

Multivalent Hosts and Guests for the Composition of Multiply Interlocked Architectures

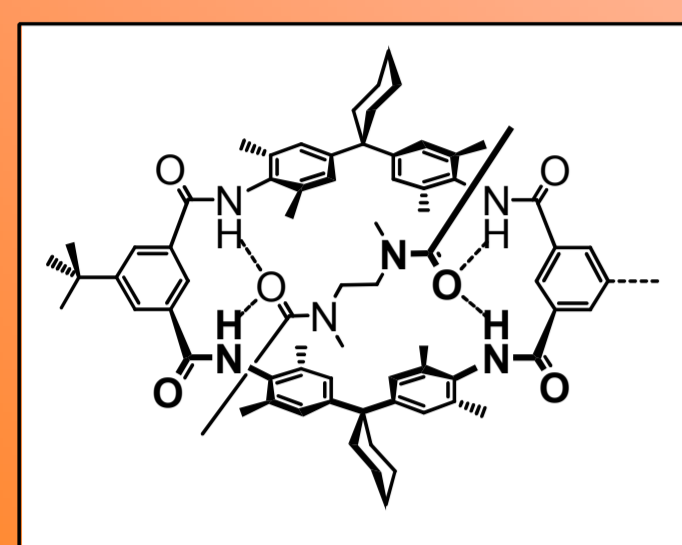
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I. Introduction

The simultaneous association of multiple ligands on one entity with multiple receptors on another - multivalent binding - is supposed to play a fundamental role in myriad biochemical processes, including signal transduction, pathogenic infection, and the immune response and it is involved in the bottom-up molecular self-assembly of nanoscale architectures^[1].

The tetralactam macrocycles (or wheels) **1a**, **1b** and **1c** can be easily functionalized by coupling reactions to yield flexible or rigid branched multimacrocylic hosts^[2]. Additionally, several tetralactam macrocycles can be connected with each other, or with a central spacer, and also metal-coordination sites like phenanthroline or bipyridine can also be attached to the macrocycles.



These molecules allow to build a variety of multiply interlocked architectures by threading axes through the macrocycles via H-bonding and connect them with each other or to other linkers.

[1] For recent reviews, see: a) J. D. Badjić, A. Nelson, S. J. Cantrill, W. B. Turnbull, J. F. Stoddart, *Acc. Chem. Res.* **2005**, *38*, 723 – 732; b) L. L. Kiessling, J. E. Gestwicki, L. E. Strong, *Angew. Chem., Int. Ed.* **2006**, *45*, 2348 – 2368.

[2] B. Baycten, S.S. Zhu, B. Brusilowski, J. Illigen, J. Ranta, J. Huuskonen, K. Rissanen, L. Kaufmann, C.A. Schalley, *Chem. Eur. J.* **2008**, *14*, 10012 – 10028.

II. Motivation

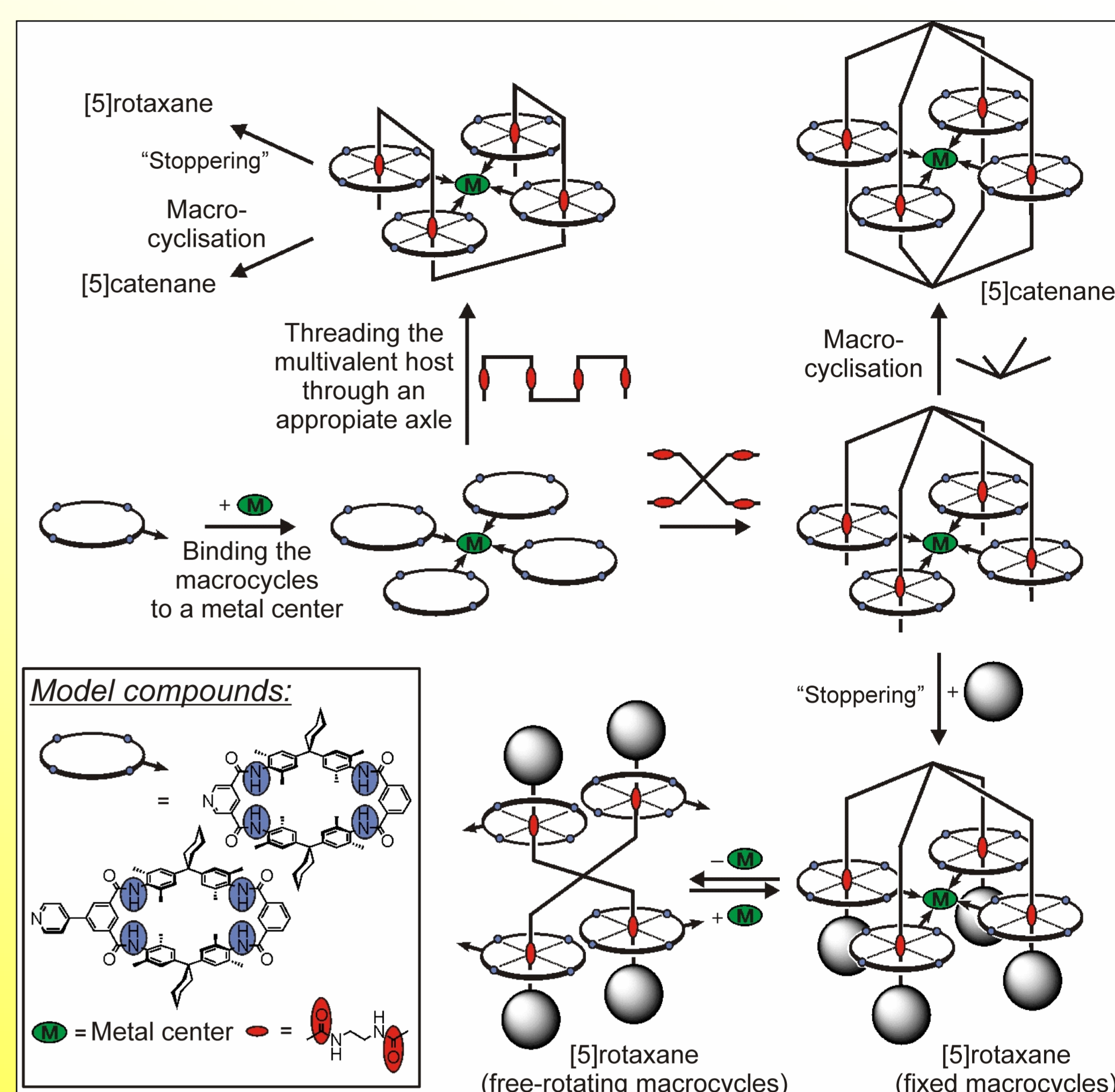
The aim of this project is the synthesis, characterisation and application of a great variety of components (different metals, macrocycles, axles, spacers and linkers, components with different functionalities,...) for:

