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Selective Synthesis of Hetero-Sequenced Aza-Cyclophanes

Matthias Otte*[a,b], Martin Lutz[c] and Robertus J. M. Klein Gebbink[a]

Abstract: The selective synthesis of purely organic cages offering hetero-sequenced functionalized cavities is demonstrated. The strategy to obtain these compounds is based on a stepwise approach using thermodynamically controlled imine condensations. To accomplish this, the amine building blocks offer additional azide functionalization, acting as masked amines enabling the synthesis of the desired cavities. This approach enables a precise control of interior functionalization, the substitution pattern and the cage size, which is demonstrated by the selective synthesis of four cages. The largest described cage has been investigated towards its ability for guest encapsulation and is able to selectively encapsulate functionalized arenes that offer a matching substitution pattern.

The development of functional molecular cage compounds offering defined cavities and pores is of major importance in modern chemistry. To date, such cages have found numerous applications including their use as hosts for selected compounds,[1] for gas storage,[2] as molecular switches,[3] to stabilize highly reactive reagents[4] or as catalysts.[5] Synthetic approaches towards these compounds involves very often self-assembly via metal-ligand coordination[6] or hydrogen bonding interactions.[7] Due to self-assembly phenomena, the desired cage compounds are often obtained in high yields. They are usually highly symmetric, resulting in a highly symmetric interior functionalization. Notably, interior functionalization is of great importance as it is together with exterior functionalization and pore design the major handle to steer the cage function.

The selective synthesis of less symmetrical cavities is thus a great challenge for the chemistry in cavities. One approach of great interest is to obtain less symmetrical cages via metal-ligand coordination. First examples of those coordination cages have been recently obtained via so-called social self-sorting.[8] However, the occurrence of social self-sorting is currently hard to predict and the same holds for the forecast which product will be obtained. In addition, social self-sorting often comes with the cost of a different cavity geometry compared to the symmetrical cages, as building blocks of different shapes need to be employed. Furthermore, unsymmetrical cages can sometimes only be obtained via substitution of building blocks from an already assembled highly symmetric cage.

Purely organic covalent cages might be an alternative to metal-coordination cages to create cavities of lower symmetry.[9] However, examples for the selective synthesis of cages that offer a less symmetrical interior are rare and use reactions that occur under kinetic control.[10,11] Those reactions bear the disadvantage that once a bond that leads to an undesired oligomer has been formed it cannot be repaired. The appearance of dynamic combinatorial chemistry (DCC) made the synthesis of numerous new purely organic macrocycles and cages possible as this concept allows the high yielding synthesis of the desired organic compounds under thermodynamic control.[12] DCC is an important addition to the portfolio of cavity design, which has so far been dominated by approaches based on supramolecular interactions. Zhang and co-workers reported that DCC offers the opportunity to synthesize hetero-sequenced macrocycles with unsymmetrical cavities via imine-condensation followed by olefin metathesis.[13] Martinez and Dufaud reported the synthesis of catalytically active 1+1 cages via a reductive amination strategy.[14]

3+2 aza-cyclophanes are important organic cage compounds, which have demonstrated great ability for the selective encapsulation of sugars.[15] In addition, the porosity of the analogous 6+4 aza-cyclophanes has been widely investigated.[16] Moreover, *β*-diketiminate-(nacnac)-functionalized aza-cyclophanes form first row transition metal complexes that can activate small molecules such as N_2 and CO_2.[17,18] While the synthesis of numerous symmetrical 3+2 aza-cyclophanes have been reported by now,[19] the selective synthesis of the analogous and less symmetric 2+2+1 or 2+1+2 cages has not been described as statistical mixtures are obtained. Reported approaches to less symmetrical aza-cyclophanes so far employ the installation of amide instead of amine groups or use a combination of amide and amine groups.[9,10] To accomplish those cage synthesis, low yielding kinetically controlled reactions leading to macrocyclic precursors or the final cage products are employed.

