

PHD THESIS

**Synthesis and theoretical study of resorcin[4]arene-based
supramolecular systems**

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2018

1 Introduction

During the last three decades supramolecular chemistry became an intensively expanding field. On the one hand it deals with the investigation of molecular assemblies held together via intermolecular forces, on the other hand supramolecular chemistry aims at the synthesis, spectroscopic and theoretical study of novel macromolecules. The synthesis of macromolecules is based on the molecular self-assembly well-known from biology, in this way interesting and exciting novel materials can be prepared frequently used in physics, chemistry, nanotechnology and electronics.

The resorcin[4]arenes and the related cavitands are bowl-shaped macrocyclic compounds consisting of multiple aromatic rings connected by different linkers to a conformationally rigid structure. Similarly to cyclodextrines and calixarenes, cavitands have excellent molecular recognition ability, hence they are highly applicable in host-guest chemistry. Cavitands are also known to offer excellent starting points for the construction of large molecular entities possessing a well-formed hydrophobic cavity. Therefore, cavitands and similar structures show promise with potential applications as gas sensors, nanoreactors and drug delivery systems. Cavitands offer a wide application in the preparation of capsule-like self-assemblies. Ferrocene-substituted resorcinarenes were found to be redox-switchable dynamic systems, in which the ferrocene moieties serve as electroactive hydrophobic fragments.

Deepening the inner cavity was mainly accomplished by conventional organic reactions, nevertheless, homogeneous catalytic cross-coupling reactions were meagerly employed as well. Our research team developed some novel synthetic procedures for the molecular enlargement of cavitands using the palladium-catalyzed Stille-coupling, Suzuki-Miyaura, Sonogashira and aminocarbonylation reactions as well as copper(I)-catalyzed azide-alkyne cycloadditions (CuAAC). Beside the simplicity, the excellent reaction efficiency makes the latter 'click' reactions frequently employed in the field of organic synthesis. During my doctoral research, I aimed to expand further the applicability of this versatile methodology by the synthesis of a novel series of elongated cavitands.

Theoretical study of these rather large molecules like cavitands is a considerably complicated and computationally demanding procedure. Hence, very few scientific papers can be found in the literature focusing quantum chemical calculations of cavitands and related structures. Despite the difficulties, nowadays the different computational techniques offer excellent additional investigation procedures beside the spectroscopic methods. Molecular dynamics is a very fast tool to find the global minimum and semiempirical methods, included the study of electrostatic potential surface, offer the possibility to reveal the charge distribution within the whole molecule. DFT calculations and other quantum chemical methods can shed light on the intra- or even the intermolecular forces as well.

2 Aims

During my doctoral research I dealt with synthesis, spectroscopic analysis and theoretical study of deepend cavitand structures. My aims can be summarized as follows:

1. Synthesis of novel resorcin[4]arene-based cavitands decorated on the upper rim with various functional groups. Synthesis of triazole ring containing cavitands to improve the molecular recognition ability and building ferrocenyl moieties in the cavitand scaffold for electrochemical purposes.
2. Widening the range of homogeneous catalytic processes applied on the cavitand scaffold, that is hydroformylation, Suzuki-Miyaura and Sonogashira coupling, 'click' reactions, amino- and azidocarbonylation.
3. To describe the effect of reaction conditions and the different nucleophiles on the selectivity.
4. Analytical characterization of the novel synthesized compounds.
5. Theoretical study of the new host molecules including the geometry optimization at DFT level and calculating theoretical chemical shifts comparing the measured NMR shifts.
6. Revealing the inter- and intramolecular weak interactions with QTAIM analysis and NCI calculations which have strong influence on the cavitand structures.

3 Methods

Standard inert Schlenk line (vacuum gas manifold) and high-pressure autoclave techniques were applied during the laboratory work. Experiments involving high pressure were carried out in stainless steel autoclave. The products were identified by infrared spectroscopy, ^1H and ^{13}C -NMR measurements, mass spectroscopy and elemental analysis.

3.1 Computational details

The geometries were calculated without any symmetry constraints at all levels of theory. For the stationary points, the Hessian was evaluated to characterize the genuine minimum (no imaginary frequencies). Molecular dynamics simulations were carried out with the Schrödinger Suite 2015 MacroModel application using the OPLS_2005 force field and the PRCG (Polak-Ribiere Conjugate Gradient) method. For the geometry optimization at the semiempirical PM6 and PBEPBE/6-31G(d,p) levels, the electronic structure calculation at the B3LYP-D3/def2-TZVP level and the theoretical NMR chemical shift calculations at the B3LYP-D3/6-31G(d,p) GIAO level the Gaussian 09.D01 suite of programs was used. The test of different DFT methods for geometry optimization at the M06-2X/6-31G(d,p), M06-L/6-31G(d,p), B97-D3/6-31G(d,p),

B3LYP-D3/6-31G(d,p) and PBE-D3/6-31G(d,p) levels was carried out with ORCA 4.0.0 software. Bader analyses were carried out with the AIMAll software to investigate the electron density of the optimized structures. NCI isosurfaces were generated with the NCIPLOT program.