- Generating architectures with different features (for example flexibility)
- Metal-directed self-assembly of macrocycles and rotaxanes to obtain multivalent precursors and hosts.
- Analysing the relationship between structural units and features
- Better understanding of multivalency

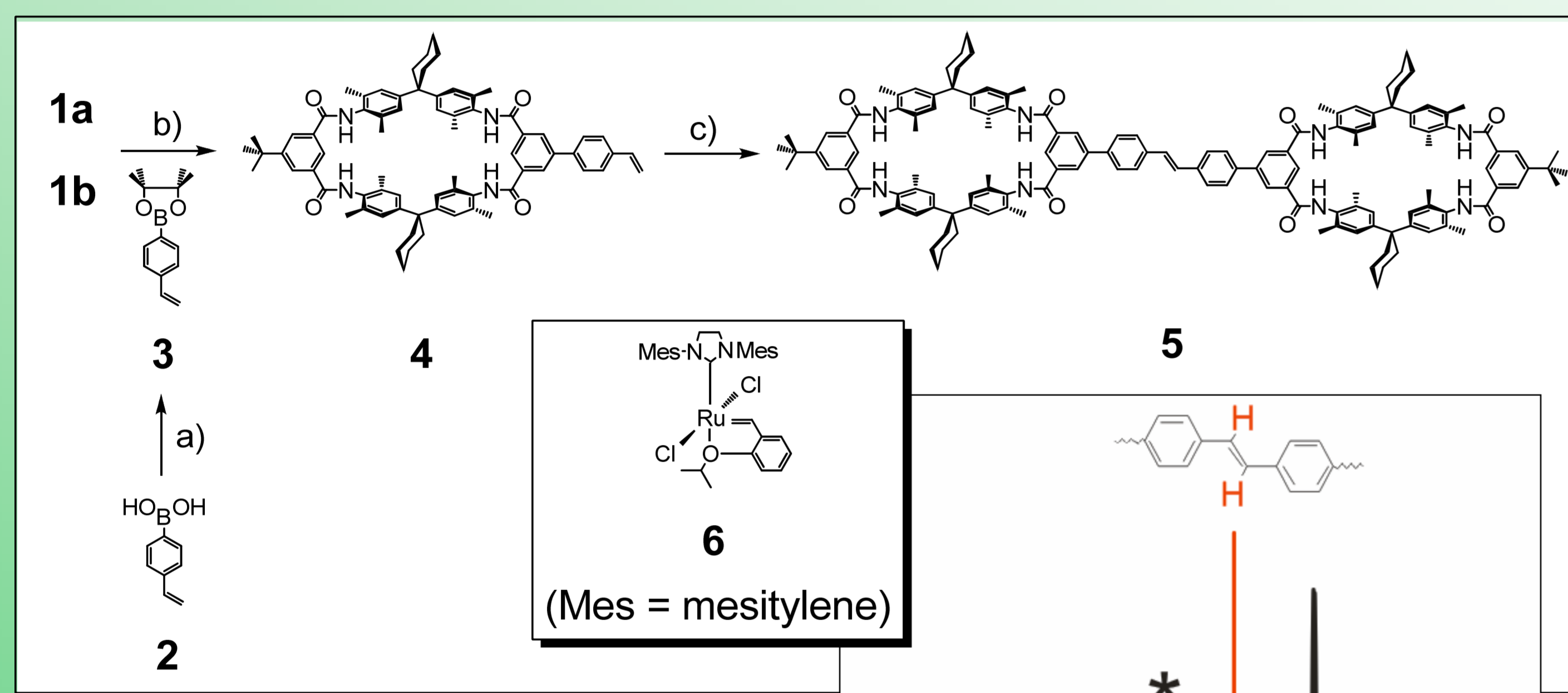
(Multivalency = host-guest interactions existing simultaneously between two or more binding sites)

Multivalency^[3] is an important concept, which enables the examination of many binding sites and the effect of their multiple interactions on binding other molecules. This could yield in an increase of the binding strength. Furthermore, it could lead to a more efficient preparation of rotaxanes and catenanes with new topologies and functions. The application of such topological architectures could revolutionize the field of molecular machines.

