UNIVERSITA' DEGLI STUDI DI PADOVA

DIPARTIMENTO DI SCIENZE CHIMICHE

CORSO DI LAUREA IN CHIMICA

POST FUNCTIONALISATION OF SELF-ASSEMBLED SUPRAMOLECULAR STRUCTURES.

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Anno Accademico 2020/2021

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1.INTRODUCTION

1.1 SUPRAMOLECOLAR CAGES

Species with well-defined inner void spaces capable of accommodating guests have been an interesting field of research over the last few years. This type of molecules includes different classes of container, with different physicochemical properties and functions. According to IUPAC, a supramolecular cage is a ‘‘polycyclic compound with the shape of a cage’’. [1]

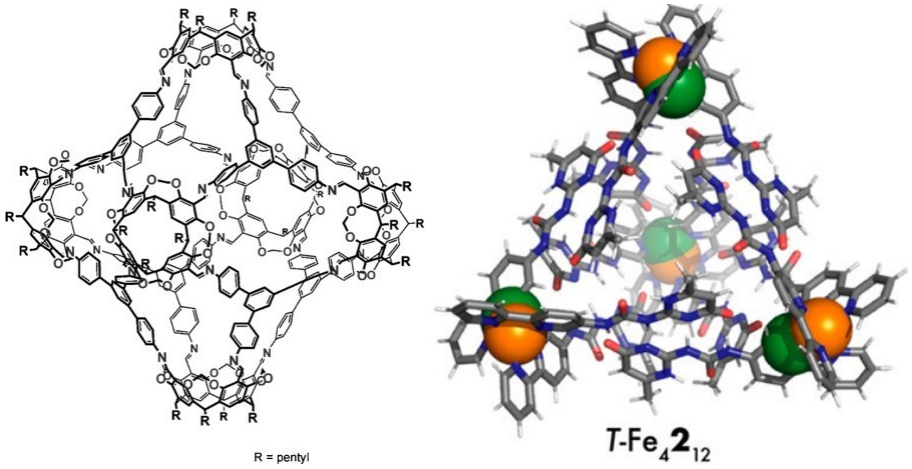


Figure 1: different type of supramolecular cages: using covalent bonds on the left [2] and by hydrogen bonds on the right [3]. Adopted from reference

These shape-persistent macrocycles are characterized by a defined interior, large enough to host other molecules, and are formed by a normal carbon backbone and a structure that does not collapse to a more restricted one. [4]

Examples of these cages can be found in enzymes, where the defined structure is fundamental for the catalytic function of these molecules. The study of synthetic cages has been widely inspired by the one found in nature, with purposes ranging from stabilizing reactive intermediates and running reactions within the cavities to studying recognition events.

Catalytic properties for supramolecular cages can be obtained by using supramolecular coordination chemistry. The host–guest interactions, fundamental in the function of enzymes, can be replicated by taking advantage of functional metal– organic architectures with confined spaces of various sizes and shapes. In particular, supramolecular coordination chemistry has recently

developed into two novel branches: metal–organic cages (MOCs) [5] and metal–organic frameworks (MOFs).[6]

Metal–organic cages can be obtained via self-assembly with an appropriate metal center and ligands containing multiple binding sites oriented in specific geometries. [7]

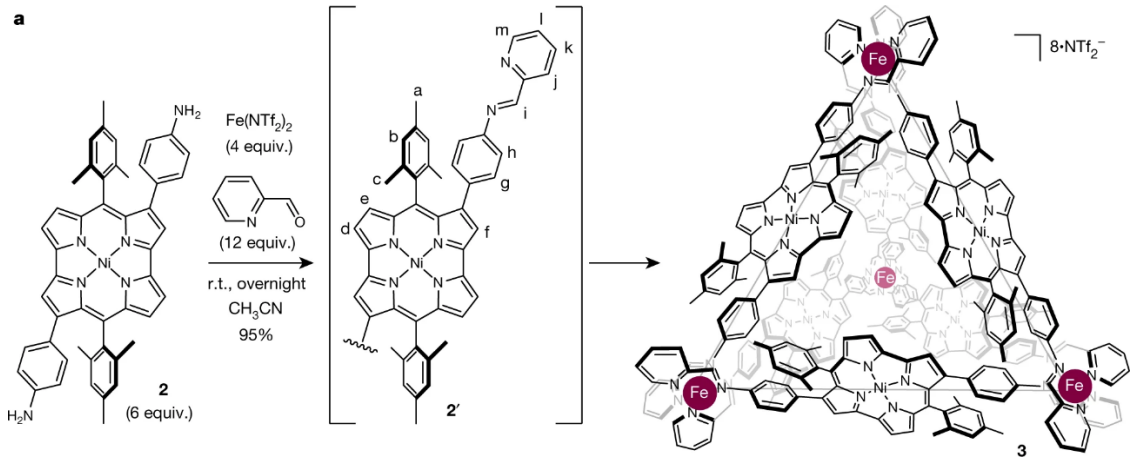


Figure 2: A self-assembled cage composed of four metal ions with six identical aromatic walls. Adapted from reference [7].

