycol substituents and TBABF₄, was obtained as its NaBF₄ complex after purification by silicagel chromatography,^[27] and was obtained free of BF₄⁻ anion by water continuous extraction over 1 week.^[8] All these reported methods are burdensome and time consuming. It is worthy of note that chloride-free biotin[6]uril was obtained by treatment of its chloride complex with TiNO₃,^[28] although this procedure has never been applied to bambusurils. After unsuccessful attempts using these reported decomplexation processes,^[3,9,13] we set up a new method to obtain anion-free allyl₁₂BU[6] **17** from X@allyl₁₂BU[6].TBA **3**. Treatment of Cl@allyl₁₂BU[6].TBA **3** with silver hexafluoroantimonate AgSbF₆ in MeOH generated instantaneously a white precipitate. This precipitate, containing allyl₁₂BU[6] **17** and AgCl, was recovered by centrifugation. Washings with NH₄OH solution allowed dissolution of AgCl, while the insoluble anion-free allyl₁₂BU[6] **17** was isolated by filtration (Scheme 6, 67% yield).^[29]



Cl@allyl₁₂BU₆.TBA **3**, R = CH₂-CH=CH₂
 I@allyl₁₂BU[6].TBA **2**, R = CH₂-CH=CH₂
 Cl@Bn₁₂BU₆.TBA **18**, R = CH₂C₆H₅
 Cl@((CO₂Me)₁₂BU₆.TBA **13**, R = (CH₂)₃S(CH₂)₂
 Br@((ROAc)₁₂BU₆.TBA **11**, R = (CH₂)₃S(CH₂)₂
 allyl₁₂BU₆ **17**, 67% yield
 allyl₁₂BU₆ **17**, 70% yield
 Bn₁₂BU₆ **19**, 60% yield
 ((RCO₂Me)₁₂BU₆ **20**, 83% yield
 ((ROAc)₁₂BU₆.TBA **21**, 80% yield

Scheme 6. New decomplexation method to prepare anion-free BU[6]**17,19-21**

The release of the chloride anion from the bambusuril cavity was evidenced notably by the fact that allyl₁₂BU[6] **17** was not soluble in CHCl₃, while Cl@allyl₁₂BU[6].TBA **3** easily dissolves in CHCl₃. Furthermore, ¹⁹F NMR and HRMS analyses of the isolated product confirmed the absence of residual SbF₆⁻ and the emptiness of the cavity. We therefore deduced that SbF₆⁻ interacts weakly with allyl₁₂BU[6] **17**. This was confirmed by ¹H NMR titration of **17** with either AgSbF₆ or BMIm-SbF₆ (BMIm⁺ = 1-butyl-3-methylimidazolium) in [D]₆DMSO. The absence of ¹H NMR shift variations upon

addition of large excess of both salts, is a proof of the very low affinity, if any, of **17** for the SbF₆⁻ anion in DMSO. This is in accordance with the low binding constant of SbF₆⁻ reported for Bn₁₂BU[6] **19** in chloroform.^[11c] DFT calculations strengthen our experiments as they show that the interaction of SbF₆⁻ with allyl₁₂BU[6] **17** is also weak (see below for details and discussion). Finally, it is worthy to note that, while we used NH₄OH in our procedure, the very hydrophilic hydroxide anion has in general negligible affinity for bambus[6]uril.^[6]

Moreover, I@allyl₁₂BU[6]@TBA **2**, enclosing an iodine anion in its cavity, was efficiently decomplexed to allyl₁₂BU[6] **17** in 70% yield (Scheme 6). To prove the efficiency of AgSbF₆ as an halide releasing reagent, the method was also applied to Cl@Bn₁₂BU[6].TBA **18**.^[30] The known anion-free Bn₁₂BU[6] **19** was successfully isolated (60% yield, Scheme 6) and it exhibited spectroscopic features identical to those previously reported by Sindelar.^[3] Similarly, treatment of Cl@((CH₂)₃S(CH₂)₂CO₂Me)₁₂BU[6].TBA **13** with AgSbF₆ provided anion-free BU[6] **20** (83% yield, Scheme 6). Finally submission of Br@((CH₂)₃S(CH₂)₂OAc)₁₂BU[6].TBA **11** to decomplexation, afforded anion-free BU[6] **21** (80% yield, Scheme 6). These results show that this facile and efficient decomplexation method can be employed to easily remove halide (I, Br or Cl) in various organic solvent soluble bambus[6]urils.