[3] For recent reviews, see: a) A. Mulder, J. Huskens, D. N. Reinhoudt, *Org. Biomol. Chem.* **2004**, *2*, 3409 – 3424; b) M. Mammen, S.-K. Chio, G. M. Whitesides, *Angew. Chem.* **1998**, *110*, 2908 – 2953; *Angew. Chem., Int. Ed.* **1998**, *37*, 2754 – 2794.

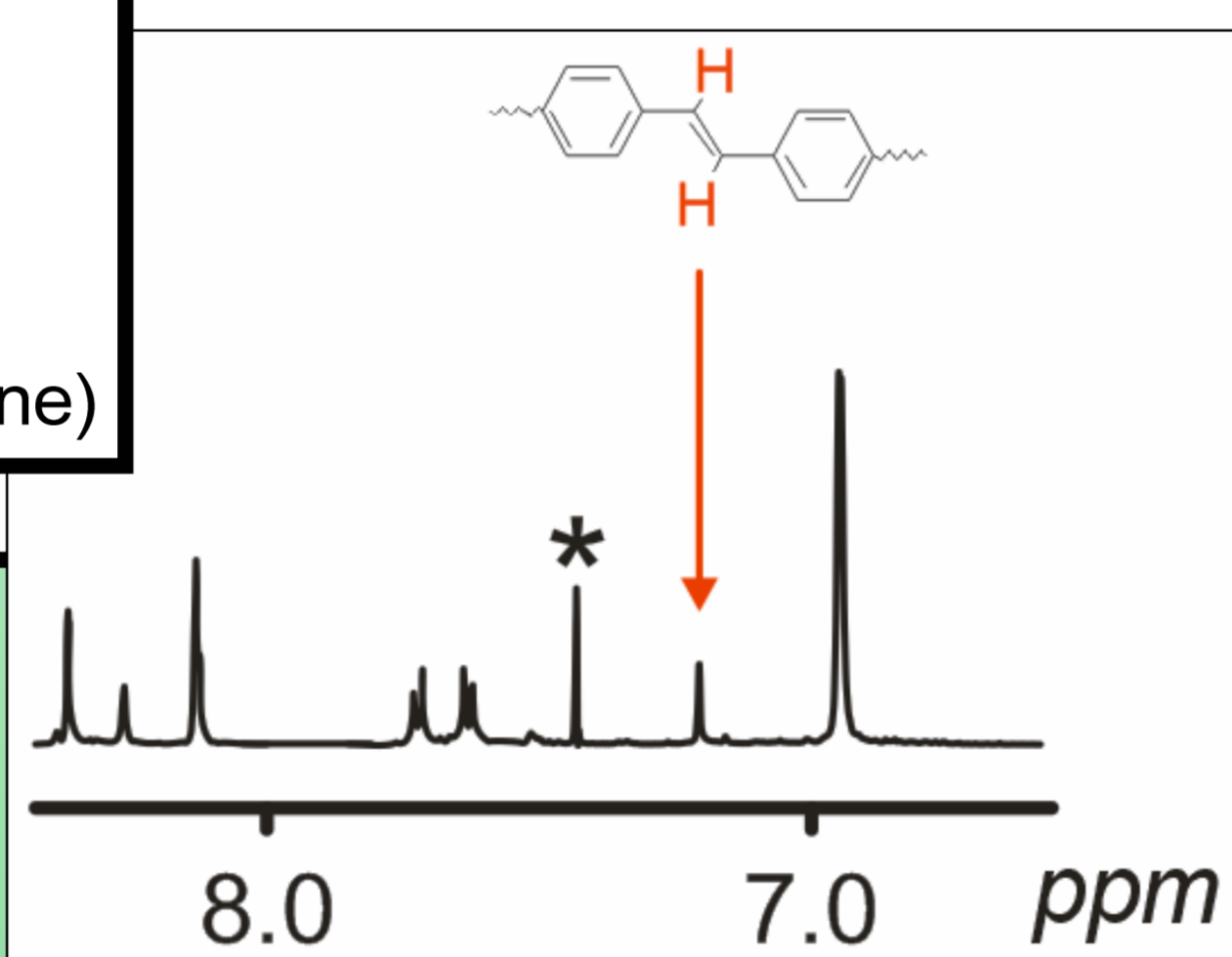
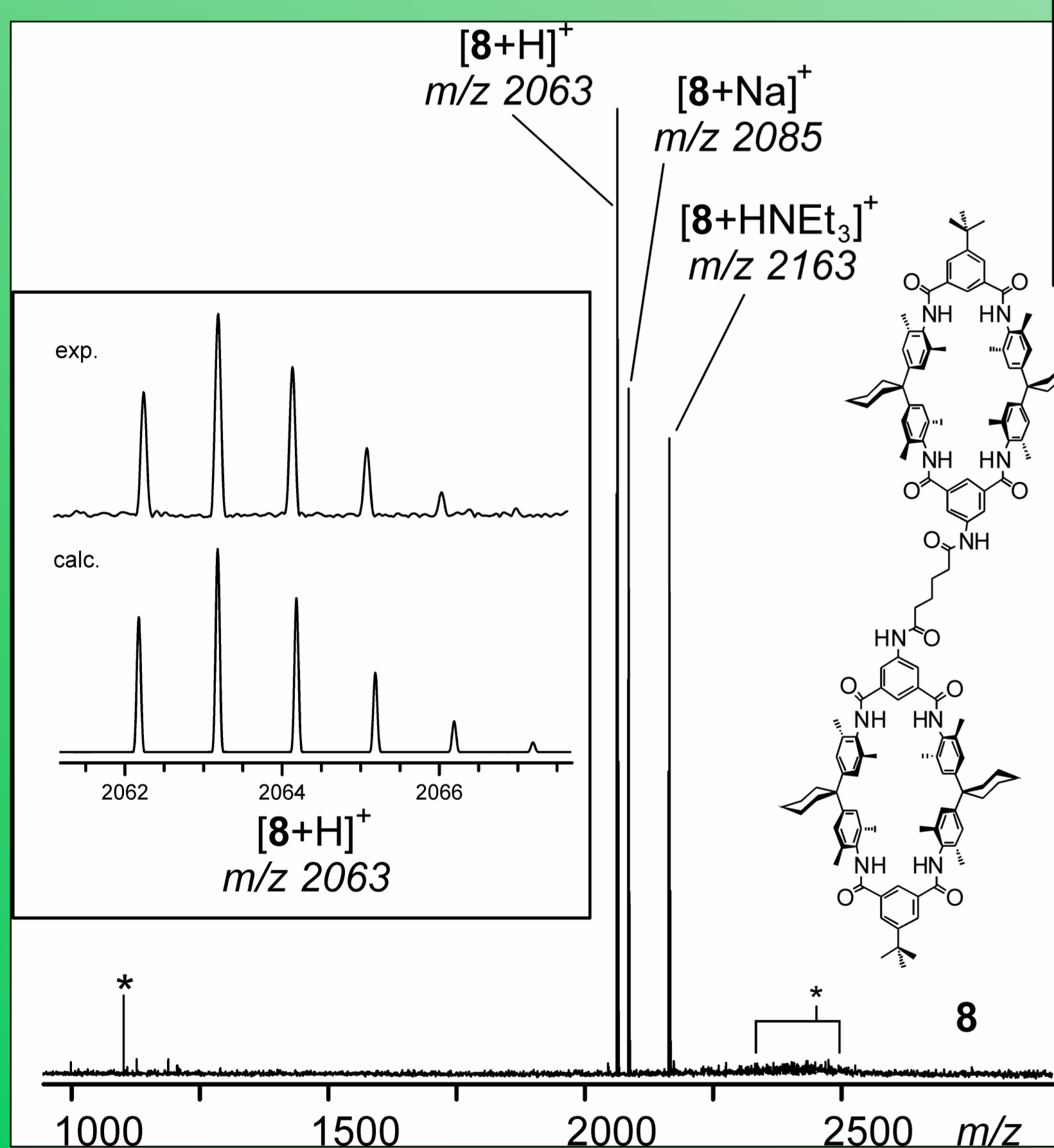