4 Results

1. Cavitand **3** bearing four cyclopentadienyl groups on the upper rim was synthesized (Figure 1) via nucleophilic substitution reaction using tetrabromo-cavitand (**1**) as starting material.

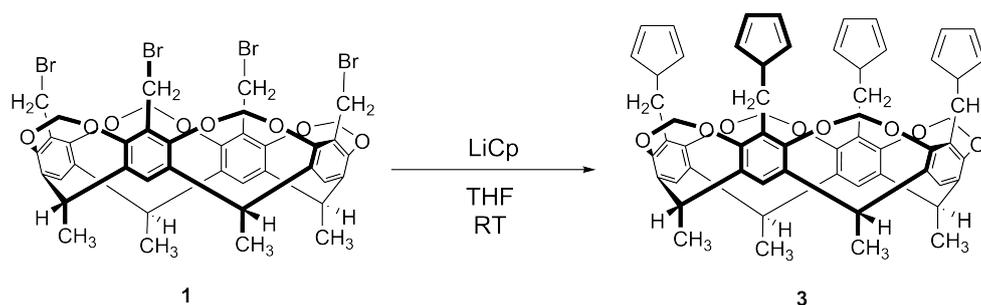


Figure 1: Synthesis of cyclopentadienyl-cavitand

After deprotonation of compound **3** it can be reacted (Figure 2) with anhydrous iron salt (FeCl_2) which results in *ansa*-ferrocene cavitand structure (**4**). Detailed theoretical study was carried out on the cavitand **4**.

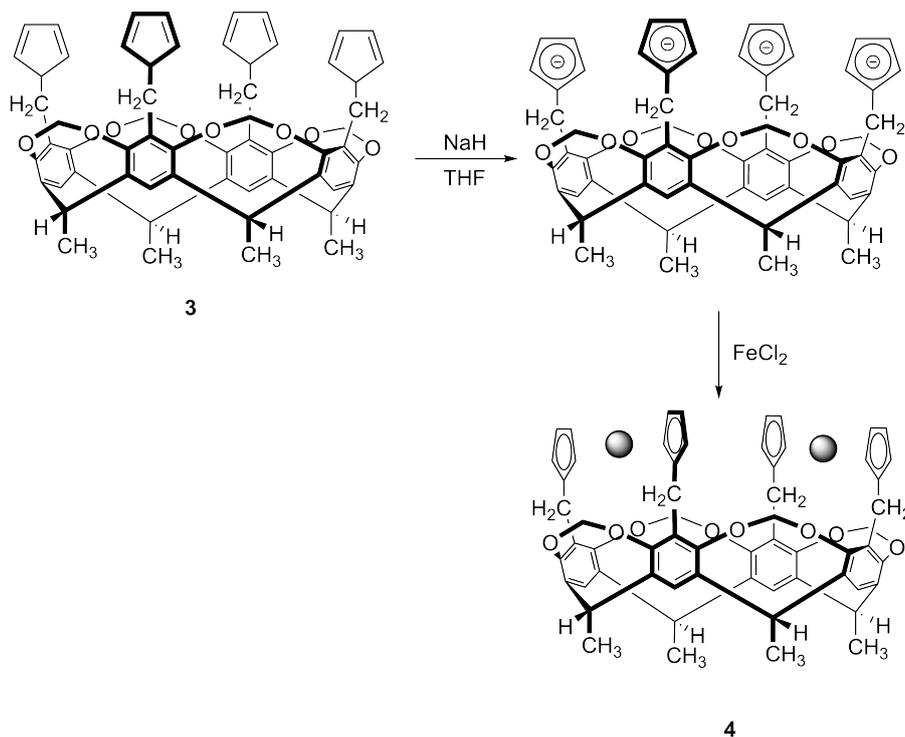


Figure 2: Synthesis of *ansa*-ferrocene cavitand

The geometries of **4** and the model *ansa*-ferrocene complexes were optimized at the same level. Comparing the optimized structures it has been found that the charge distribution on the central Fe atom strongly depends on the relative position of the Cp rings. The partial charge of the iron atom of **4** is more positive than the partial charges of iron atoms of model *ansa*-ferrocene complexes.

After geometry optimization QTAIM analysis was carried out on all the structures. Among the QTAIM descriptors, the ρ_{BCP} (electron density at the bond critical points) and the $\delta(A, B)$ (delocalization indices) were chosen to compare the electron structures. According to the values of electron density (at the BCPs) it has been shown that the Fe–C bond strengths of **4** are very similar than those of *ansa*-ferrocene complexes but the growth of the bond strengths are reversed due to the reversed position of the Cp rings of **4**. Delocalization indices show the bond orders and can be related to the changes of electron density caused by the geometry. The strain energy of **4** was examined and estimated in isodesmic reactions. It has been found that the strain energy of Cp rings of **4** is quite low, hence the insolubility of **4** (probably caused by a polymerization reaction) is not related to the strain of Cp rings.