Based on the importance of aza-cyclophanes and our interest in the design of precisely functionalized hetero-sequenced cavities,[20] we were wondering if the selective synthesis of the 2+2+1 aza-cyclophane **1** can be achieved via a modified reductive amination protocol (Scheme 1a). To accomplish the synthesis of **1** we envisioned a three step synthetic approach from known building block **2**, which has two benzyl amine groups and one benzyl azide functionality.[21] **2** can be synthesized in three steps starting from commercially available 1,3,5-triethylbenzene. We chose **2** as its azide functional group is known to tolerate the reaction conditions for the reductive amination.[21] As azides can be transformed into amines, one could see the azide in **2** as a masked amine. When reacting a 1:1 mixture of **2** and 2,6-pyridinecarboxyaldehyde (**3**) for 20 h at room temperature followed by the addition of $NaBH_4$ the desired macrocyclic product **4** was obtained with 55% yield. With **4** in hand its transformation into the corresponding amine was investigated. As the substrate contains benzyl amine functionalities we avoided the use of a palladium hydrogenation catalyst and applied a Staudinger reaction protocol instead. Addition of four equivalents triphenylphosphine to **4** in THF, followed by the addition of water gave **5** after purification via column chromatography with a yield of 74%.

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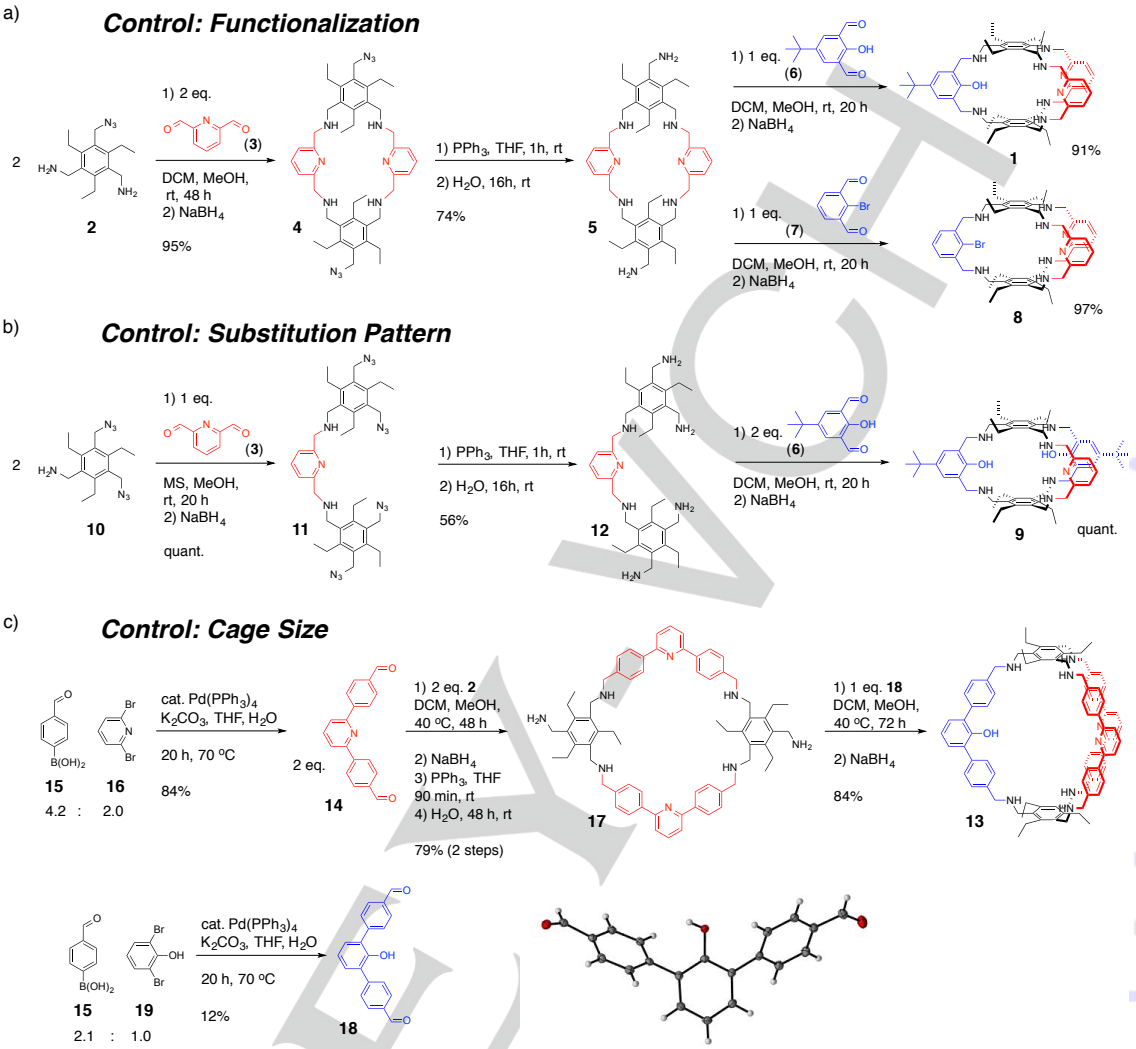

