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

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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

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Abstract: New sulfide-functionalized bambus[4]urils ($(RS)_8$BU[4]) and bambus[6]urils ($(RS)_{12}$BU[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 $allyl_{12}$BU[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 $AgSbF_6$ 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 Me_{12}BU[6],[2] Bn_{12}BU[6], [3] Bn_8BU[4],[3] Pr_{12}BU[6],[3] $allyl_8$BU[4], and $allyl_{12}$BU[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 $allyl_8$BU[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 $allyl_8$BU[4] **1** and I@$allyl_{12}$BU[6].TBA **2,** [4] we herein report the synthesis of Cl@$allyl_{12}$BU[6].TBA **3**, and Br@ $allyl_{12}$BU[6].TBA

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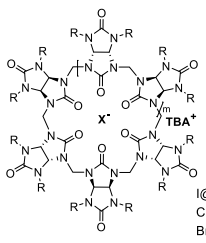
4 and we show that the enclosed halide can alter the reactivity of allyl$_{12}$BU[6] 2-4. (Figure 1). We synthesized new sulfide-functionalized bambusurils **8-16** through a thiol-ene reaction of allyl$_8$BU[4] **1** or halide@allyl$_{12}$BU[6] **2-4**. New R$_8$BU[4] and R$_{12}$BU[6] bearing respectively 8 or 12 thioether functions were obtained (Figure 1). We also report a new method using $AgSbF_6$ 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 ^{1}H NMR spectroscopy. Quantum chemistry calculations were used to understand our results.

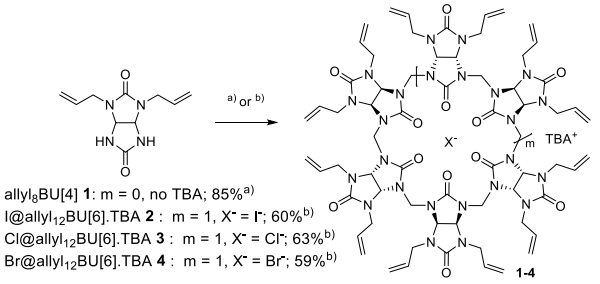


allyl$_8$BU[4] **1** : R= $CH_2CH=CH_2$, m = 0, no TBAX
I@allyl$_{12}$BU[6].TBA **2** : R= CH_2-CH=CH_2, m = 1, X^- = I^-
Cl@allyl$_{12}$BU[6].TBA **3** : R= CH_2-CH=CH_2, m = 1, X^- = Cl^-
Br@allyl$_{12}$BU[6].TBA **4** : R= CH_2-CH=CH_2, m = 1, X^- = Br^-
Cl@Pr$_{12}$BU[6].TBA **5** : R= $(CH_2)_2CH_3$, m = 1, X^- = Cl^-
Br@Pr$_{12}$BU[6].TBA **6** : R= $(CH_2)_2CH_3$, m = 1, X^- = Br^-
(OAc)$_8$BU[4] **8** : R = $(CH_2)_3S(CH_2)_2OAc$, m = 0, no TBAX
I@(OAc)$_{12}$BU[6].TBA **9** : R = $(CH_2)_3S(CH_2)_2OAc$, m = 1, X^- = I^-
Cl@(OAc)$_{12}$BU[6].TBA **10** : R = $(CH_2)_3S(CH_2)_2OAc$, m = 1, X^- = Cl^-
Br@(OAc)$_{12}$BU[6].TBA **11** : R = $(CH_2)_3S(CH_2)_2OAc$, m = 1, X^- = Br^-
I@(CO$_2$Me)$_{12}$BU[6].TBA **12** : R = $(CH_2)_3S(CH_2)_2CO_2Me$, m = 1, X^- = I^-
Cl@(CO$_2$Me)$_{12}$BU[6].TBA **13** : R = $(CH_2)_3S(CH_2)_2CO_2Me$, m = 1, X^- = Cl^-
Br@(CO$_2$Me)$_{12}$BU[6].TBA **14** : R = $(CH_2)_3S(CH_2)_2CO_2Me$, m = 1, X^- = Br
Sugar$_8$BU[4] **15** : R =$(CH_2)_3$Sglucose-tetraOAc), m = 1, no TBAX; Br@Sugar$_{12}$@BU[6].TBA **16** : R =$(CH_2)_3$Sglucose-tetraOAc), m = 1, X^- = Br^- , allyl$_{12}$BU[6] **17**: R= CH_2-CH=CH_2, m = 1, no TBAX
Cl@Bn$_{12}$BU[6].TBA **18** : R= CH_2Ph, m = 1, X^- = Cl^- , Bn$_{12}$BU[6] **19** : R= CH_2Ph, m = 1, no TBAX
(CO$_2$Me)$_{12}$BU[6] **20** : R = $(CH_2)_3S(CH_2)_2CO_2Me$, m = 1, no TBAX; (OAc)$_{12}$BU[6] **21** : R = $(CH_2)_3S(CH_2)_2OAc$, m = 1, no TBAX.