- Novel, elongated triazole ring containing cavitands (**6-9**) were prepared via copper(I)-catalyzed azide-alkyne cycloaddition (Figure 3) started from tetraazido-cavitand (**5**). These derivatives were decorated on the upper rim with different functional groups such as phenyl (**6**), ferrocenyl (**7**), pinacol-boronate (**8**) and androst-16-en-17-yl (**9**) groups.

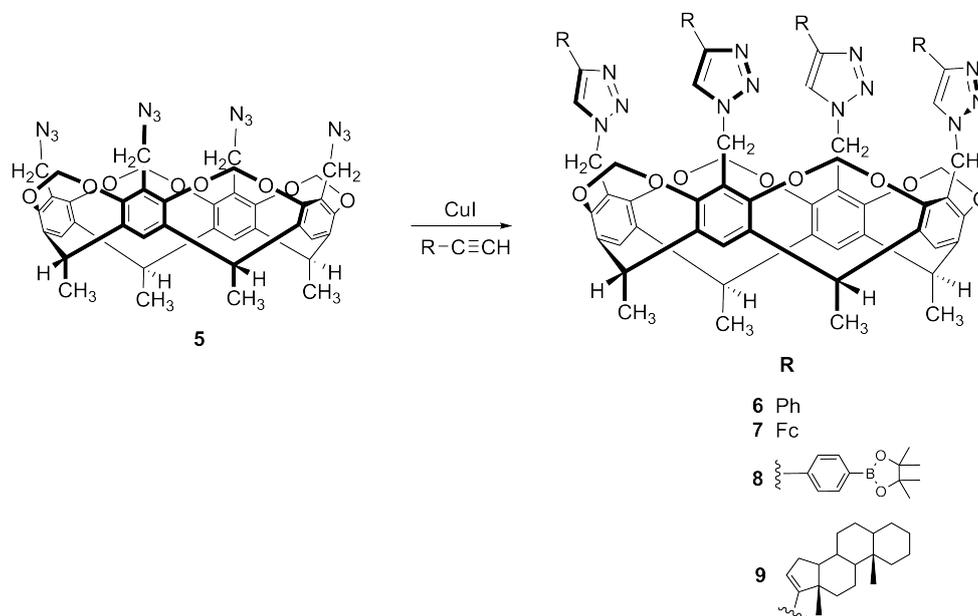


Figure 3: 'Click' reactions on tetraazido-cavitand scaffold

Multi-step theoretical study was developed to find the global minimum of the structures. Initially, molecular dynamics simulations were carried out on cavitand **6-9**. Following the dynamics simulations, the second step of our theoretical process was the re-optimization of the lowest energy conformers of **6-9** at the semiempirical PM6 level. To test which

DFT method is the best for further optimization of the geometry, cavitand **6** (the smallest molecule) was minimized with the different functionals combined with the 6-31G (d,p) basis set. The geometry optimized at the PBEPBE level showed symmetrical C_4 structures while the other structures optimized with different dispersion correction methods showed distorted geometries where the cavitand branches were drifted away and the symmetry has been reduced to C_1 completely disagreeing with the NMR data.

Energy calculations were carried out on the cavitand structures (**6-9**) with the tetramethylsilane (TMS) as reference. In all cases, the calculated and the measured chemical shifts showed very close values to each other especially in CDCl_3 solvent. The QTAIM analysis and the NCI calculations shed light on the fact that numerous intramolecular interactions have been established between the cavitand arms and those interactions are the most significant which are related to the triazole rings (cavitand **6-9**) and the pinacolboronate moieties (cavitand **8**). These intramolecular interactions can hold the cavitand branches together and stabilize the molecular structures even in solutions but they are sufficiently flexible to make the cavitand structures capable to act as a host molecule.

3. Tetraethynyl- (**11**) and tetraferrocenyl-cavitand (**12**) were prepared via Sonogashira coupling using **2** as starting material (Figure 4). The tetraethynyl derivative is applicable for further homogenous catalytic reaction such as reversed 'click' (CuAAC) reaction.

Elongated, triazole ring containing multilevel cavitands (with more than 2000 g/mol molar mass) possessing various functional groups on the upper rim were synthesized (Figure 5) started from **11**. These functional groups were the following: iodophenyl (**13**), phenyl (**14**), ferrocenylmethyl (**15**), substituted pyridazine rings (**16-18**) and steroid moiety (**19**).

Detailed theoretical study was accomplished on the cavitand **16, 17** comparing them with the different intermediates (**1, 2, 11**). Initially, molecular dynamics study was carried out on **16** to find the lowest and the highest energy conformer. These two conformers were re-optimized at the PBEPBE/6-31G(d,p) level of theory and were investigated regarding their energies and structures. It has been found that there are lots of differences in both the energy and the structure of the conformers. This conformational change can be established only by the effect of high-energy UV photon.