Scheme 1. Synthesis of the hetero-sequenced cages **1**, **8**, **9** and **13** and molecular structure of **18** in the crystal (Figure S1).

With **5** in hand its ability to react to a 2+2+1 aza-cyclophane was investigated. Gratefully, addition of one equivalent of 4-*tert*-butyl-2,6-diformylphenol (**6**) to one equivalent of **5** gave after *in situ* reduction of the formed imines the hetero-sequenced 2+2+1 cage **1** in 91% yield. **5** is likely to adopt a conformation, which favors cage closing reaction with **6** over the competing oligomerization. Cage **1** was characterized by using mass spectrometry, NMR and IR techniques. ESI-MS analysis revealed the formation of **1** by showing signals with m/z values of 879.6398 and 440.3180 corresponding to **1**+H$^+$ and **1**+2H$^+$. Furthermore, host-guest complexes like **1**+2H$_2$O+H$^+$ have been observed during ESI-MS analysis. It is very important to note that no symmetrical 3+2 cages, such as the all phenol or the all pyridine cage, nor the corresponding 2+1+2 (1 pyridine; 2 phenol) cage have been observed. Interestingly, a minor signal at m/z at 1759.2037 was observed that corresponds to 2*__4__+H$^+$. To see if this stems from the formation of a larger 4+4+2 cage or if it might be a cluster in the gas phase DOSY-NMR was performed. The DOSY-NMR indicated only formation of products of one size, which rules out the formation of significant amounts of the 4+4+2 cage. Further NMR analysis gave additional support for the selective formation of **1** (see supporting information). To prove the generality of this approach we substituted **6** for 2-Bromoisophthalaldehyde (**7**) (Scheme 1a). We were delighted to observe the formation of the bromo-functionalized cage **8** with an excellent yield of 97%. In this regard, our modular approach enables the precise control of cage functionalization, which happens via the introduction of functional groups at a late synthetic stage.

As we demonstrated the selective synthesis of the 2+2+1 cages **1** and **8** we became interested if the selective synthesis of the 2+1+2 cage **9** could be accomplished in a similar way. We started our synthetic approach with building block **10** (Scheme 1b), which was obtained as a side product from the synthesis of **2**.[21] We reacted two equivalents of **10** with one equivalent of **3** followed by reduction with NaBH$_4$. After purification via column chromatography **11** was obtained with quantitative isolated yield. The following Staudinger reaction gave the tetraamine **12** after column chromatography with 56% yield. The cage synthesis was finalized via a reductive amination of one equivalent of **12** with two equivalents of **6**. The desired cage **9** was obtained with quantitative yield and was characterized via ESI-MS, ^{1}H-NMR, ^{13}C-NMR and IR (see supporting information). Similar to **1** signals corresponding to **9**+H$^+$ and **9**+2H$^+$ at m/z values of 950.7000 and 475.8539 were observed. No formation of undesired cage **1** or any 3+2 cages was observed. It should be noted that a small signal corresponding to 2*__9__+H$^+$ or the 4+2+4 cage was again observed at m/z = 1901.4873. However, the synthesis of cages **1** and **9** demonstrates, that our approach is suitable to control the functionalization pattern in hetero-sequenced purely organic cages.