Binding properties of allyl₁₂BU[6] **17**, ((CH₂)₃S(CH₂)₂CO₂Me)₁₂BU[6] **20** and ((CH₂)₃S(CH₂)₂OAc)₁₂BU[6] **21** with chloride and iodide anions were then explored. Experimental and processing details are provided in the Supporting Information.

In the absence of anion, the N-CH protons of the glycoluril units of allyl₁₂BU[6] **17** resonate at 5.44 ppm in [D]₆DMSO (signal b) on Figure 3a, 0 eq., full spectrum supplied in Figure S1). In the presence of TBAI, giving I@allyl₁₂BU[6].TBA **2**, these N-CH protons resonate at 5.56 ppm (signal a on Figure 3a, 0.4-3.2 eq.). The binding constant of I⁻@**17** is rather low, close to 5x10³ M⁻¹ (Figure S1), compared to that reported for I⁻@Bn₁₂BU[6] **19** in CDCl₃, which is in the range 4x10⁹ – 3x10¹⁰ M⁻¹.^[3,11c] We hypothesize that this far lower binding constant may be due to a significant competition with DMSO. This is based on above reported quantum chemistry calculations showing that DMSO is more stabilized in **17** cavity than CHCl₃ (Figure 4). Thus, despite its much lower stabilization than iodide into the cavity of **17**, DMSO, of 14M concentration as the solvent, may efficiently compete with the anion, of millimolar concentration, for complexation of the bambusuril. This is confirmed by the absence of modification of the chemical shift of the N-CH protons of **17** during its titration with TBACl in DMSO, even with the addition of 24 equivalents of TBACl (Figure S2); this indeed denotes a very weak, if any, binding constant between **17** and chloride in DMSO. This is coherent with the results of Sindelar's group showing that in CDCl₃, the chloride inclusion complex with Bn₁₂BU[6] **19** is about 10³ times less stable than the corresponding iodide one.^[3] This is also in agreement with the titration of Cl@allyl₁₂BU[6] **3** with TBAI in CDCl₃, showing that iodide

binds at least 120 times more strongly to allyl₁₂BU[6] **17** than chloride does (Figure S3).

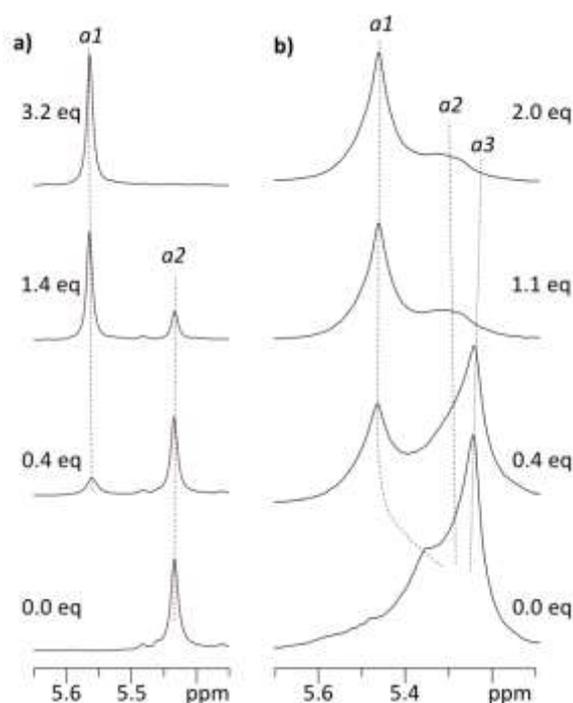


Figure 3. Titration of allyl₁₂BU[6] **17** giving complex I@allyl₁₂BU[6].TBA **2** (Fig 6a) and of ((CH₂)₃S(CH₂)₂CO₂Me)₁₂BU[6] **20** giving complex I@((CH₂)₃-S-(CH₂)₂CO₂Me)₁₂BU[6].TBA **12** (Fig 6b) in [D]₆DMSO with TBAI. Parts of ¹H NMR spectra corresponding to NCH protons. Dashed lines are guidelines for signals a1, a2 and a3, see text. Full spectra are provided in SI (see Figures S2 and S6).