The polarizability and the Pearson acid-base character were examined at B3LYP-D3/def2-TZVP level in the case of **16, 17** and the intermediates (**1, 2, 11**). All the geometries were optimized at the same level. The investigation shed light on the fact, that cavitand **16, 17** are more polarizable and show softer character than the intermediates, moreover, the HOMO and LUMO orbitals are moderately delocalized in all cases. While the HOMO orbitals were localized on the same molecular moieties the localization of LUMO orbitals showed quite large differences.

4. Aminocarbonylation reactions were performed (Figure 6) on an elongated multilevel cavitand derivative (**13**) with five different *N*-nucleophiles (*tert*-butyl-amine, L-alanine

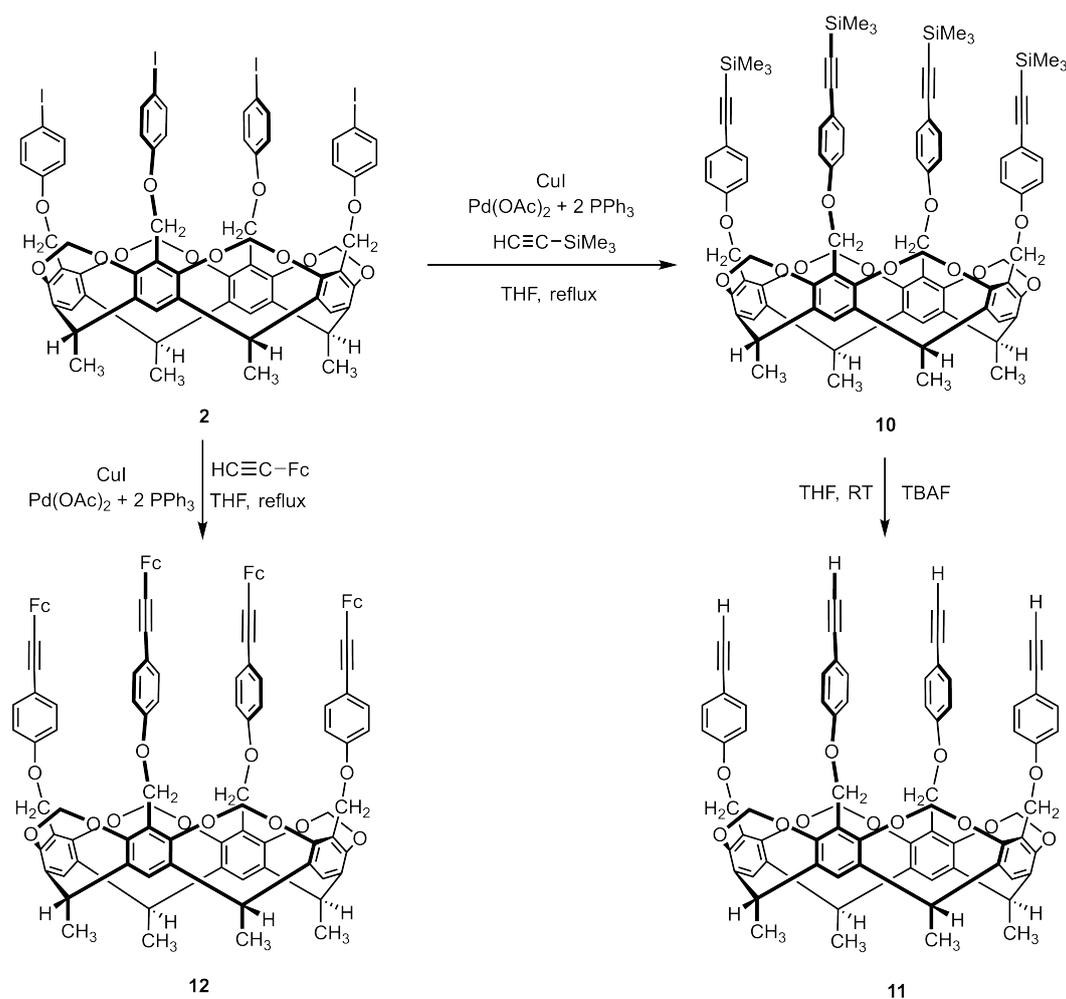


Figure 4: Sonogashira coupling on tetraiodo-cavitand scaffold

methyl ester, piperidine, morpholine and pyrrolidine). The reactions were implemented at high (90 bar) and low (atmospheric) pressure also. It has been proved that at high pressure the formation of tetrakis(ketocarboxamido) derivatives is favoured while at low pressure the tetracarboxamido cavitands are the favourable products. Although remarkable tetra-selectivities were observed in all cases, the near 100% chemoselectivity was achieved in only one case (applying *tert*-butyl-amine as nucleophile and 90 bar CO pressure).

