

PhD Thesis

**Synthesis of resorcinarene-based cavitands by new and
conventional synthetic methods**

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1. INTRODUCTION

The main feature of the supramolecular systems is, among others, that they can be assigned properties with pre-programmed selectivity that can be used in wide variety of applications. The proper construction of a molecule with supramolecular properties, enables it to select the most suitable structural unit, molecule, reaction pathway from several alternative options due to the conscious structural design.

This selectivity can be understood as the result of the communication of appropriate parts of complex and sometimes quite complicated supramolecular structures. The common 'language' of communication between subunits is based on noncovalent intramolecular interactions. The energy of these interactions ($2\text{-}350\text{ kJmol}^{-1}$), similarly to the energy of the first-order interactions ($100\text{-}1000\text{ kJmol}^{-1}$), can vary widely, but in terms of value it is usually one order of magnitude smaller. These intramolecular bonds are weak, so many of them need to be formed and placed in the right position in the molecule to get the expected effect.

Organic compounds, that have a cavity of suitable size into which simple molecules or ions can be complexed by reversible forces, are called cavitands. Resorcinarene-based cavitands (hereinafter only cavitands) are derived from the calix[n]arene compound family. An important difference between calix[n]arenes and cavitands is that the abovementioned compounds are much more conformationally flexible, and there may be several conformers in the solution phase, separated only by a small energy barrier. In contrast, the cavitand skeleton is fixed on both the lower and upper rims, resulting in a cyclic oligomer with a rigid structure.

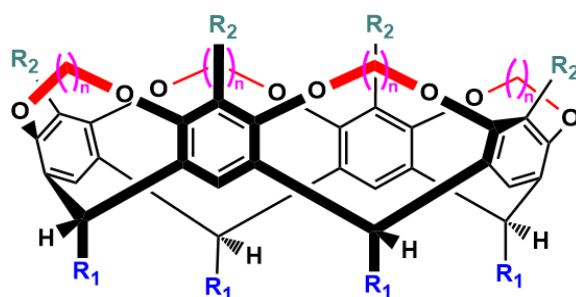


Figure 1. A general structure of the cavitand skeleton.

The parent skeleton has three strategically important structural parts [Figure 1], where targeted modifications can be made according to the subsequent use: **1.** Feet (**R₁**) - by appropriate selection of the alkyl or aromatic aldehyde derivative used in the condensation reaction, the solubility in the chosen medium can be optimized and a moiety of attachment to the solid surface can be created. **2.** An alkyl, halogen or hydroxyl group in position-2 of the starting resorcinol compound (**R₂**) provides an opportunity to implement both classical and modern chemical synthesis strategies before or after upper rim closure. **3.** At closing the upper rim with different bis-electrophiles the opposite phenolic hydroxy groups can be attached each other, providing good opportunity to fine tuning of the diameter of the upper rim resulting in different inner cavities and limited flexibility.

1. Aims

As main aim of the doctoral research, the synthesis of resorcinarene-based cavitands by new and conventional synthetic methods, and structural analysis of the obtained compounds by different spectroscopic methods were planned. The aims can be detailed as follows:

1. Design of functional units on the lower and/or upper rim with functional groups which allows us to use the new types of resorcinarene-based cavitands in aqueous, aqueous-alcoholic media to study 'host-guest' interactions.
2. Creation of marker groups on the upper rim that provide selective binding of a particular "target" element, compound.
3. In addition to the conventional homogeneous catalytic synthetic pathways, used for the functionalization of the cavitand skeleton, the development and optimization of new and high-yielding synthetic methods, such as Sonogashira couplings, 'click' reactions, and aminocarbonylation reactions.
4. Investigation and optimization of the reaction conditions, and to find correlation between the effect of different nucleophiles and selectivity in transition metal catalysed reactions.
5. Investigation of inter- and intramolecular interactions that fundamentally affect the structure of cavitand products formed in aminocarbonylation reaction.
6. Analytical characterization of the novel synthesized compounds.