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 allyl$_8$BU[4] **1** and I@allyl$_{12}$BU[6].TBA **2** starting from 2,4-diallylglycoluril and paraformaldehyde with *p*-toluenesulfonic acid.[4] The 4-membered allyl$_8$BU[4] **1** was prepared in chloroform (85% yield) in an experiment where no anion has been added, while 6-membered I@allyl$_{12}$BU[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@allyl$_{12}$BU[6].TBA **3** and Br@allyl$_{12}$BU[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).



allyl$_8$BU[4] **1**: m = 0, no TBA; 85%[a]
I@allyl$_{12}$BU[6].TBA **2** : m = 1, X^- = I^-; 60%[b]
Cl@allyl$_{12}$BU[6].TBA **3** : m = 1, X^- = Cl^-; 63%[b]
Br@allyl$_{12}$BU[6].TBA **4** : m = 1, X^- = Br^-; 59%[b]

Reagents and conditions: [a] $(CH_2O)_n$, PTSA, $CHCl_3$, MW, 75°C, 4 h;
[b] $(CH_2O)_n$, PTSA, TBAX, toluene, MW, 110 °C, 4 h

Scheme 1. Synthesis of allyl$_8$BU[4] **1** and X@allyl$_{12}$BU[6].TBA **2-4** , X = I, Cl or Br.

Our results are coherent with Sindelar's work reporting that I@Bn$_{12}$BU[6].TBA and Cl@Bn$_{12}$BU[6].TBA were isolated in comparable yields (65% and 53% respectively).[3]

Crystals of Cl@allyl$_{12}$BU[6].TBA **3** were obtained by their slow evaporation in CH_2Cl_2/MeOH (9/1 v/v) and Br@allyl$_{12}$BU[6].TBA **4** was recrystallized in CH_2Cl_2/Et_2O (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@allyl$_{12}$BU[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).