QTAIM analysis and NCI calculations were carried out on cavitand **14**, **16**, **20a**, **20b**, **22a**, **22b** to reveal the intramolecular weak interactions established between the cavitand branches. The wavefunction calculations shed light on numerous stabilizing interactions similarly to the smaller triazole ring containing derivatives. Among these interactions the strongest ones were related to the triazole rings (in all cases) and the NH–CO bonds in the case of cavitands possessing amido groups (**20a**, **20b**, **22a**, **22b**)

5. Deepend tetravinyl-cavitand (**25**) were synthesized via Suzuki-Miyaura coupling and was used as starting material in hydroformylation process (Figure 7). The hydroformylation reactions were performed with five different catalysts and it has been found that the chemo- and regioselectivities were very similar as compared to those of hydroformylation

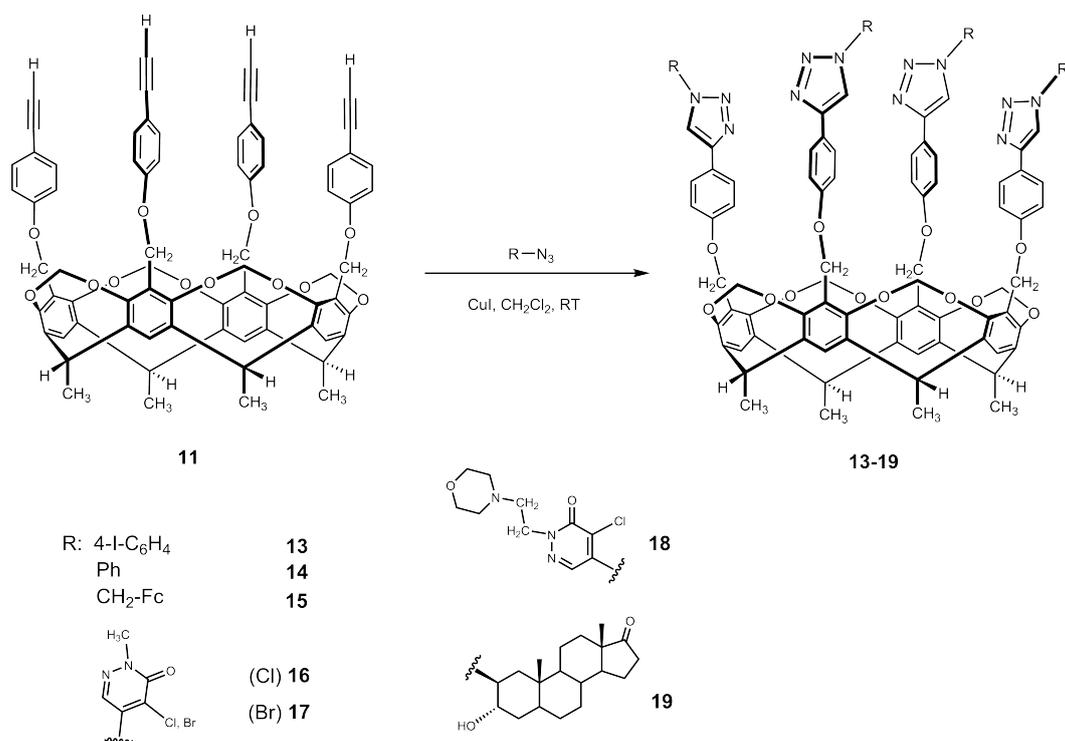


Figure 5: 'Click' reactions on tetraethynyl-cavitand scaffold