2. Methods

Standard inert Schlenk-technique and high-pressure autoclave method was used. The experiments involving high pressure (10-90 bar) were performed in a 100 ml stainless steel autoclave.

The conversions and the product distributions were determined by ^1H - and ^{13}C -NMR measurements. The products were identified by MS-MALDI-TOF, IR, 1- and 2D NMR measurements and element (C, H, N) analyses.

4. Results

The research activity carried out during my doctoral work covers two areas: transition metal-catalyzed reactions such as palladium-catalyzed aminocarbonylation reaction of tetrakis[4-iodo-phenoxy]methyl]cavitand in the presence of various N-nucleophiles at different carbon monoxide pressures (1-90 bar), copper(I)-catalyzed azide-alkyne cycloaddition, *i.e.*, the 'click' reaction, palladium-catalyzed cross-coupling reaction (Sonogashira coupling), as well as conventional high-efficiency nucleophilic substitution reaction (Williamson ether synthesis).

My results and observations are summarized as follows:

1. It was proved during the aminocarbonylation reactions of tetrakis[4-iodo-phenoxy]methyl]cavitand, that N-heteroaromatic structural units on the upper rim can be formed with complete conversion using picolyamine derivatives as N-nucleophiles [Figure 2]. It was established that the carboxamide/2-ketocarboxamide ratio can be regulated by the carbon monoxide pressure.

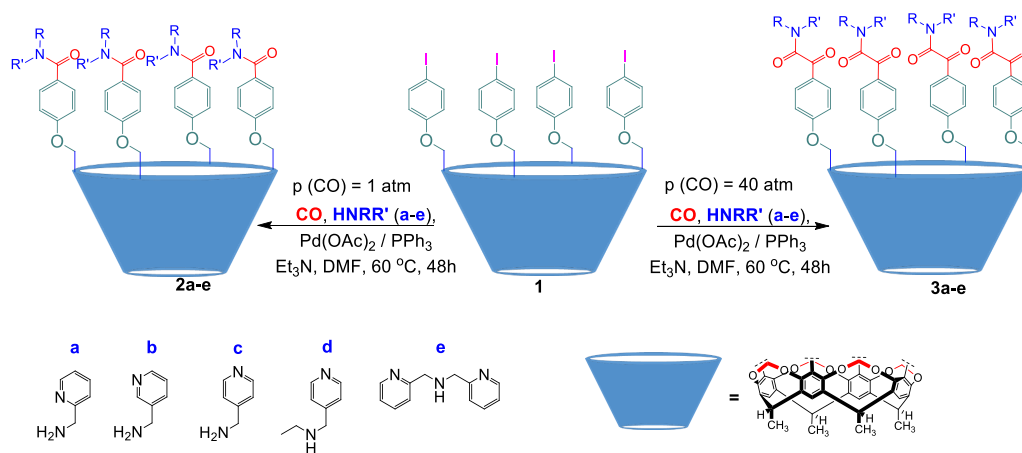


Figure 2. Aminocarbonylation of tetrakis[4-iodo-phenoxy]methyl]cavitand in the presence of picolyamine derivatives as N-nucleophiles.

2. I found that a chiral environment on the upper rim can be constructed by palladium-catalyzed aminocarbonylation when N-nucleophiles with stereogenic centers (3-aminosteroids) are used [Figure 3]. During the reactions, the formation of host-guest interaction between the product and the starting substrate was detected. Furthermore, the effect of carbon monoxide pressure on the carboxamide / 2-ketocarboxamide ratio was observed.