The situation is more complicated when ((CH₂)₃S(CH₂)₂CO₂Me)₁₂BU[6] **20** is concerned. In the ¹H NMR spectrum of Cl@((CH₂)₃S(CH₂)₂CO₂Me)₁₂BU[6].TBA **13** in CDCl₃, the signals assigned to N-CH-N protons of the glycoluril units and to N-CH₂-N protons between two glycoluril units have a complex shape spanning a range of 0.25 to 0.3 ppm (Figure S4). In the course of the titration of **20** with TBAI, these shapes are modified and signals tend to be sharper, particularly at the end of the titration, when the complex I@BU[6] **12** prevails in solution. Furthermore, iodide is at least a 40 times better guest than chloride to **20** (Figure S4), a result consistent with the known higher affinity of bambus[6]urils for iodide versus chloride anions.^[5, 11c,13,31] These observations are consistent with the following hypothesis: the long and flexible arms of ((CH₂)₃S(CH₂)₂CO₂Me)₁₂BU[6] **20** are able to explore the BU's cavity, competing with anions used for titration, whereas shorter arms in allyl₁₂BU[6] **17** cannot explore the cavity. This exploration induces conformational variation at the millisecond timescale of the cavity of **20**, resulting in large ¹H NMR signals. Competition between flexible arms and anion inside the cavity turns out to be more in favor of the iodide complex **12**, than when chloride complex **13** is concerned, explaining the sharper signals for complex **12**. Moreover, iodide, a bigger anion than chloride, should stabilize the cavity in a more rigid

conformation. Finally, the NMR spectra obtained during the titration of Cl@allyl₁₂BU[6] **3** with TBAI giving I@allyl₁₂BU[6] **2** (Figure S3) exhibit sharp and well-defined signals, tending to show that shorter arms are unable to explore the bambusuril cavity. It is in agreement with titrations of Bn₁₂BU[6] **19**, another bambusuril with short arms,^[3,11c] and with previous observations dealing with the influence of the length of carboxylic arms in other BU[6] derivatives.^[6]

The titration of ((CH₂)₃S(CH₂)₂CO₂Me)₁₂BU[6] **20** with TBAI in DMSO is the most complex situation, as three competitors are involved for the access to the cavity of **20**, namely, the iodide anion, the long and flexible arms and the solvent. The spectral complexity observed in the course of the titration is in agreement with this interpretation (Figure 3b, spectra of the full titration in Figure S5). As an example of this complexity, three signals characteristic of N-CH protons are observed and experience chemical shifts and line-width variations during the titration (signals a1, a2 and a3 in Figure 3b). a1 signal increases in intensity during the titration of **20** with TBAI and is therefore assigned to N-CH protons in formed complex I@((CH₂)₃S(CH₂)₂CO₂Me)₁₂BU[6] **12**. The chemical shift variation of a1 signal reflects a relatively fast exchange process corresponding to the binding competition between the three competitors. a2 signal is persistent throughout the titration, even after the addition of 60 equivalents of TBAI. A broadening of signal a2 is observed by increasing the temperature (Figure S6a). This suggests that signal a2 corresponds to a minor conformer with a lifetime decreasing with temperature. Moreover, the line-width of a2 signal increases with the concentration of bambusuril (Figure S6b). This concentration-dependence suggests that signal a2 corresponds to N-CH protons of self-aggregated bambusurils. Indeed, a2 signal is relative to intermolecular interactions between the long and flexible arms of cage **12** and the cavity of the neighboring molecule that might stabilize such assemblies.^[35] Finally, a3 signal becomes undetectable with a strong excess of TBAI (Figure 3b). a3 signal is thus assigned to N-CH protons of BU[6] **20**. The complexity of this system prevents the binding constant to be estimated from either the chemical shift variations or the intensity changes of any ¹H NMR signal. This complexity is however fully consistent with the competition of anions, solvent molecules and long and flexible arms for their occurrence in BU[6] cavities.