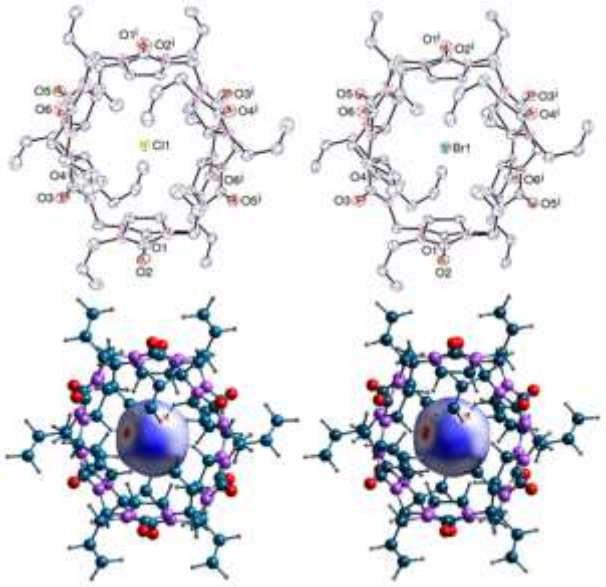


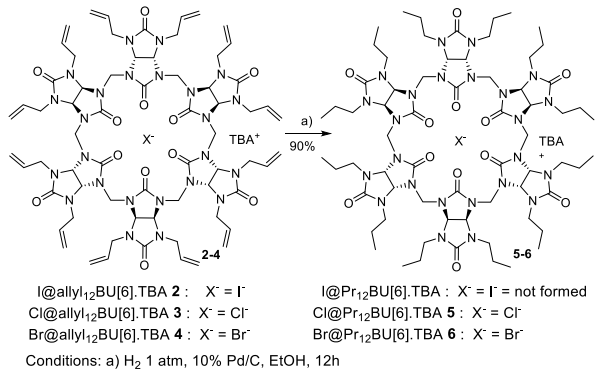
Figure 2. Top row: Crystal structures of Cl@allyl$_{12}$BU[6] **3** (left) and Br@allyl$_{12}$BU[6] **4** (right). Displacement ellipsoids are shown at the 30% probability level. Counterions and hydrogen atoms are omitted. Symmetry code: i = 3/2 – *x*, 1/2 – *y*, 1 – *z*. Bottom row: Views of the Hirshfeld surface of the chlorine (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@Me$_{12}$BU[6],[2] and I@Pr$_{12}$BU[6][3] although complexation of two chloride anions, one at each portal, has been found for Bn$_{12}$BU[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, allyl$_8$BU[4] **1** and X@allyl$_{12}$BU[6].TBA **2-4** are valuable molecules for post-functionalization.

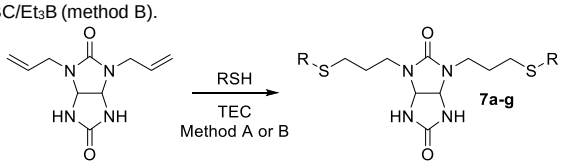
First, we studied the reactivity of allylbambus[n]urils in hydrogenation conditions. We have previously shown that the reaction of allyl$_8$BU[4] **1** with H_2 and Pd/C (10 wt % loading) in ethanol and as catalyst, afforded quantitatively Pr$_8$BU[4].[4] However, I@allyl$_{12}$BU[6].TBA **2** remained 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@allyl$_{12}$BU[6].TBA **3** and Br@allyl$_{12}$BU[6].TBA **4** afforded the expected Cl@Pr$_{12}$BU[6].TBA **5** and Br@Pr$_{12}$BU[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.

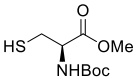
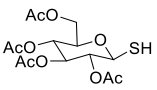


Scheme 2. Hydrogenation of halides@allyl$_{12}$BU[6] **2**-**4**.

Then we decided to transform the allyl arms of allyl$_8$BU[4] **1** and X@allyl$_{12}$BU[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 allyl$_8$BU[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)$_{12}$Cucurbit[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 CH_2Cl_2 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/Et$_3$B (method B).



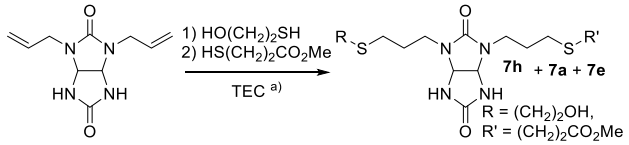
Entry	RSH	Product **7**	Method A Yield (%)	Method B Yield (%)
1	$HO(CH_2)_2SH$	**7a**	76	82
2	$HO(CH_2)_3SH$	**7b**	nd	43
3	$CH_3CH(OH)$-$CH(CH_3)SH$	**7c**	nd	30
4	$HOCH_2CH(OH)CH_2SH$	**7d**	nd	52
5	$MeO_2C(CH_2)_2SH$	**7e**	40	50
6		**7f**	51	77
7		**7g**	nd	36