III. Synthesis of divalent components with different features for the investigation of multivalency



Reaction conditions: a) Pinacole, CH_3COOH (cat.), Toluene, rt, 18 h, 98 %; b) $\text{Pd}(\text{PPh}_3)_4$ (cat.), Cs_2CO_3 , Toluene/DMF 1:1, 120 – 130 °C, 18 h, 72 %; c) Grubbs-Hoveyda IInd Generation, CH_2Cl_2 , rt, 3 days, 56 % (rt = room temperature, cat = catalytical amounts).

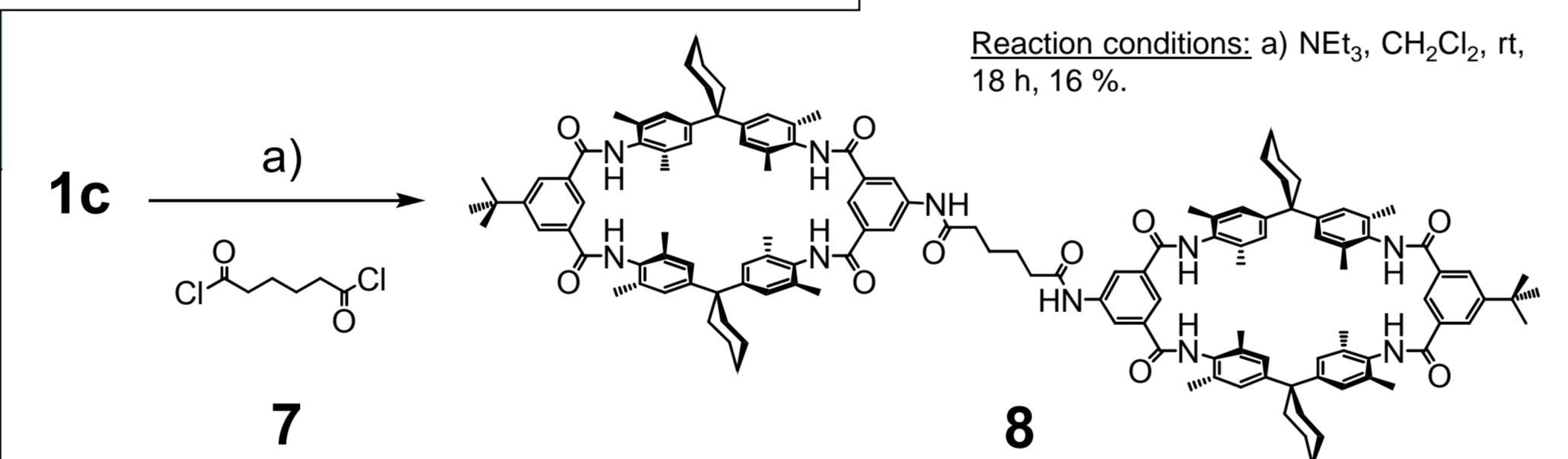
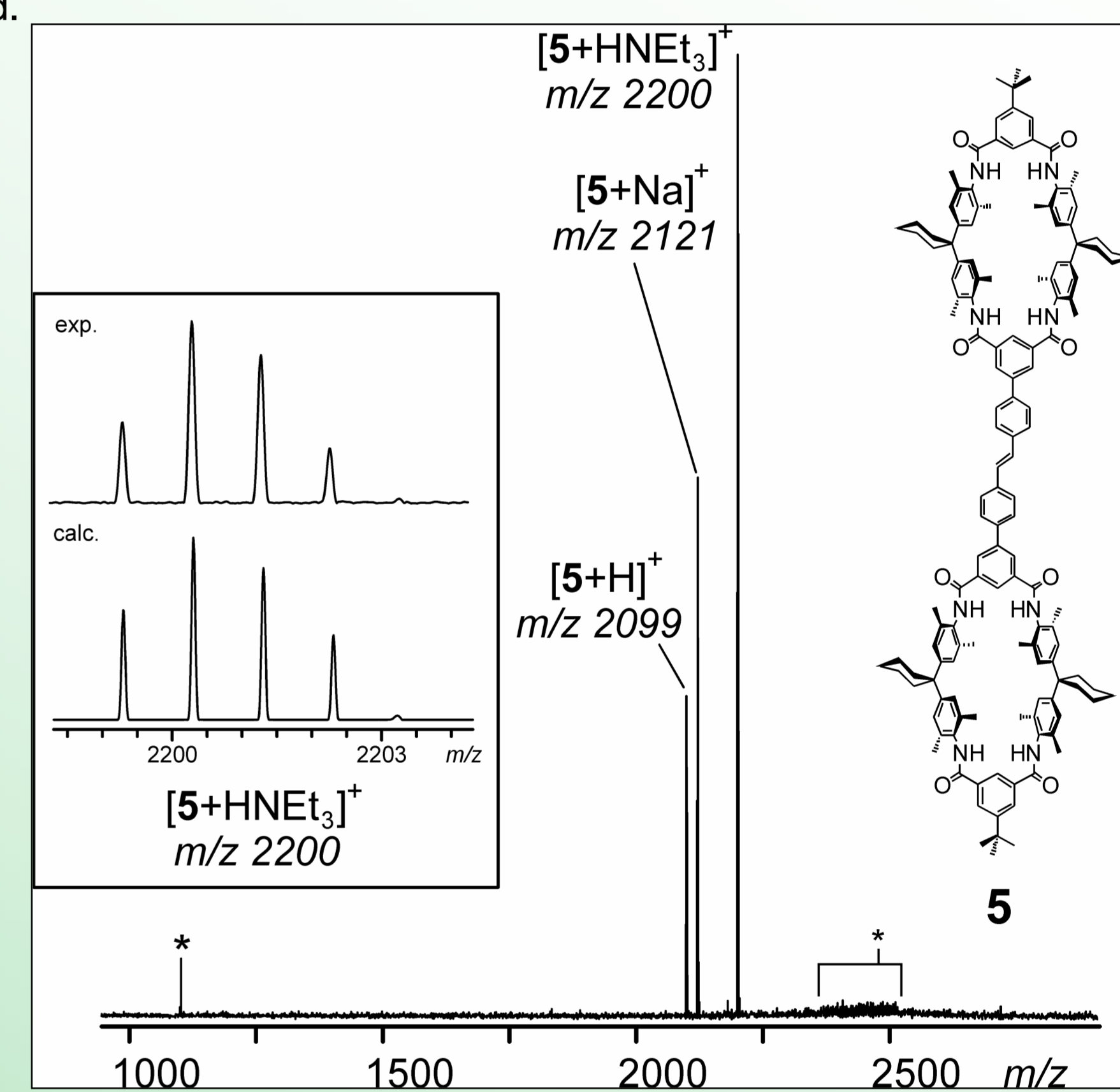
The ESI-MS spectrum of **5** shows $[\text{8+H}]^+$ as the main peak. Also, $[\text{8+Na}]^+$ and $[\text{8+HNEt}_3]^+$ are visible. The isotopic pattern of the experimental and calculated $[\text{8+H}]^+$ -ion are in good agreement.