The titration of ((CH₂)₃S(CH₂)₂OAc)₁₂BU[6] **21** with TBACl in acetone denotes also complex phenomena (Figure S7). The N-CH₂ signal indicates a slow exchange between two environments even in the absence of chloride. When TBACl is added to **21**, the down-field shifted signal is increasing rapidly and becomes predominant with 0.5 equivalent of TBACl. This signal is assigned to the N-CH₂ protons bordering the cavity of **21** binding either chloride, or a long and flexible (CH₂)₃S(CH₂)₂OAc arm of **21**. The up-field shifted signal is assigned to those same protons of an empty BU[6] **21** or of **21** binding a solvent molecule. This signal is significantly broadened even at only 0.5 equivalent of TBACl showing the short lifetime of the corresponding environment. A competition between arms and chloride supports this observation, although a

quantification of binding constants cannot be obtained. However, when bambusuril **21** containing 1.15 equivalent of TBACl is titrated by TBAI, a slow exchange is observed on N-CH signal (Figure S8). This denotes a competition between guests. Both signals are assigned to (i) bambusuril **21** binding chloride or a thioether arm, and (ii) iodide, respectively. Using N-CH₂ signal, also in slow exchange but much closer to the coalescence, it has been deduced that iodide is a better guest than chloride to bambusuril **21** but only by a factor 4 (the fit is in accordance with values in the range 3-15). We note that this is a lesser ratio than that observed in the case of allyl₁₂BU[6] **17**, bearing much smallest arm. This might be due to the competition of the anion with arms to the bambusuril binding, non-negligible even when the anion is iodide, one of the most stable guest of bambusurils ever observed. This will be explore in more details in the future.

DFT calculations were set up for a better understanding of the stability of the halides@allyl₁₂[BU] complexes **2-4** and the relevance of our decomplexation method using AgSbF₆ (see Supporting Information for details).

The factors determining the stability of the allyl₁₂BU[6] **17** complexes can be best visualized by applying an energy decomposition analysis scheme (see Figure 4 and Supporting Information for details and Table 1).

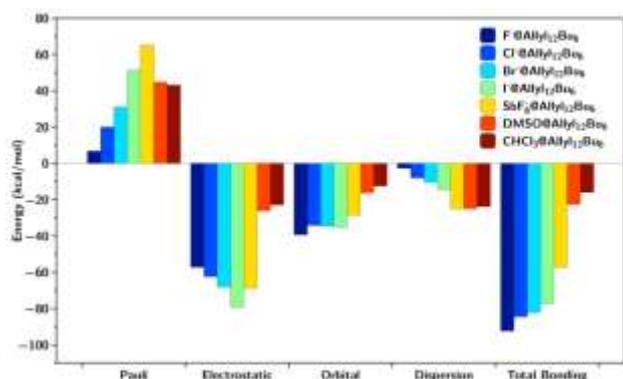


Figure 4. ZORA-DFT/PBE0-D3(BJ) bonding energy analysis with respect to the anion and bambus[6]uril fragments.

The dominating contribution to the interaction energy stems from the electrostatic interaction (ca 60% to the total attractive interactions), followed by the orbital interaction (ca 20-40% to the total attractive interactions). Positive values of the molecular electrostatic potential (MEP) were obtained inside the cavity of allyl₁₂BU[6] **17** (Figure 5), demonstrating the ability of the receptor to bind negatively charged groups or anions and explaining the dominance of the electrostatic term in the intermolecular stabilization.

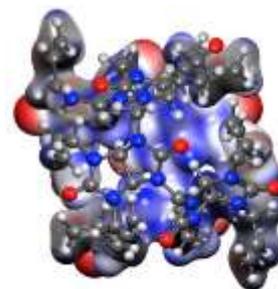


Figure 5. Calculated (DFT/B97-D3(BJ), def2-TZVP) molecular electrostatic potential of allyl₁₂BU[6] **17** mapped onto an isodensity surface of 0.02 eÅ⁻³. Positive values in blue, negative values in red.

To a lesser extent, the presence of the CH...X and dispersion interactions also contribute to the stability of the complexes. This can be easily deduced from a non-covalent interaction analysis (NCI) (Figure 6, see Supporting Information for details). Pauli repulsion energy (Figure 4) increases in the halogen series from F⁻ to I⁻ following the same trend as the ionic radii.

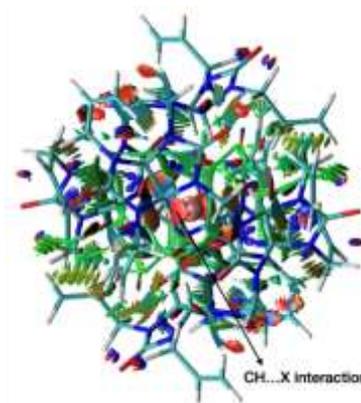


Figure 6. Spatial regions of non-covalent interaction of I@allyl₁₂BU[6] **2**. The attraction regions are shown in red, the van der Waals in green and the repulsion in blue. The CH...X bonds are clearly identified between H and I.