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), CH_2Cl_2, 12 h at RT. nd = not determined

Then, we tested the hydrothiolation method, reported by the group of Renaud, using triethylborane (Et$_3$B) 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 Et$_3$B/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

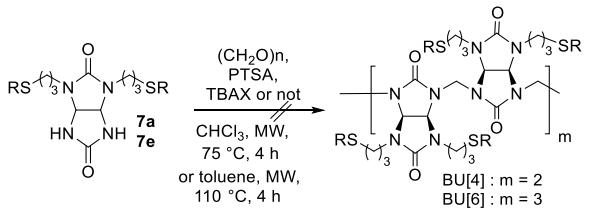
TEC products in higher yields compared to the UV method (method A), and more interestingly method B required a weaker excess of thiol (1.5 *vs* 6 equivalents by alkene).

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/Et_3B 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), $HO(CH_2)_2SH$ (1 equiv), $HS(CH_2)_2CO_2Me$ (1 equiv), Et_3B (2.4 equiv), TBC (2.4 equiv), CH_2Cl_2, 12 h, at RT.

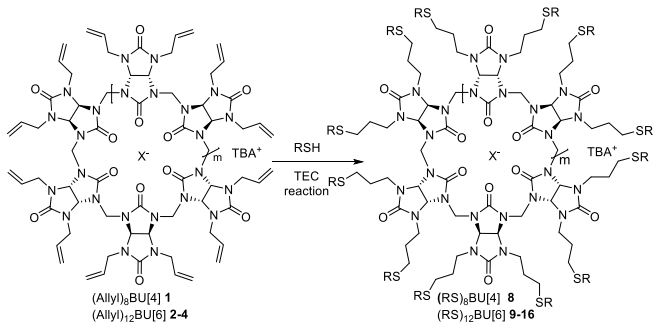
Having thioether glycolurils **7** in hand, we then attempted to prepare the corresponding bambusuril. Thus glycolurils **7a** and **7e** were reacted with paraformaldehyde and *p*-toluenesulfonic acid under MW irradiation, in $CHCl_3$ or toluene, with or without TBAX (Scheme 4).



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 $allyl_8BU[4]$ **1** and $X@allyl_{12}BU[6].TBA$ **2-4** with various thiols so as to check the influence of the enclosed anion in BU[6] (Scheme 5).



Scheme 5. Hydrothiolation of $allyl_8BU[4]$ **1** and $X@allyl_{12}BU[6].TBA$ **2-4**

The most efficient TEC conditions using Et_3B 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**

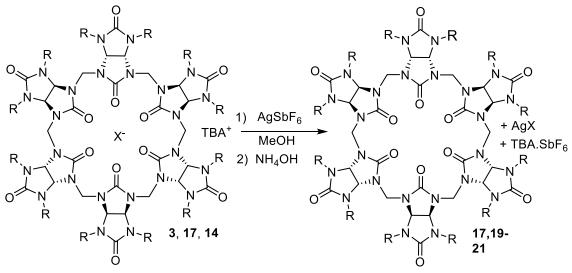
Entry	(Allyl)BU	RS =	(RS)BU	Yield (%)
1[a]	$Allyl_8BU[4]$ **1**	$S(CH_2)_2OAc$	**8**	89
2[a]	$I@allyl_{12}BU[6]$ **2**	$S(CH_2)_2OAc$	**9**	20
3[a]	$Cl@allyl_{12}BU[6]$ **3**	$S(CH_2)_2OAc$	**10**	57
4[a]	$Br@allyl_{12}BU[6]$ **4**	$S(CH_2)_2OAc$	**11**	51
5[b]	$I@allyl_{12}BU[6]$ **2**	$S(CH_2)_2CO_2Me$	**12**	49
6[b]	$Cl@allyl_{12}BU[6]$ **3**	$S(CH_2)_2CO_2Me$	**13**	55
7[b]	$Br@allyl_{12}BU[6]$ **4**	$S(CH_2)_2CO_2Me$	**14**	52
8[b]	$Allyl_8BU[4]$ **1**	$S(CH_2)_2Sugar(OAc)_4$	**15**	61
9[b]	$Br@allyl_{12}BU[6]$ **4**	$S(CH_2)_2Sugar(OAc)_4$	**16**	43