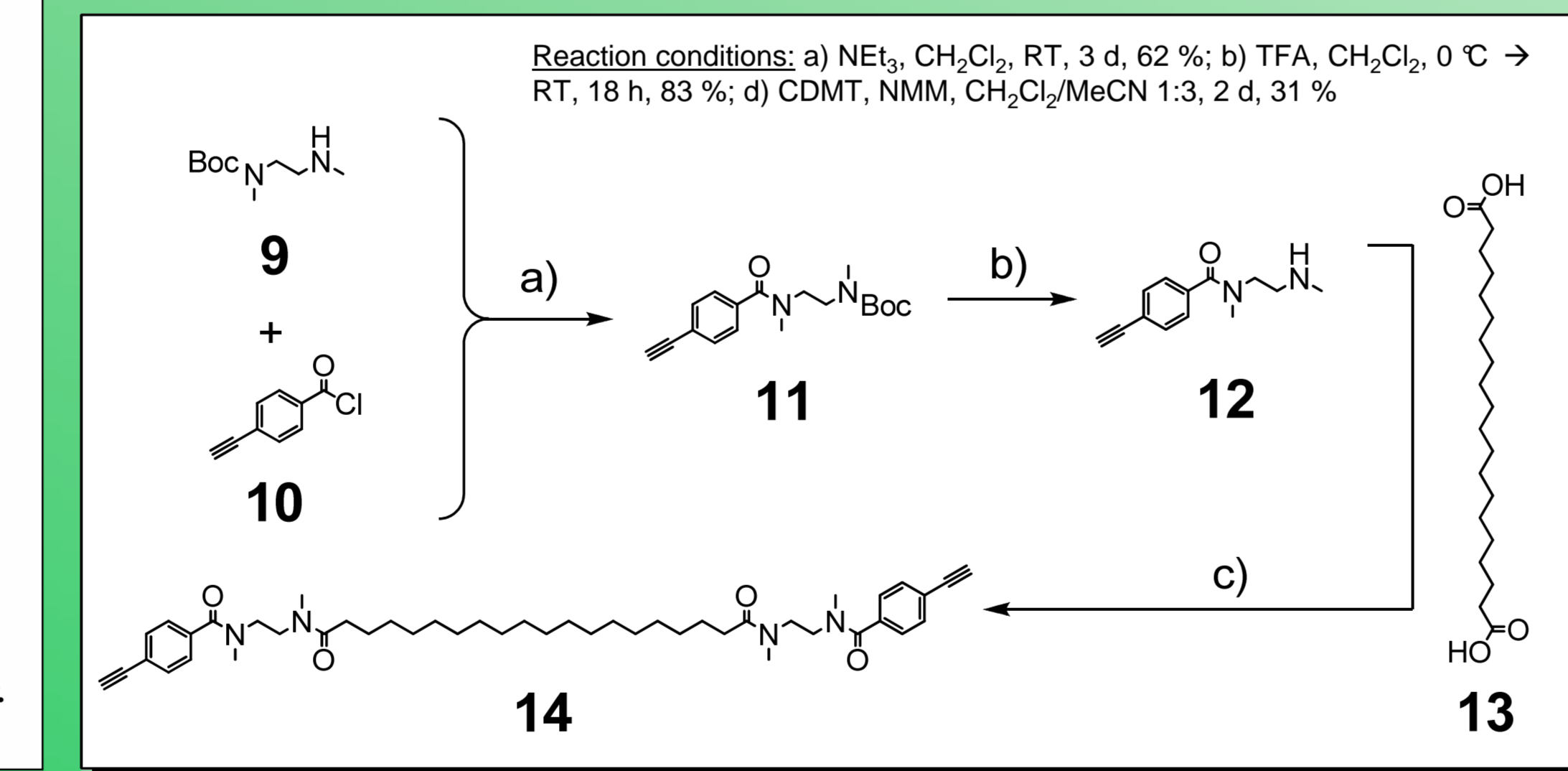
The synthesis of the new divalent host **5** begins with the esterification of the 4-vinylphenylboronic acid **2** with pinacole under room temperature conditions. The resulting boronic acid pinacol ester **3** is then used in the Suzuki coupling with the bromo wheel **1a** (or iodo wheel **1b**) to yield the modified wheel **4**. The esterification in the first step is essential to achieve good yields under Suzuki coupling conditions. The last step of the synthesis is the metathesis of **4** with itself to the desired compound **5**. The Grubbs-Hoveyda IInd Generation catalyst **6**, which is more active than the usual Grubbs catalysts but also quite expensive, was used to get **5** in satisfying yield.