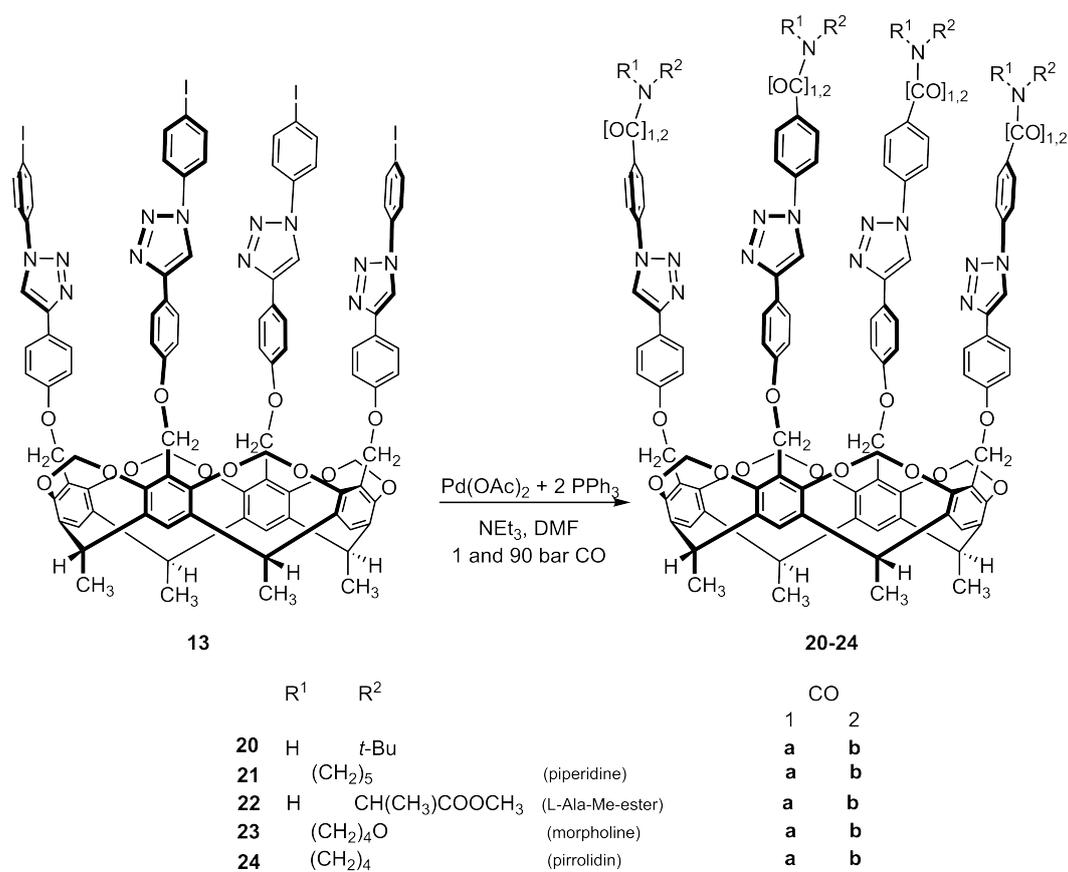


Figure 6: Aminocarbonylation on elongated tetraiodo-cavitand scaffold

of styrene. The rhodium-catalyzed reactions showed 100% chemoselectivity and about 90% regioselectivity toward the branched product (**26a**). In the case of platinum cat-

alysts the chemoselectivities showed moderate values, furthermore, the linear aldehyde (**26b**) was the favourable product. Hydrogenation process was carried out on **25** with platinum-catalyst which resulted in the reduced product (**26c**) with 100% conversion and chemoselectivity.

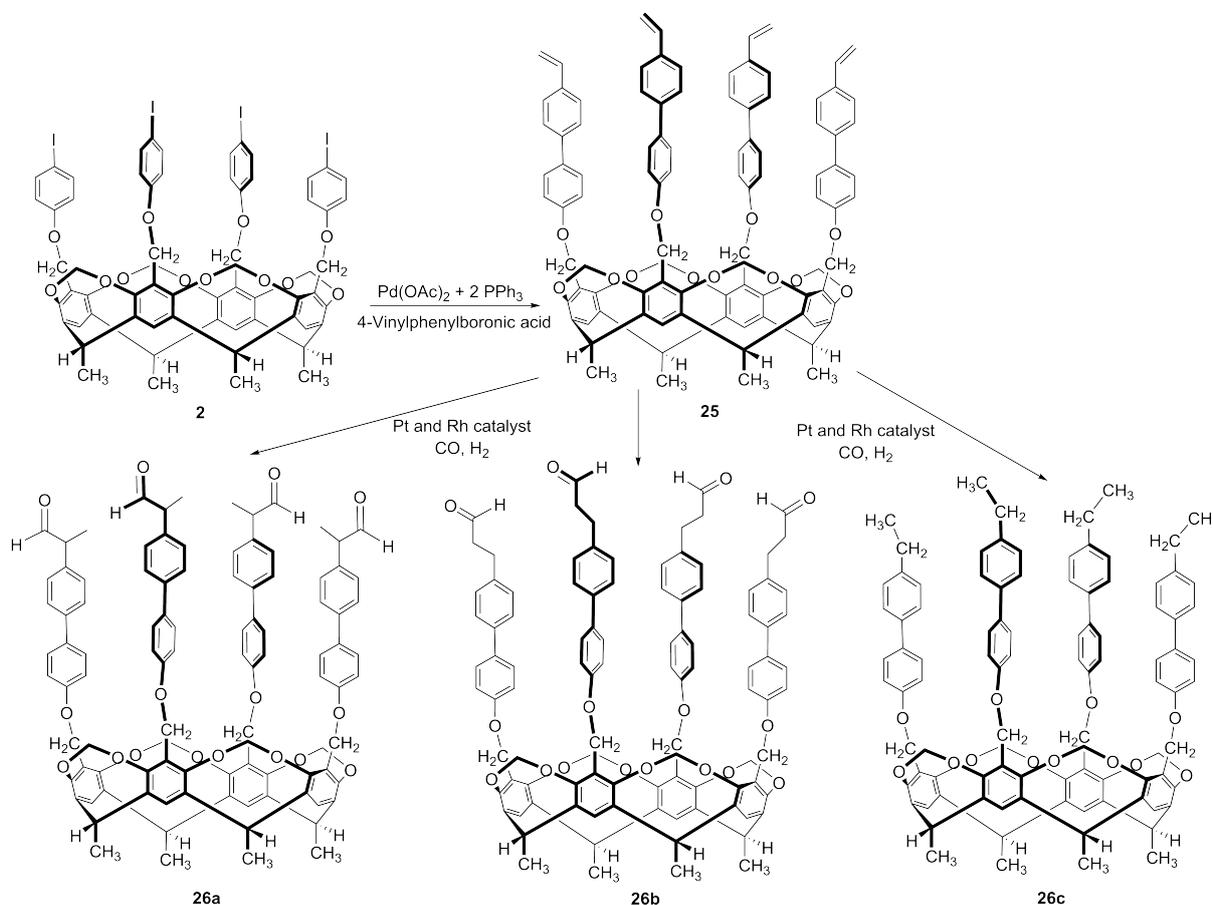


Figure 7: Hydroformylation on deepend cavitand scaffold

- Azidocarbonylation reaction was accomplished on **2** in the presence of palladium catalyst (Figure 8). At 50°C the conversion and the chemoselectivity was 100% toward the amido-derivative (**27**). The aroyl-derivative (**28**) has been formed only at room temperature with 60% conversion.