Reagents and conditions: [a] i) $HO(CH_2)_2SH$, TBC/Et_3B, CH_2Cl_2, RT, 12 h; ii) Ac_2O, pyridine, RT, 2 h, iii) NaOMe, MeOH, RT, 4 h; [b] RSH, TBC/Et_3B, CH_2Cl_2, RT, 12 h.

To our delight when $allyl_8BU[4]$ **1** was reacted with mercaptoethanol, followed by acetylation to facilitate the purification step, $((CH_2)_3S(CH_2)_2OAc))_8BU[4]$ **8** containing eight thioether moieties was isolated in good yield (entry 1, 89% yield both steps). TEC performed on $I@allyl_{12}BU[6].TBA$ **2** with mercaptoethanol afforded $((CH_2)_3S(CH_2)_2OAc))_{12}BU[6].TBA$ **9** in a disappointing 20% yield (entry 2). Hydrothiolation of $Cl@allyl_{12}BU[6].TBA$ **3** or $Br@allyl_{12}BU[6].TBA$ **4** under the same conditions yielded functionalized $Cl@(thioether)_{12}BU[6].TBA$ **10** and $Br@(thioether)_{12}BU[6]$ **11** in 57 and 51% yield, respectively (entries 3, 4). This result consolidate 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 $I@allyl_{12}BU[6].TBA$ **2** or $Cl@allyl_{12}BU[6].TBA$ **3** or $Br@allyl_{12}BU[6].TBA$ **4** afforded corresponding BU[6] **12, 13** or **14,** bearing 12 ester moities, 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) moities on $allyl_8BU[4]$ **1** to generate $(RS)_8BU[4]$ **15** in 61% yield (entry 8, Table 2). TEC reaction of $Br@allyl_{12}BU[6].TBA$ **4** with (1-thio-β-D-glucose tetraacetate) provide 12 sugars grafted $(RS)_{12}BU[6]$ **16** (43% yield, entry 9, Table 2). The yield obtained for $(RS)_{12}BU[6]$ **16** is slightly lower 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 HSO_4^- can be converted to their corresponding anion-free BU[6] by a treatment with basic water.[6] More recently (trioxadecyl)$_{12}$BU[6], bearing polyethylene glycol substituents and $TBABF_4$, was obtained as its $NaBF_4$ complex after purification by silicagel chromatography, [27] and was obtained free of BF_4^- anion by water continous 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 $TlNO_3$;[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 allyl$_{12}$BU[6] **17** from X@allyl$_{12}$BU[6].TBA. Treatment of Cl@allyl$_{12}$BU[6].TBA **3** with silver hexafluoroantimonate $AgSbF_6$ in MeOH generated instantaneously a white precipitate. This precipitate, containing allyl$_{12}$BU[6] **17** and AgCl, was recovered by centrifugation. Washings with NH_4OH solution allowed dissolution of AgCl, while the insoluble anion-free allyl$_{12}$BU[6] **17** was isolated by filtration (Scheme 6, 67% yield).[29]