The reactions under metathesis conditions often yield a mixture of cis/trans conformers. In this case, only the trans compound **5** is formed. The ¹H-NMR spectrum (in $\text{CDCl}_3/\text{CD}_3\text{OD}$ 2:1) shows a peak at 7.2 ppm, which can be assigned to the protons of the styrene double bond in trans conformation. For the isomeric cis conformation, a peak at 6.5 ppm should be observed, which is not present in the ¹H-NMR spectrum of **5**.

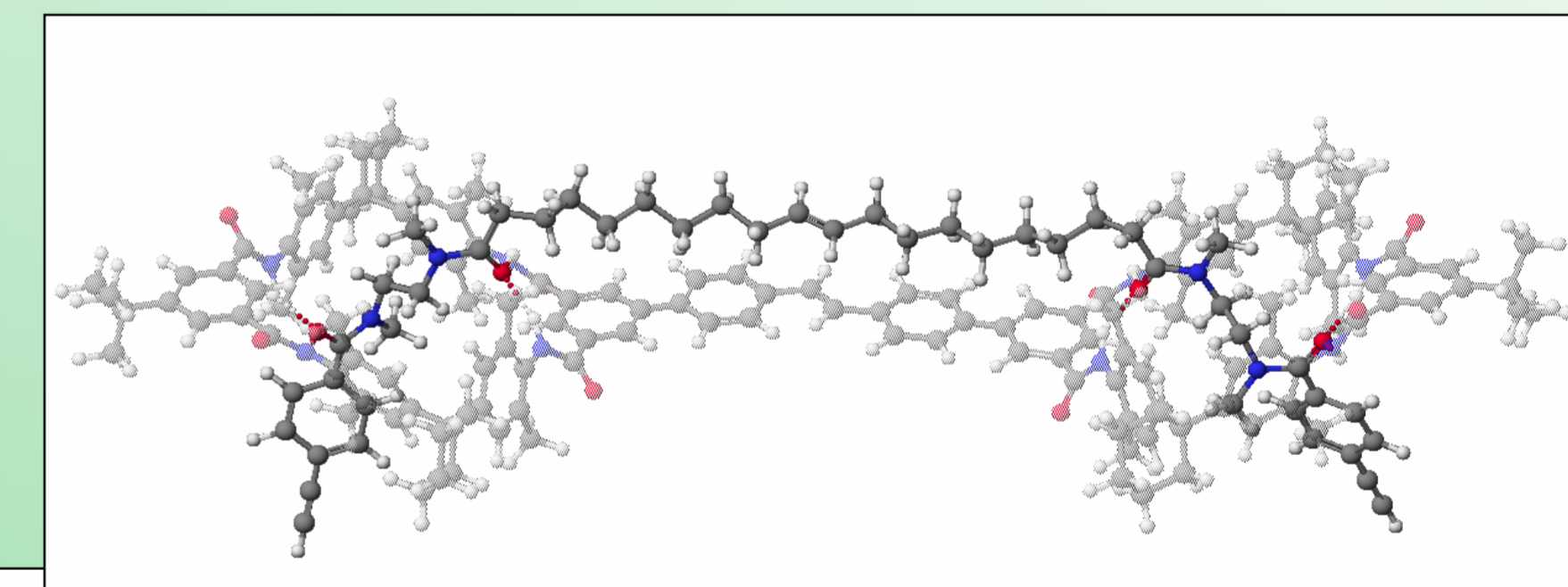
The ESI-MS spectrum of **5** shows $[\text{5+HNEt}_3]^+$ as the main peak. Also, $[\text{5+H}]^+$ and $[\text{5+Na}]^+$ are visible. The addition of NEt_3 is often necessary, because it gives higher abundance intensities in the ESI-MS spectra of tetralactam macrocycles.