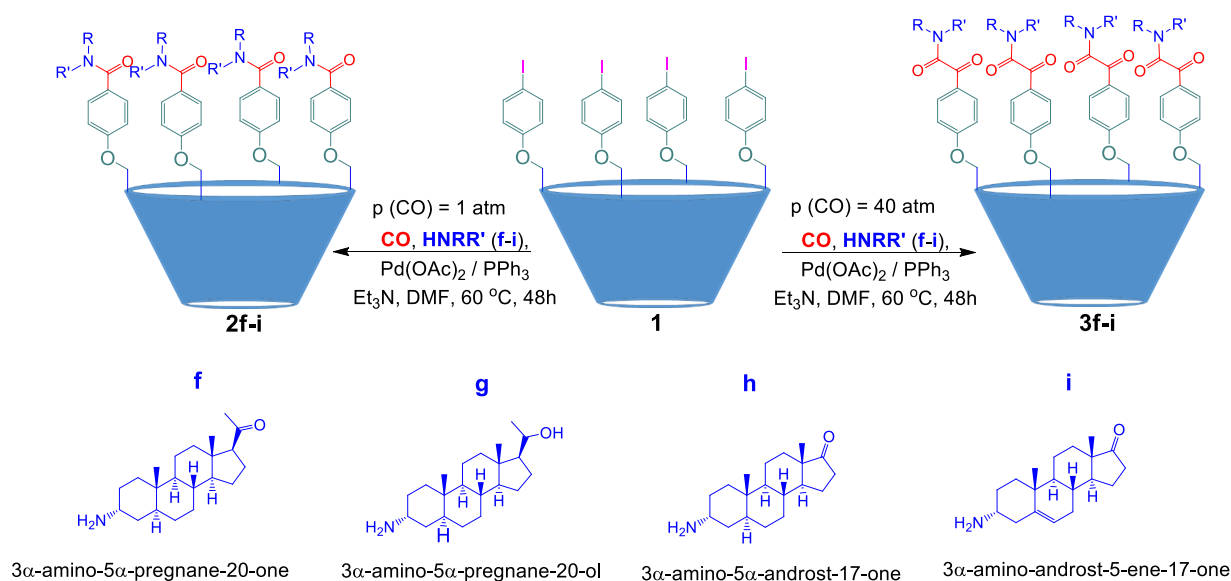


Figure 3. Synthesis of cavitand–steroid conjugates with chiral moieties on upper rim by aminocarbonylation reaction.

3. I found that competitive palladium-catalyzed carbonylation reactions with binary [Figure 4] and quaternary amine mixtures resulted in the formation of carboxamide derivatives possessing the same amine in polar media. The observed symmetry-driven narcissistic self-sorting is presumably kinetically controlled, which may be supported by thermodynamic data from semiempirical calculations at the PM6 level and the amine reactivity.

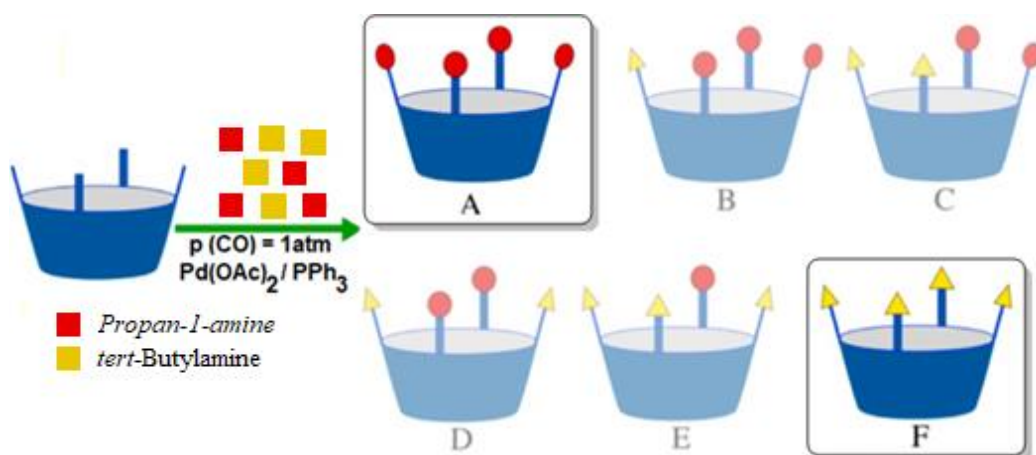


Figure 4. Competitive palladium-catalyzed carbonylation reaction with binary amine mixtures.