Cl@allyl$_{12}$BU$_6$.TBA **3**, R = CH_2-CH=CH_2
I@allyl$_{12}$BU[6].TBA **2**, R = CH_2-CH=CH_2
Cl@Bn$_{12}$BU$_6$.TBA **18**, R = $CH_2C_6H_5$
Cl@(RCO$_2$Me)$_{12}$BU$_6$.TBA **13**, R = $(CH_2)_3S(CH_2)_2$
Br@(ROAc)$_{12}$BU$_6$.TBA **11**, R = $(CH_2)_3S(CH_2)_2$

allyl$_{12}$BU$_6$ **17**, 67% yield
allyl$_{12}$BU$_6$ **17**, 70% yield
Bn$_{12}$BU$_6$ **19**, 60% yield
(RCO$_2$Me)$_{12}$BU$_6$ **20**, 83% yield
(ROAc)$_{12}$BU$_6$.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 allyl$_{12}$BU[6] **17** was not soluble in $CHCl_3$, while Cl@allyl$_{12}$BU[6].TBA **3** easily dissolves in $CHCl_3$. Furthermore, ^{19}F NMR and HRMS analyses of the isolated product confirmed the absence of residual SbF_6^- and the emptiness of the cavity. We therefore deduced that SbF_6^- interacts weakly with allyl$_{12}$BU[6] **17**. This was confirmed by ^{1}H NMR titration of **17** with either $AgSbF_6$ or BMIm-SbF_6 ($BMIm^+$ = 1-butyl-3-methylimidazolium) in [D]$_6$DMSO. The absence of ^{1}H 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 SbF_6^- anion in DMSO. This is in accordance with the low binding constant of SbF_6^- reported for Bn$_{12}$BU[6] **19** in chloroform. [11c] DFT calculations strengthen our experiments as they show that the interaction of SbF_6- with allyl$_{12}$BU[6] **17** is also weak (see below for details and discussion). Finally, it is worthy to note that, while we used NH_4OH in our procedure, the very hydrophilic hydroxide anion has in general negligible affinity for bambus[6]uril.[6]

Moreover, I@allyl$_{12}$BU[6]@TBA **2**, enclosing an iodine anion in its cavity, was efficiently decomplexed to allyl$_{12}$BU[6] **17** in 70% yield (Scheme 6). To prove the efficiency of $AgSbF_6$ as an halide releasing reagent, the method was also applied to Cl@Bn$_{12}$BU[6].TBA **18**.[30] The known anion-free Bn$_{12}$BU[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@((CH$_2$)$_3$S(CH$_2$)$_2$CO$_2$Me))$_{12}$BU[6].TBA **13** with $AgSbF_6$ provided anion-free BU[6] **20** (83% yield, Scheme 6). Finally submission of Br@((CH$_2$)$_3$S(CH$_2$)$_2$OAc))$_{12}$BU[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 allyl$_{12}$BU[6] **17,** ((CH$_2$)$_3$S(CH$_2$)$_2$CO$_2$Me))$_{12}$BU[6] **20** and ((CH$_2$)$_3$S(CH$_2$)$_2$OAc))$_{12}$BU[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 allyl$_{12}$BU[6] **17** resonate at 5.44 ppm in [D]$_6$DMSO (signal b) on Figure 3a, 0 eq., full spectrum supplied in Figure S1). In the presence of TBAI, giving I@allyl$_{12}$BU[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 $5x10^3$ M^{-1} (Figure S1), compared to that reported for I^-@Bn$_{12}$BU[6] **19** in $CDCl_3$, which is in the range $4x10^9$ – $3x10^{10}$ 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 $CHCl_3$ (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 $CDCl_3$, the chloride inclusion complex with Bn$_{12}$BU[6] **19** is about 10^3 times less stable than the corresponding iodide one.[3] This is also in agreement with the titration of Cl@allyl$_{12}$BU[6] **3** with TBAI in $CDCl_3$, showing that iodide

binds at least 120 times more strongly to allyl$_{12}$BU[6] **17** than chloride does (Figure S3).