5 Theses

- Two novel cavitands were synthesized via nucleophilic substitution reactions, a cavitand bearing four cyclopentadienyl groups and an *ansa*-ferrocene compound. Theoretical study was carried out on the latter and it has been found that the geometry has strong influence on the charge of the iron central atom, hence the iron atom of *ansa*-ferrocene cavitand is more positive than those of ferrocene complexes. Moreover, it has been shown that the Fe–C bond strengths of *ansa*-ferrocene cavitand are very similar than those of *ansa*-ferrocene complexes.

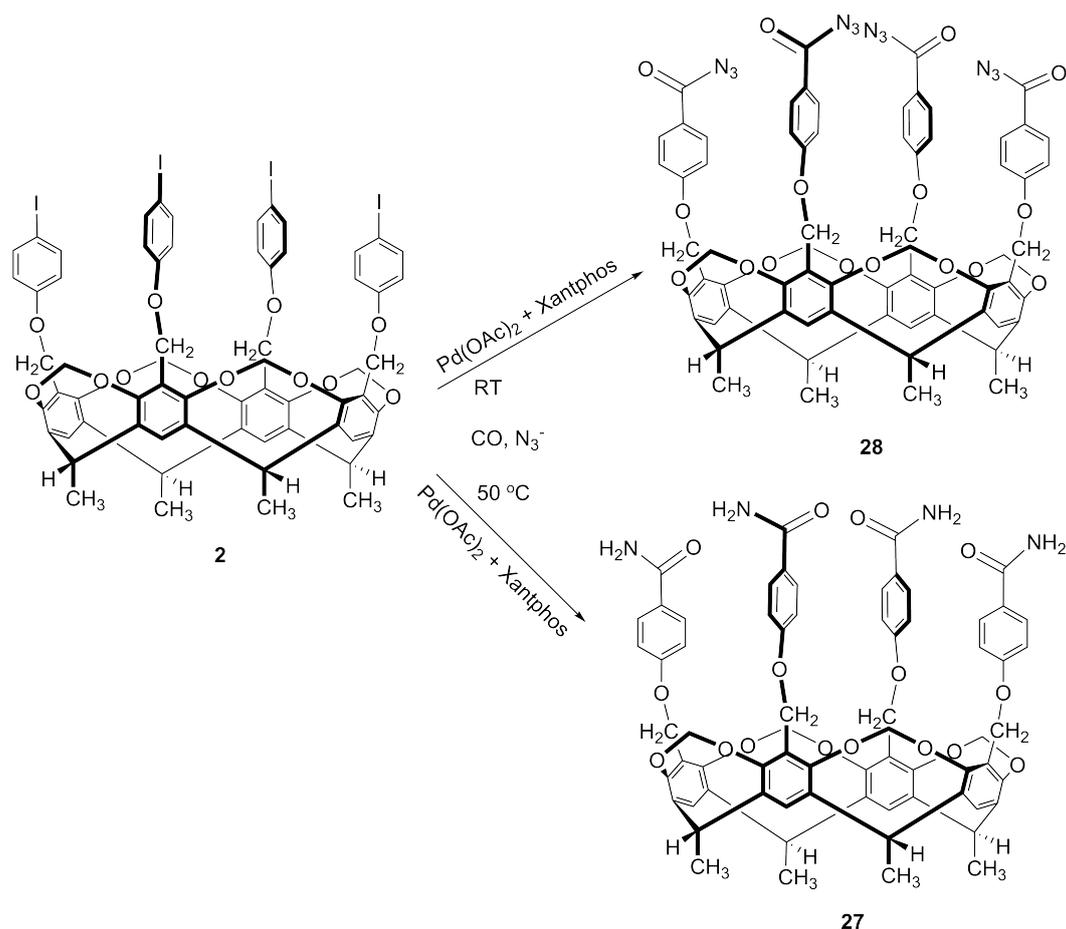


Figure 8: Azidocarbonylation on tetraiodo-cavitand scaffold

- Four triazole ring containing cavitands were synthesized via azide-alkyne cycloaddition started from tetraazido-cavitand. Multistep theoretical study was performed on these novel compounds and it has been found that these cavitands have goblet-shaped C_4 symmetrical structures stabilized with numerous intramolecular interactions. The strongest interactions were related to the triazole rings in all cases.
- Two elongated cavitands, bearing tetraethynyl and tetraferrocenyl groups, were prepared via Sonogashira coupling started from tetraiodo-cavitand. Tetraethynyl-cavitand was used as starting material in reverse azide-alkyne cycloaddition and seven more deepend triazole ring containing compounds were synthesized. Theoretical study was carried out on the cavitands decorated with different pyridazine groups and it has been shown that significant conformational change can be established by the effect of high-energy UV photon. Furthermore, it has been found that the molecular orbitals are moderately delocalized and that cavitands bearing substituted pyridazine rings are more polarizable and show softer character than the intermediates.
- Aminocarbonylation was performed on elongated tetraiodo-cavitand at atmospheric and high pressure with five different amines. It has been proved that at high pressure the formation of tetrakis(ketocarboxamido) derivatives is favoured while at low pressure the tetracarboxamido cavitands are the favourable products. QTAIM analysis and NCI cal-

culations were carried out on six elongated cavitand derivatives and the wavefunction calculations shed light on numerous stabilizing interactions similarly to the smaller triazole ring containing derivatives. Among these interactions the strongest ones were related to the triazole rings (in all cases) and the NH–CO bonds in the case of cavitands possessing amido groups.

5. Hydroformylation process was implemented on deepend tetravinyl-cavitand which was synthesized via Suzuki-Miyaura coupling. The hydroformylation reactions were performed with five different catalysts and it has been found that the rhodium-catalyzed reactions showed 100% chemoselectivity and about 90% regioselectivity toward the branched product. In the case of platinum catalysts the chemoselectivities showed moderate values, furthermore, the linear aldehyde was the favourable product. Hydrogenation process was carried out with platinum-catalyst which resulted in the reduced product with 100% conversion and chemoselectivity.