Metal–organic frameworks, instead, are extended crystalline networks wherein metal centers or clusters are bridged by multitopic organic linkers. [8]

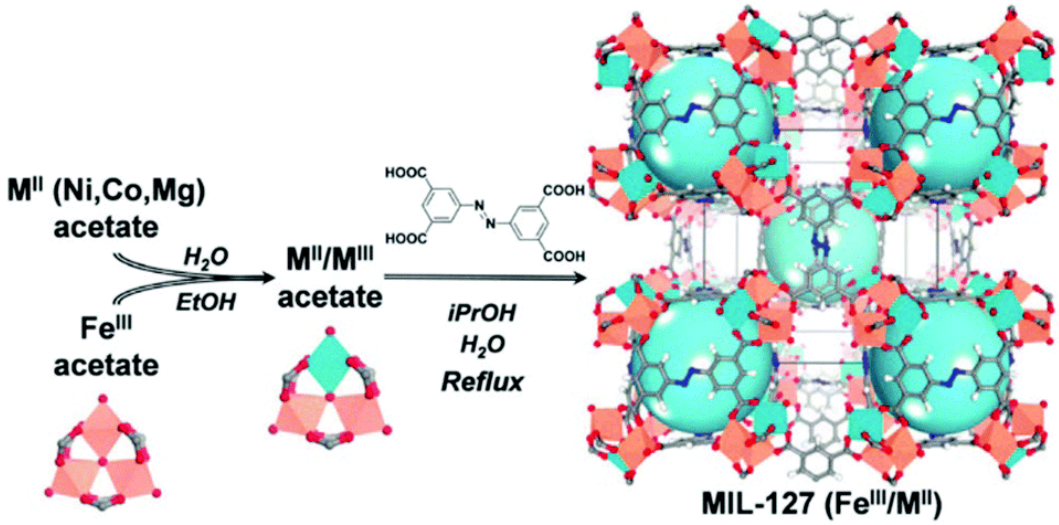


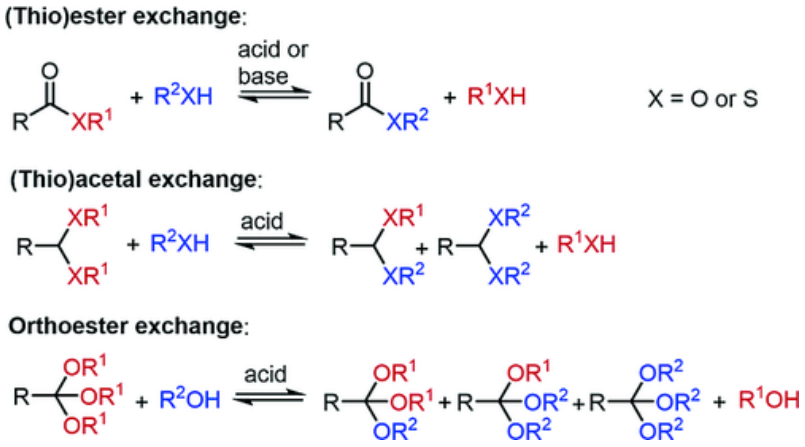
Figure 3: Schematic representation of the SBU approach for the synthesis of mixed-metal MIL-127 materials. Adapted from reference [8]

The difference between the two types of method stands in the formation of discrete structures for MOFs architectures and infinite reticulate structures for MOCs.

1.2 DYNAMIC COVALENT CHEMISTRY

In the synthesis of supramolecular cages, the use of sets of reversible reactions working under equilibrium conditions is preferred to the use of kinetically controlled chemistry, because in such systems the complexity level is similar to the one of the system in exam. The use of kinetically controlled reactions, which results in the formation of the faster forming product over the most thermodynamically favorite, is useful because the irreversibility of such reactions guarantees that the back reaction has no effect on determining the products distribution. In complex systems the presence of multiple reaction paths and side reactions can lower the final product yield.

Examples of reversable reactions commonly used are Michael reaction, Diels-Alder reaction, aldolic condensation and the formation of imine.



Scheme 1: Examples of reversable reactions used in DCC [9]

These groups of reactions are defined by Dynamic Covalent Chemistry, which includes a series of thermodynamically controlled reactions that ensure that once the final equilibrium is reached, the product distribution is based only on their relative stability.