As we have shown that the selective synthesis of **1**, **8** and **9** is possible, we were wondering if our approach might also be suitable to obtain larger purely organic and hetero-sequenced cages. To test this hypothesis we envisioned synthesizing the 2+2+1 cage **13** (Scheme 1c). Cage **13** has additional phenyl groups between the amine linker and the pyridine/phenol moieties thus resulting in a larger cavity. We started with the synthesis of the pyridine containing building block **14** via Suzuki-coupling of 4-formylphenylboronic acid (**15**) and 2,6-dibromopyridine (**16**). Applying a reductive amination with **2**, followed by a Staudinger reaction, **14** was transformed into macrocycle **17**. To complete the cage synthesis building block **18** was synthesized from 2,6-dibromophenol (**19**) and **15** in 12% yield using a Suzuki-coupling. **18** was obtained as a yellow/greenish powder, which is fluorescent in $CDCl_3$. When a NMR sample of **18** was kept standing for several days crystals suitable for X-ray diffraction were obtained (see supporting information for a detailed discussion of the crystal structure). With **17** and **18** in hand the reductive amination towards cage **13** was investigated. Performing the reaction at 40 °C resulted in the formation of a major and a minor fraction, which could be separated via column chromatography. Mass spectrometry investigations of the major fraction revealed a signal at the m/z value of 1279.8217 corresponding to **13**+H^+. In addition, the m/z values of 640.4017, 427.2672 and 320.7004 corresponding to the higher charged species **13**+$2H^+$, **13**+$3H^+$ and **13**+$4H^+$ were observed as well. Furthermore, DOSY-NMR confirmed that **13** is a single compound (see supporting information). The formation of **13** was further confirmed by ^{1}H-NMR, ^{13}C-NMR and IR (see supporting information). Given our analysis we conclude that **13** has been isolated within 84% yield. In addition to **13**, we were also able to separate a second fraction. ^{1}H-NMR signals of this fraction are unfortunately very broad. Mass spectrometry analysis revealed signals of a double charged species with a m/z value of 1279.9606 corresponding to 2***13**+$2H^+$. The yield of 2***13** would be 15%. The structure of this compound is currently under further investigation. Although 2***13** has been formed as a side product, the synthesis of **13** with an isolated yield of 84% demonstrates that our approach is also suitable to control the cage size.

Table 1. Study of **13** as host for functionalized guests.

Entry[a]	Guest	Encapsulation observed
1	β-Lactose	no
2	L-Tyrosine	no
3	L-Lysine	no
4	**3-Hydroxypyridine (20)**	**yes**
5	2,6-dipyridinecaboxylic acid	no
6	Pyridine	no
7	Phenol	no
8	3-Iodopyridine	no
9	2-Hydroxypyridine	no
10	**Resorcinol (21)**	**yes**
11	Catechol	no

[a] All experiments at room temperature in $CDCl_3$; for detailed information see supporting information.

With **13** in hand we investigated if the hetero-sequenced functionalized cavity might be suitable to host functionalized guests. As similar cages have been shown to be suitable hosts for sugars,[10,15] we started our investigations with the study of the encapsulation behaviour of several poly-functionalized natural products (Table 1). Unfortunately, neither β-Lactose, nor the amino acids L-Tyrosine and L-Lysine (entries 1-3) gave any indication to be encapsulated within **13**. We turned our focus then towards the encapsulation of functionalized arenes as we assumed that the planar nature of those might favour the interaction with the functional groups of the cage interior. We envisioned that compounds offering proton donor and acceptor moieties might be well suited as guests as **13** offers a complementary cavity functionalization.

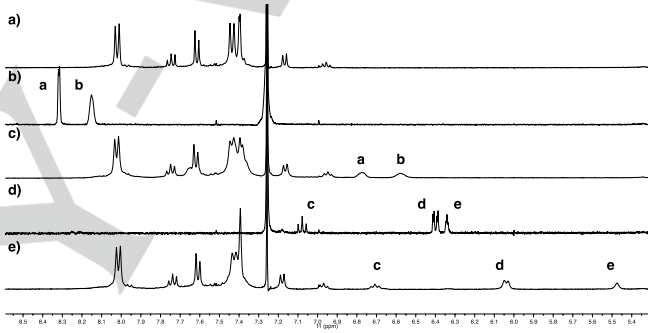

Figure 1. ^{1}H-NMR (8.55 – 5.30 ppm) of encapsulation experiments of **13** with 3-hydroxypyridine (**20**) and resorcinol (**21**); a) **13**; b) **20** c) **20@13**; d) **21** e) **21@13**; all spectra recorded in $CDCl_3$ at room temperature.