The divalent guest **14** was synthesized starting from the single Boc-protected diamine **9** and the acid chloride **10** yielding compound **11**, which can be deprotected under acidic conditions to the amide **12**. The double amide coupling of **12** with the acid **13** complete the synthetic route to **14**.



The synthesis of the second new divalent host **8** is based on the amino wheel **1c**, which could be coupled to the commercially available adipoyl chloride.



Based on MM2 calculations^[4], compound **14** fits perfectly into the divalent hosts **5** and **8**. Stoppers with azide groups can yield [3]-rotaxanes.

[4] The modelling was performed by CaChe5.0 software [http://www.cachesoftware.com]

V. Conclusion/Outlook

As we have shown here, the wheels **1a**, **1b** and **1c** are very important for the design of multivalent building blocks and multiply interlocked architectures.

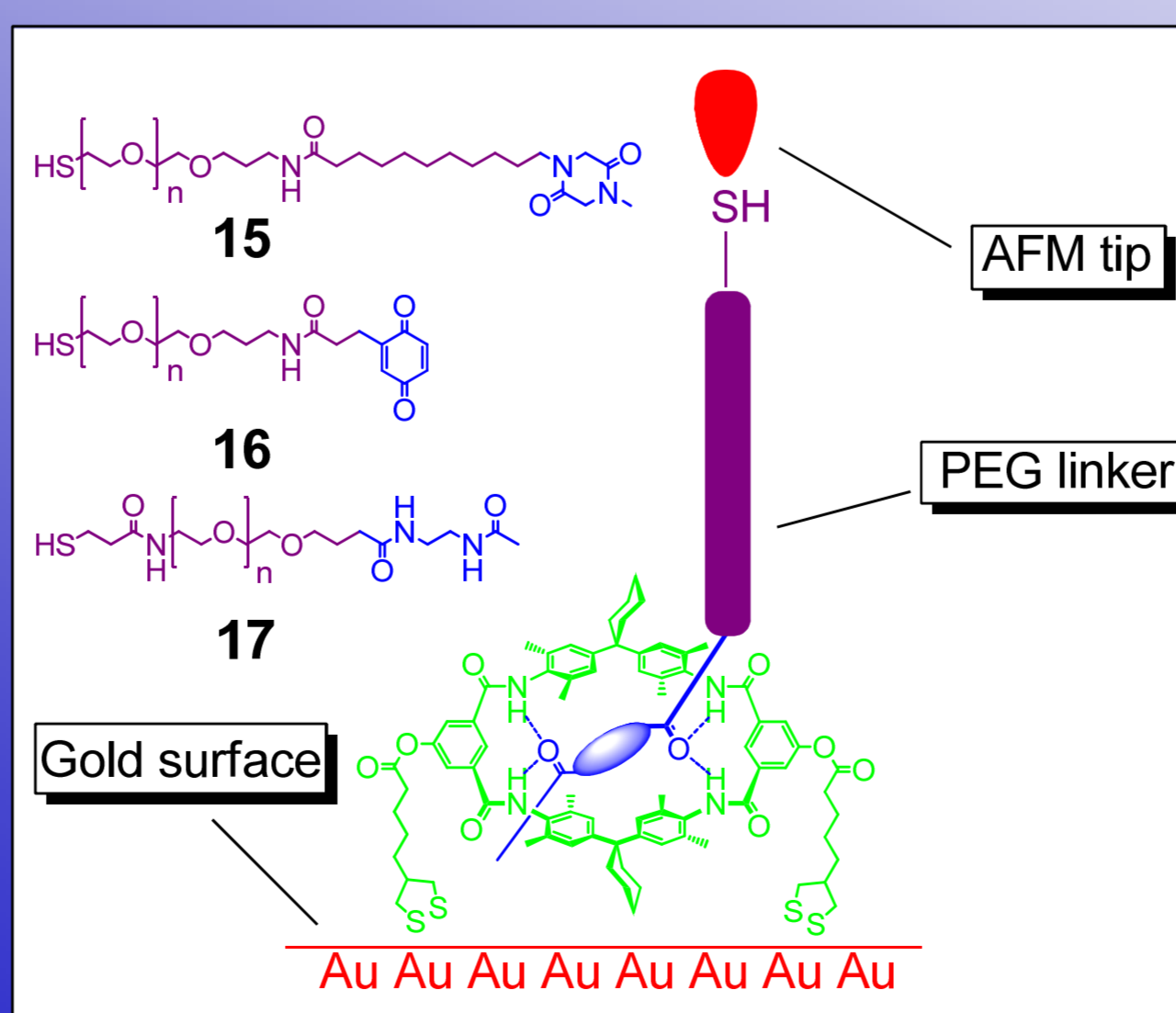
The divalent hosts **5** and **8** as well as the divalent guest **14** were synthesized by modern reaction methods in good to excellent yields. The next steps will be the ITC (isothermal titration calorimetry) measurements to investigate the multivalency effect on this system. Furthermore, the synthesis of [3]-Rotaxanes under the influence of stoppers with azide functional groups is intended.