6. Azidocarbonylation reaction was accomplished on tetraiodo-cavitand in the presence of palladium catalyst which resulted in two novel cavitand derivatives. At higher temperature the conversion and the chemoselectivity was 100% toward the amido-derivative and at room temperature the aroyl-derivative has been formed with 60% conversion.

6 Publications related to the PhD thesis

Tímea Kégl, György Csekő, Gábor Mikle, Anikó Takátsy, László Kollár, Tamás Kégl
The Role of Weak Interactions in Supramolecular Compounds: A Synthetic and Theoretical Study of Novel Elongated Cavitands
CHEMISTRYSELECT 2:(27) pp. 8337-8345. (2017)

Tibor Zoltán Jánosi, Géza Makkai, Tímea Kégl, Péter Mátyus, László Kollár, Jánor Erostyák
Light-Enhanced Fluorescence of Multi-Level Cavitands Possessing Pyridazine Upper rim
JOURNAL OF FLUORESCENCE 26:(2) pp. 679-688. (2016)

Dániel Filotás, Lívia Nagy, Tímea Kégl, Zsolt Csók, László Kollár, Géza Nagy
Synthesis and Electrochemical Properties of the Tetraferrocenyl-Cavitand in Dimethyl Formamide Solvent Using Platinum and Carbon Working Electrodes
ELECTROANALYSIS 27:(3) pp. 799-807. (2015)

Tímea Kégl, László Kollár, Tamás Kégl
Electronic Structure of Ferrocene-Substituted Cavitands. A QTAIM and NBO Study
JOURNAL OF QUANTUM CHEMISTRY 2014: Paper 521037. 5 p. (2014)

Zsolt Csók, Tímea Kégl, Yin Li, Rita Skoda-Földes, László Kiss, Sándor Kunsági-Máté, Matthew H Todd, László Kollár

Synthesis of elongated cavitands via click reactions and their use as chemosensors

TETRAHEDRON 69:(38) pp. 8186-8190. (2013)

7 Conferences related to the PhD thesis

Kégl Tímea, Skodáné Földes Rita, Kollár László

Tetraferrocenil-kavitand származékok szintézise

MKE 2. Nemzeti Konferencia

Hajdúszoboszló, 2015. augusztus 31. – szeptember 2.

Tímea Kégl, László Kollár, Zsolt Csók

Synthesis of enlarged cavitands and capsules via homogeneous catalysis

17th IUPAC Conference on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 17)

Fort Collins, CO, USA, July 28 – August 1, 2013

8 Other publications

Tímea Kégl, László Kollár, Tamás Kégl

Relationship of QTAIM and NOCV descriptors with tolman's electronic parameter

Advances in Chemistry, vol. 2016, 2016.

Tímea Kégl, László Kollár, Tamás Kégl

DFT study on the oxidative addition of 4-substituted iodobenzenes on Pd (0)- phosphine complexes

Advances in Physical Chemistry, vol. 2015, 2015.

György Csekő, Ying Hu, Yanan Song, Tímea Kégl, Qingyu Gao, Sergei V. Makarov, and Attila K. Horváth

Kinetic evidence of tautomerism of thiourea dioxide in aqueous acidic solutions

European Journal of Inorganic Chemistry, vol. 2014, no. 11, pp. 1875– 1879, 2014.