Then we used DFT calculations to support our above reported experimental findings, using AgSbF₆ as reagent to remove anion from the cavity of BU[6]. DFT calculations confirm that the interaction of SbF₆⁻ with allyl₁₂BU[6] **17** is also weak. These experimental findings are in contrast with the actual cavity size computed for anion-free allyl₁₂BU[6] **17** (ca. 139 Å³) which should be large enough to encapsulate SbF₆⁻ anion (ca. 82 Å³, see Figure S9 for details). The volume of the latter is in agreement with the recently reported values of 81.8 Å³ [31] and 75 Å³ [32] and moreover lies close to the volume of the iodide anion (72 ± 16 Å³). [33] If one compares the complexation ability of **17** towards SbF₆⁻ and I⁻, it becomes obvious that the size effect is not enough to account for the difference in binding affinity. Quantum chemistry calculations performed on SbF₆⁻ uptake by **17** indicate the formation of a stable SbF₆@allyl₁₂BU[6] complex. This complex has a significantly lower stabilization energy (-57 kcal/mol) than that with iodide (I@allyl₁₂BU[6] **2**, -77 kcal/mol), which is mainly

due to a higher Pauli repulsion term and a lower stabilizing electrostatic term in $\text{SbF}_6^- @ \text{allyl}_{12}\text{BU}[6]$ (see Figure 4).

Quantum chemistry calculations evidence also a weak energy stabilization of DMSO with $\text{allyl}_{12}\text{BU}[6]$ **17** (-22 kcal/mol), due to a partial polarization of its S=O bond, inducing a negative charge on the oxygen atom. However, when used as a solvent, DMSO may compete efficiently with anions binding into the BU[6] cavity. CHCl_3 is slightly less stabilized than DMSO upon complexation with a binding energy of -16 kcal/mol with **17** and a similar interaction energy pattern (see Figure 4).

Conclusion

In summary, thioether-functionalized BU[4] and BU[6] were synthesized by thiol-ene coupling reactions of $\text{allyl}_8\text{BU}[4]$ and $\text{allyl}_{12}\text{BU}[6]$. These new functionalized $(\text{RS})_8\text{BU}[4]$ and $(\text{RS})_{12}\text{BU}[6]$, with an alternate spatial arrangement of glycoluril building blocks, might find applications as scaffolds to build multivalent systems with 8 to 12 ligands or inhibitors. We report that the nature of the anion enclosed in the cavity of $\text{allyl}_{12}\text{BU}[6]$ modifies the reactivity of the allyl arms linked to the portal. Indeed, $\text{I} @ \text{allyl}_{12}\text{BU}[6].\text{TBA}$ was shown to be less reactive towards thiol-ene and hydrogenation reactions than $\text{Cl} @ \text{allyl}_{12}\text{BU}[6].\text{TBA}$ and $\text{Br} @ \text{allyl}_{12}\text{BU}[6].\text{TBA}$ that enclosed a chloride or a bromide anion respectively. A new, facile method making use of silver hexafluoroantimonate has been set up to remove halide enclosed in the cavity of BU[6]. Anion-free bambusuril portals were isolated in good yields (60-83%) and their complexation properties with different anions were studied by ^1H NMR spectroscopy, revealing a strong influence of the solvent. Binding constants are much lower in DMSO than in chloroform. This may come from the higher capacity of DMSO than CHCl_3 to be incorporated in the cavity of BU[6], resulting in stronger competition with anions. Thioether groups grafted on bambusuril portals act as competitors to anions for binding to the cavity of BU[6]. A work on the binding and competition studies of bambusuril portals functionalized by long and flexible arms is on going in our laboratory. Indeed, these twelve long and flexible arms induce self-assembly of the BU[6] in solution, a phenomenon that will be studied in more details in the near future. Quantum chemistry calculations were useful to bring additional information to experiments and to gain an understanding of the host-guest interactions. Solely referring to the volume of the anion does not make possible to understand the affinities observed experimentally and a thorough analysis of the interactions involved is required. The design of new BU[6] is in progress, to improve their affinity with anions with the aim to use them as sensors for further chemical or biological applications.

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Keywords: Bambusuril • Thiol-ene • Decomplexation • Quantum chemistry • NMR

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