Gold surfaces can easily be coated with the dilipoic acid wheel **18** as shown in some first AFM pictures. This strategy allows SMFS measurements to examine the individual host-guest interactions.

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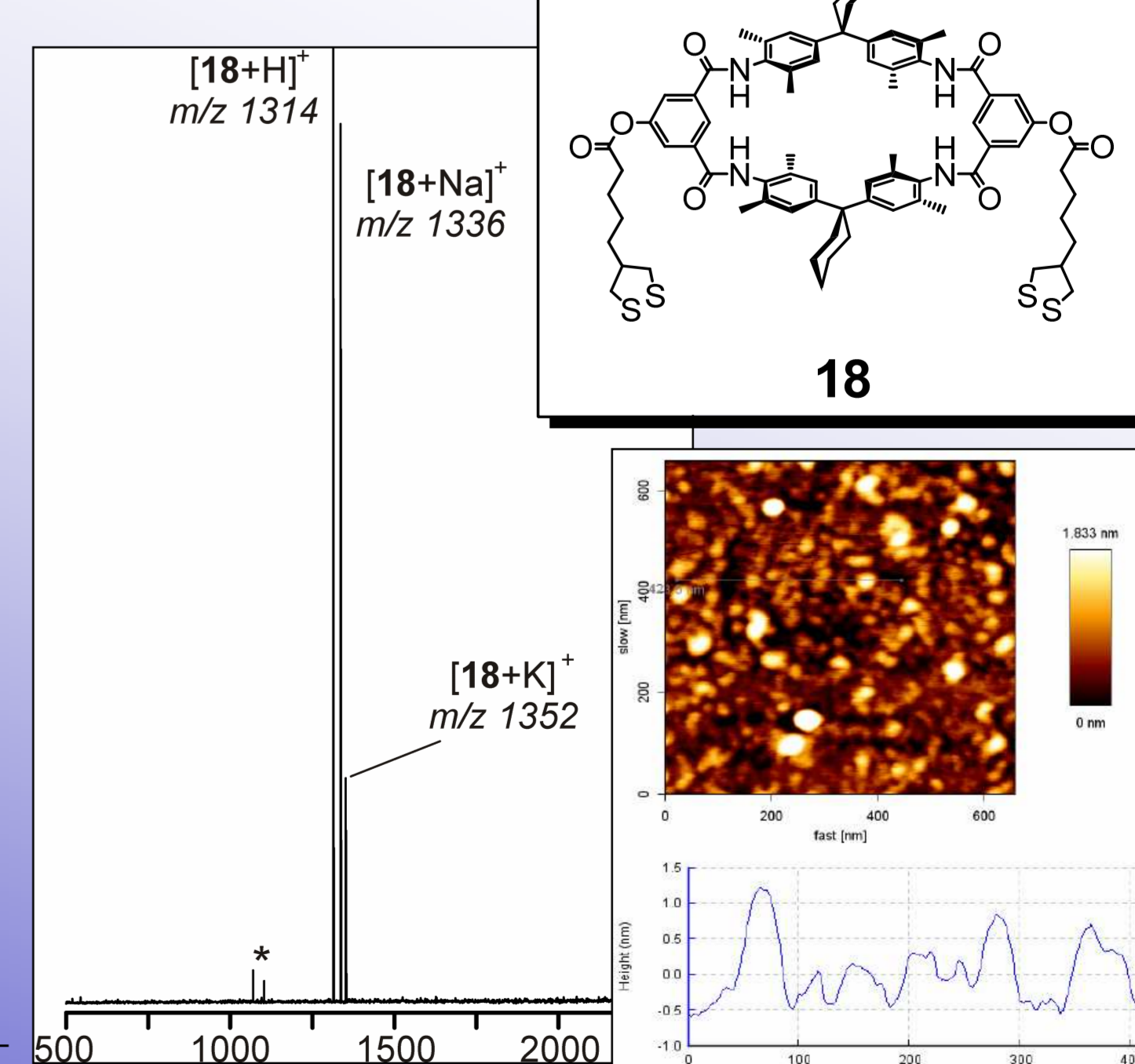
IV. Hosts and Guests for SMFS-Measurements

AFM-based single-molecule force spectroscopy (SMFS) appears to be suitable to address interaction forces from the single-molecule perspective, which have traditionally been assessed by ensemble thermodynamics^[5].



The dilipoic acid wheel **18** can be bound to a gold surface because of the thiophilic character of the surface.

With a molecule (**15**, **16** or **17**) on the SMFS head containing one or more binding sites and a long PEG linker, the interaction forces between wheel and axle can be measured.



[5] For recent reviews, see: a) W. Zhang, X. Zhang, *Prog. Polym. Sci.* **2003**, *28*, 1271–1295; b) A. Jahnhoft, M. Neitzert, Y. Oberdorfer, H. Fuchs, *Angew. Chem., Int. Ed.* **2000**, *39*, 3213 – 3237.