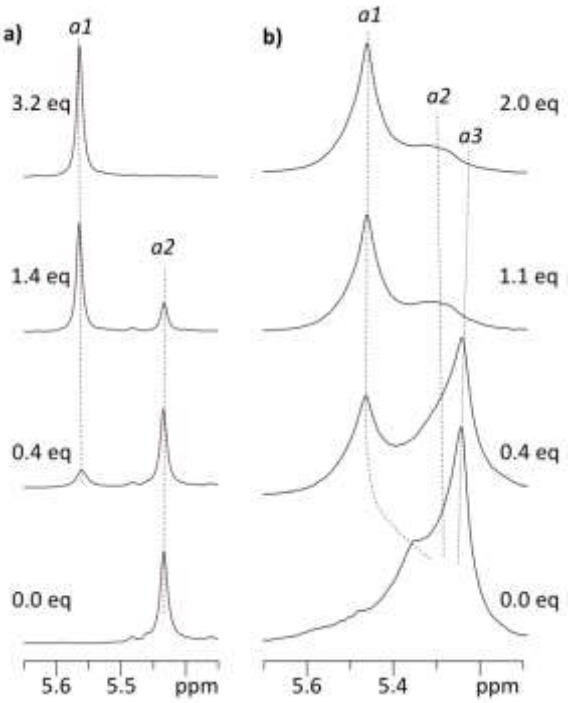


Figure 3. Titration of allyl$_{12}$BU[6] **17** giving complex I@allyl$_{12}$BU[6].TBA **2** (Fig 6a) and of ((CH$_2$)$_3$S(CH$_2$)$_2$CO$_2$Me))$_{12}$BU[6] **20** giving complex I@((CH$_2$)$_3$-S-(CH$_2$)$_2$CO$_2$Me)$_{12}$BU[6].TBA **12** (Fig 6b) in [D]$_6$DMSO with TBAI. Parts of ^{1}H NMR spectra 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 ((CH$_2$)$_3$S(CH$_2$)$_2$CO$_2$Me)$_{12}$BU[6] **20** is concerned. In the ^{1}H NMR spectrum of Cl@((CH$_2$)$_3$S(CH$_2$)$_2$CO$_2$Me)$_{12}$BU[6].TBA **13** in CDCl$_3$, the signals assigned to N-CH-N protons of the glycoluril units and to N-CH$_2$-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 ((CH$_2$)$_3$S(CH$_2$)$_2$CO$_2$Me)$_{12}$BU[6] **20** are able to explore the BU's cavity, competing with anions used for titration, whereas shorter arms in allyl$_{12}$BU[6] **17** cannot explore the cavity. This exploration induces conformational variation at the millisecond timescale of the cavity of **20**, resulting in large ^{1}H 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@allyl$_{12}$BU[6] **3** with TBAI giving I@allyl$_{12}$BU[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 Bn$_{12}$BU[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 ((CH$_2$)$_3$S(CH$_2$)$_2$CO$_2$Me))$_{12}$BU[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@((CH$_2$)$_3$S(CH$_2$)$_2$CO$_2$Me))$_{12}$BU[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 ^{1}H 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 ((CH$_2$)$_3$S(CH$_2$)$_2$OAc))$_{12}$BU[6] **21** with TBACl in acetone denotes also complex phenomena (Figure S7). The N-CH$_2$ 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-CH$_2$ protons bordering the cavity of **21** binding either chloride, or a long and flexible (CH$_2$)$_3$S(CH$_2$)$_2$OAc 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 broaden even at only 0.5 equivalent of TBACl showing the short life-time 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-CH_2 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 allyl$_{12}$BU[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@allyl$_{12}$[BU] complexes **2-4** and the relevance of our decomplexation method using $AgSbF_6$ (see Supporting Information for details).

The factors determining the stability of the allyl$_{12}$BU[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).