4. I found that the copper(I)-catalyzed azide-alkyne (3+2) cycloaddition reaction, performed on the tetrakis[4-ethynyl-phenoxymethyl]cavitand skeleton [Figure 5], is suitable for the synthesis of monosaccharide-cavitand conjugates. The glucose moiety is attached to the cavitand skeleton through a 1,2,3-triazole ring. The solubility of the prepared products was significantly increased compared to the starting compound, so it can also be used in aqueous-alcoholic media to study host-guest interaction.

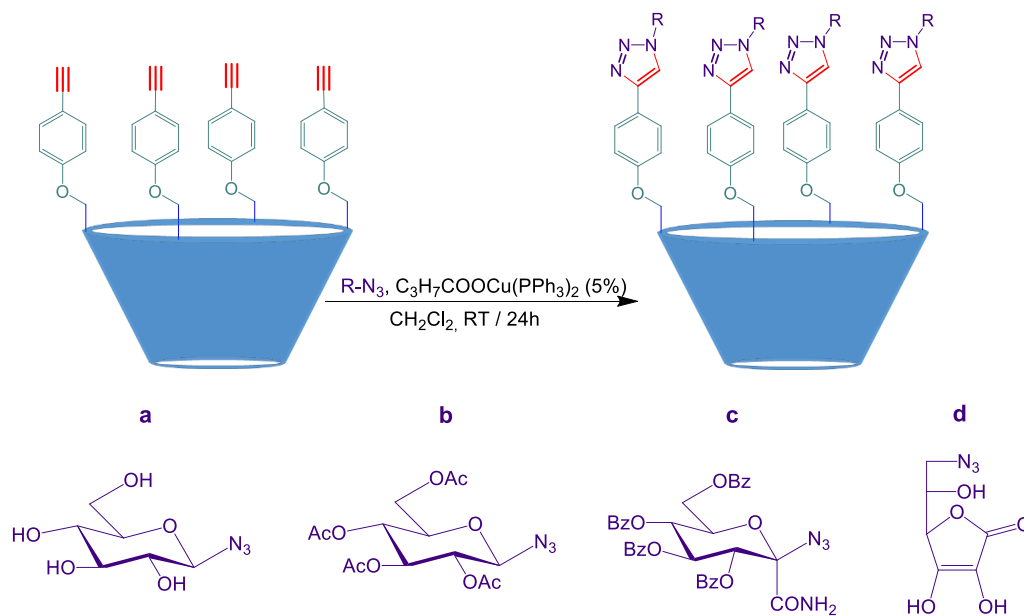


Figure 5. Copper(I)-catalyzed 'click' reaction performed on a tetrakis[4-ethynyl-phenoxymethyl]cavitand skeleton.

5. Based on the transition metal-catalyzed reactions, it can be concluded that the tetrakis[4-iodo-phenoxymethyl]cavitand (**1**) and tetrakis[4-ethynylphenoxymethyl]-

cavitand (**4**) skeletons are characterized by high 'tetra-selectivity', *i.e.*, the reaction took place at all four reaction centers with full conversion. Furthermore, the transformation with complete chemoselectivity was observed for each cavitand molecule. The hypothesis can be supported by the carbonylation reaction with half-equimolar amounts of 3-picolylamine [Figure 6]. In this reaction almost 50% of the starting compound (**1**) was recovered while 2-ketocarboxamide derivative (**3b**) was isolated in 44% yield.