Indeed, when **13** and 3-hydroxypyridine (**20**) were mixed in a 1:1 ration in $CDCl_3$, significant downfield shifts of signals corresponding to **20** were observed, indicating the formation of **13@20** (Figure 1a-c; Table 1, entry 4). Signal **a** shifted from 8.32 ppm in free **20** to 6.77 ppm in **20@13**. This corresponds to an upfield shift of 1.55 ppm. Similar to signal **a**, signal **b** shifted also by 1.57 ppm upfield. When **20** and **13** are used in a ratio of 11:1 (Table S1, Entry 5) the signals of **20** shifts to 7.99 ppm and 6.95 ppm, while showing no signals corresponding to the free **20**. The integrals suggest a **20** to **13** ratio of 3:1. The different ratio is a result of the low solubility of **20** in $CDCl_3$. The fact that at higher **20**:**13** ratios signals of encapsulated **13** shift towards the signals of free **13** is an indication that guest exchange processes occur fast on NMR time scale. Furthermore, that might also be an explanation for that we were so far not able to observe **20@13** via mass spectrometry.

Inspired by the observation of **20@13** we tested other arenes as possible guests for **13**. 2,6-Dipyridinecaboxylic acid gave no indication to be encapsulated within **13** (entry 5). The same holds for pyridine and phenol (entries 6 and 7). We were then wondering if **13** might be a suitable host for 3-iodopryidine, assuming that a hydrogen bridge between the phenol and 3-

iodopryidine may induce a halogen bonding interaction between the guest and the host pyridine.[22] Unfortunately, no indication for such a behaviour or any encapsulation phenomena was observed for 3-iodopryidine (entry 8). Interestingly, also 2-hydroxypyridine does not seem to be a suitable guest for **13** (entry 9). For entries 5 to 9 in table 1 were no or only very minor signal shifts (0.03 ppm or less) in the presence of **13** compared to the free compounds observed. Given these studies it seems that the guest selection of **13** is very sensitive with regard to the guest functionalization and it's functionalization pattern. This is further supported by the fact that resorcinol (**21**) that offers similar to **20** also a 1,3-difunctionalization is encapsulated by **13** to form **21@13** (entry 10) while the 1,2-difunctionalized catechol gives no clear indication for encapsulation. For comparison, while the signals of **20** in the presence of **13** shift up to 0.87 ppm compared to the free guest (signals **c**, **d** and **e** in Figure 1d and e) the signals corresponding to catechol shift by less then 0.10 ppm. A full list of all encapsulation experiments and detailed description can be found in the supporting information.

In conclusion, we have demonstrated here a general and modular synthetic approach towards purely organic and hetero-sequenced aza-cyclophanes. To achieve this we used the two key building blocks **2** and **10**. The azide-functionalization in those building blocks can be seen as masked amines, suitable to perform a stepwise thermodynamically controlled synthesis of the desired cage compounds. The synthesis of the 2+2+1 cages **1** and **8** demonstrates that the precise control of the cage functionalization is possible. The synthesis of 2+2+1 cage **1** and the 2+1+2 cage **9** shows that this approach is also suitable to control the substitution pattern. Furthermore, the synthesis of **13** is an example that our approach is also suitable to synthesis larger cages. In Addition, we demonstrated that **13** can act as a host for functionalized organic guests. **13** is thereby sensitive towards the guests functional groups and the functionalization pattern and prefers thus 1,3-difunctionalized guests.

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Keywords: Hetero-Sequenced Cage • Dynamic Combinatorial Chemistry • Cavity Design • Interior Functionalization • Arene Encapsulation

CCDC 1515608 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Entry for the Table of Contents

Layout 1:

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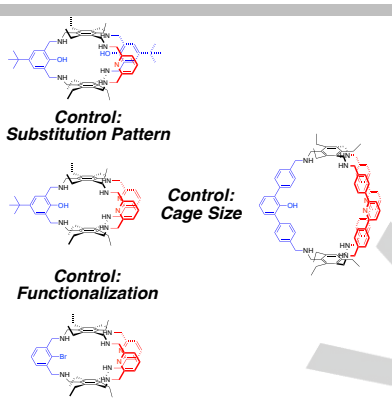
The selective synthesis of hetero-sequenced cages is demonstrated. Interior size, functionalization and substitution pattern can be controlled via this synthetic approach. Moreover, the hetero-sequenced functionalization enables one cage to be sensitive towards guest selection.



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