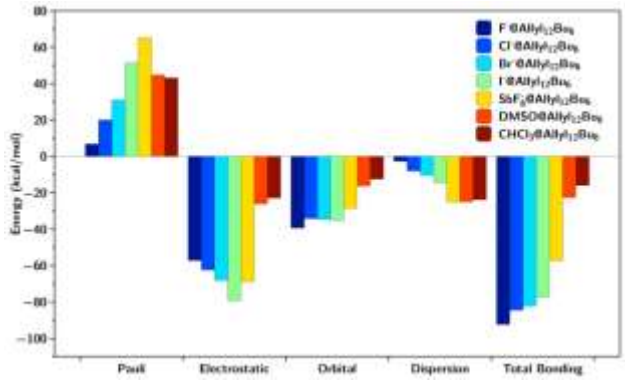


Figure 4. ZORA-DFT/PBE0-D3(BJ) bonding energy analysis with respect to the anion and bambus[6]uril fragments.

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 allyl$_{12}$BU[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.

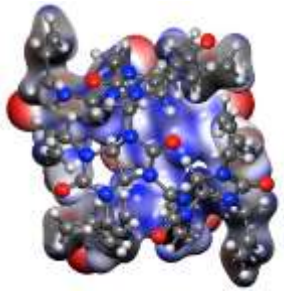


Figure 5. Calculated (DFT/B97-D3(BJ), def2-TZVP) molecular electrostatic potential of allyl$_{12}$BU[6] **17** mapped onto an isodensity surface of 0.02 eÅ^{-3}. Positive values in blue, negative values in red.

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.

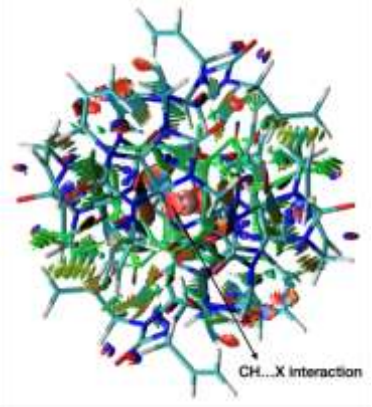


Figure 6. Spatial regions of non-covalent interaction of I^-@allyl$_{12}$BU[6] **2**. The attraction regions are shown in red, the van der Waals in green and the repulsion in blue. The CH…X bonds are clearly identified between H and I^-.

Then we used DFT calculations to support our above reported experimental findings, using $AgSbF_6$ as reagent to remove anion from the cavity of BU[6]. DFT calculations confirm that the interaction of SbF_6- with allyl$_{12}$BU[6] **17** is also weak. These experimental findings are in contrast with the actual cavity size computed for anion-free allyl$_{12}$BU[6] **17** (ca. 139 Å^3) which should be large enough to encapsulate SbF_6^- anion (ca. 82 Å^3, see Figure S9 for details). The volume of the latter is in agreement with the recently reported values of 81.8 Å^3 [31] and 75 Å^3 [32] and moreover lies close to the volume of the iodide anion (72 ± 16 Å^3).[33] If one compares the complexation ability of **17** towards SbF_6^- 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 SbF_6^- uptake by **17** indicate the formation of a stable SbF_6@allyl$_{12}$BU[6] complex. This complex has a significantly lower stabilization energy (-57 kcal/mol) than that with iodide (I@allyl$_{12}$BU[6] **2**, -77 kcal/mol), which is mainly

due to a higher Pauli repulsion term and a lower stabilizing electrostatic term in SbF_6^-@allyl$_{12}$BU[6] (see Figure 4).

Quantum chemistry calculations evidence also a weak energy stabilization of DMSO with allyl$_{12}$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 allyl$_8$BU[4] and allyl$_{12}$BU[6]. These new functionalized (RS)$_8$BU[4] and (RS)$_{12}$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 allyl$_{12}$BU[6] modifies the reactivity of the allyl arms linked to the portal. Indeed, I@allyl$_{12}$BU[6].TBA was shown to be less reactive towards thiol-ene and hydrogenation reactions than Cl@allyl$_{12}$BU[6].TBA and Br@allyl$_{12}$BU[6].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 bambus[n]urils were isolated in good yields (60-83%) and their complexation properties with different anions were studied by ^{1}H 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 bambus[6]urils 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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