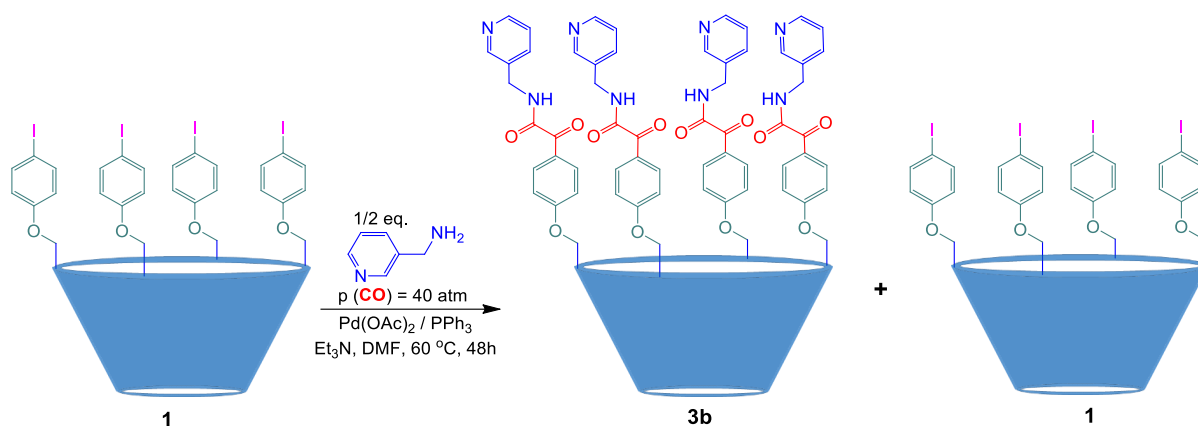


Figure 6. Investigation of 'tetra-selectivity' in the carbonylation reaction.

- The classical transformation, just like Williamson ether synthesis on tetrakis[bromo-methyl]cavitand skeleton, can also be used for the preparation of cavitand derivatives which are capable to host-guest interactions. The target products were obtained in high isolated yields (73-93%).

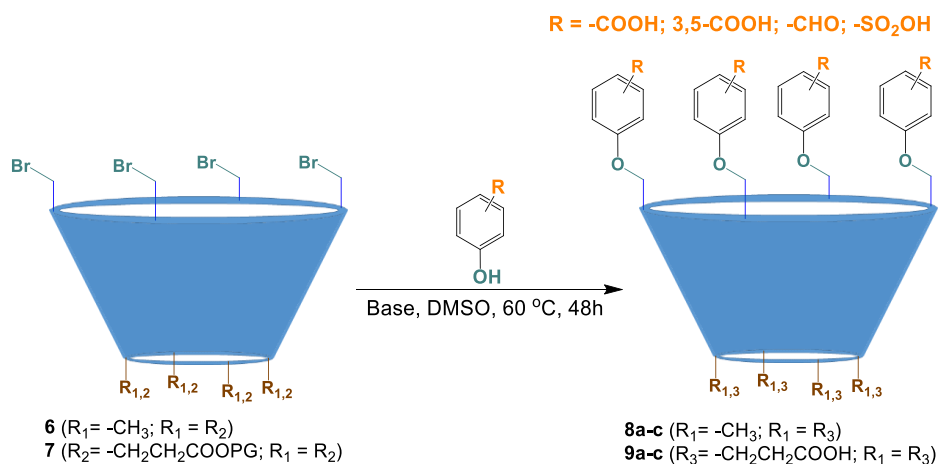


Figure 7. Synthesis of water-soluble cavitand derivatives by Williamson ether synthesis.

7. I found that the high-yielding condensation reaction of tetrakis[4-formylphenoxy]cavitand (**14**) [Figure 8] with primary amines results in the formation of presumably four-armed supramolecular ligands.

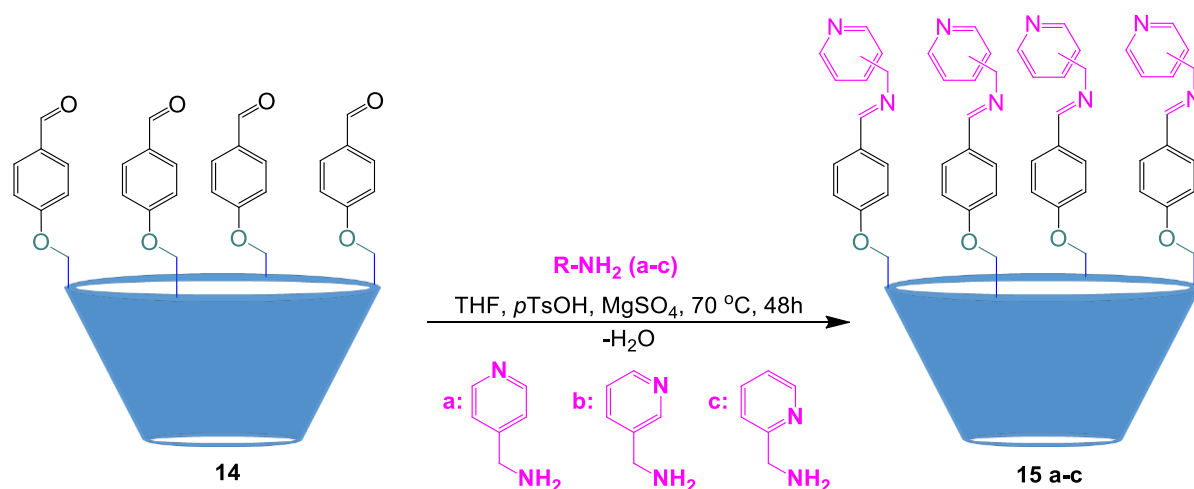


Figure 8. Synthesis of cavitand derivatives with aldimine functionalities on the upper rim.

5. Publications forming the basis of PhD dissertation

- Z. Nagymihály, L. Kollár: High-yielding synthesis of deepened cavitands bearing picolyl moieties on the upper rim. *Tetrahedron* 71 (2015) 2555-2560.
- Zs. Czibulya, É. Horváth, Z. Nagymihály, L. Kollár, S. Kunsági-Máté: Competitive processes associated to the interaction of a cavitand derivative with caffeic acid. *Supramol. Chem.* 28 (2016) 582-588.
- Z. Nagymihály, N. Caturello, A. Takátsy, L. Kollár, R. Q. Albuquerque, Zs. Csók: Palladium-Mediated Catalysis Leads to Intramolecular Narcissistic Self-Sorting on a Cavitand Platform. *J. Org. Chem.* 82 (2017) 390–396.
- Z. Nagymihály, Zs. Csók, L. Kollár: Influence of base additives on the selectivity of palladium-catalysed aminocarbonylation: Highly selective functionalization of a cavitand scaffold. *Mol. Catal.* 444 (2018) 70-75.

- Z. Nagymihály, L. Kollár, S. Kunsági-Máté: Solvent switched weak interaction of a 4-quinazolinone with a cavitand derivative. *Molecules* 25 (2020) Article number 1915.
- Z. Nagymihály; J. Wölfling; G. Schneider; L. Kollár. Synthesis of 2 - Methylresorcinol - Based Deepened Cavitands with Chiral Inlet Bearing Steroidal Moieties on the Upper Rim. *ChemistrySelect* 2020, 5 (23), 6933–6938.
- Z. Preisz, Z. Nagymihály, B. Lemli, L. Kollár, S. Kunsági-Máté: Weak interaction of the antimetabolite drug methotrexate with a cavitand derivative. *Int. J. Mol. Sci.* 21 (2020) 4345.

6. Presentations and posters forming the basis of PhD dissertation

- L. Kollár, Z. Nagymihály: High-yielding synthesis of deepened cavitands bearing picolyl moieties on the upper rim. 16th Tetrahedron Symposium Asia Edition. Shanghai, 10-13 November, 2015 (P1.84)
- Z. Nagymihály, Zs. Csók, L. Kollár: Application of palladium-catalyzed homogeneous catalytic and conventional selective reactions in the synthesis of supramolecular systems. MTA Inorganic and Organometallic Chemical Working Committee Meeting. Budapest, 18 November, 2016.
- Z. Nagymihály, N. Caturello, A. Takátsy, L. Kollár, R. Q. Albuquerque, Zs. Csók: Palladium-Mediated Catalysis Leads to Intramolecular Narcissistic Self-Sorting on a Cavitand Platform. XXIII. International Conference on Chemistry. Deva (Romania), 25-28 October, 2017.