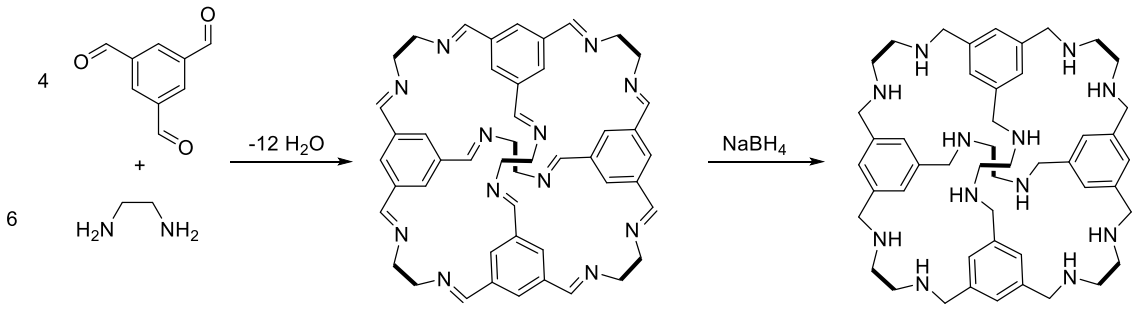
The use of DCC for the synthesis of supramolecular cages is very useful because it can provide the formation of complex architectures in high yields and purity. The dynamic aspect allows the system to divert to the more thermodynamically favorite route, if the reaction take different paths than the one that lead to the formation of the product, as it allows the reaction to go back to the reagent and the product to rearrange its chemical bonds (like rotation-restricted bonds) into the proper manner during the synthetic process.

The low stability of these type of bonds can also cause problems because it can make the molecule much easier to decompose by, for example, nucleophilic attack.

Among all possible choices of reversible reactions, imine bond formation is one of the most used in supramolecular chemistry [10].

1.3 ROBUSTING IMINE BASED CAGES

As mentioned before, most shape-persistent organic cages are synthesized by applying dynamic covalent chemistry (DCC), in particular through imine bond formation. However, the reversibility of imine bond formation can also lead to chemical instability, in particular in the presence of an acid or high amounts of water. The simplest way to stabilize an imine group is to reduce it to an amine group with hydrides. Examples of reduction of imine based supramolecular cages can be found in Cooper's work.[11] The English chemist's work treats the formation and reduction of a small cage with sodium boron hydride.



Scheme 2: Reduction of Cooper's imine cage

The amine function was formed upon reaction with either acetone or formaldehyde, in order to stabilize the structure of the cage with aminoacetals groups.

The acetone-derived structure is unstable and decomposes easily in solution, whereas the formaldehyde-derived aminoacetal cage crystals were stable at room temperature in solutions with pH between 1.7 and 12.3, for at least 12 days. Another example of a very stable amine cage is found in Mastalerz work. He reported a cage which is stable in concentrated hydrochloric acid (pH = -1), in 1 M aqueous NaOH (pH = 14), and at 100°C.[12] Even in this example, the $NaBH_4$ is used as reducing agent.

1.4 TPMA CAGES

A new type of supramolecular cage has been developed in the research group in which the thesis has been carried out. The idea at the bottom of this cage is the use of TPMA(tris(2-pyridyl)methylamine) as a precursor. The synthesis process exploits the use of dynamic covalent chemistry, whose benefits were previously discussed in this work. The cage was synthesized using an imine condensation between a TPMA-zinc complex, functionalized with three aldehyde groups and diamine molecules.

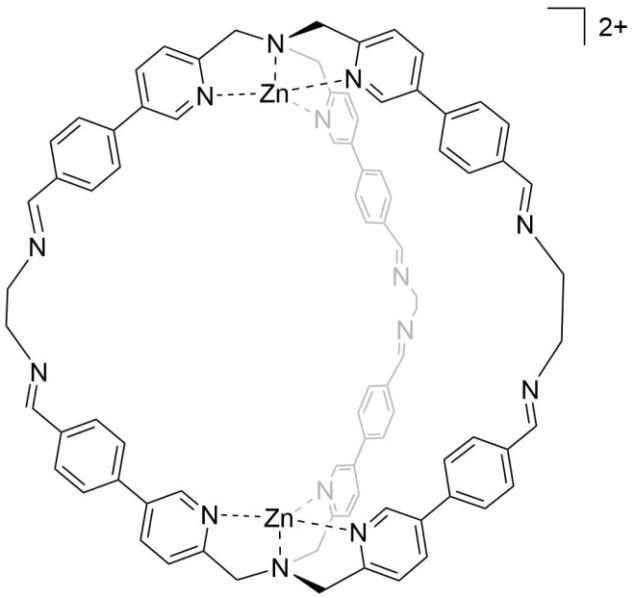
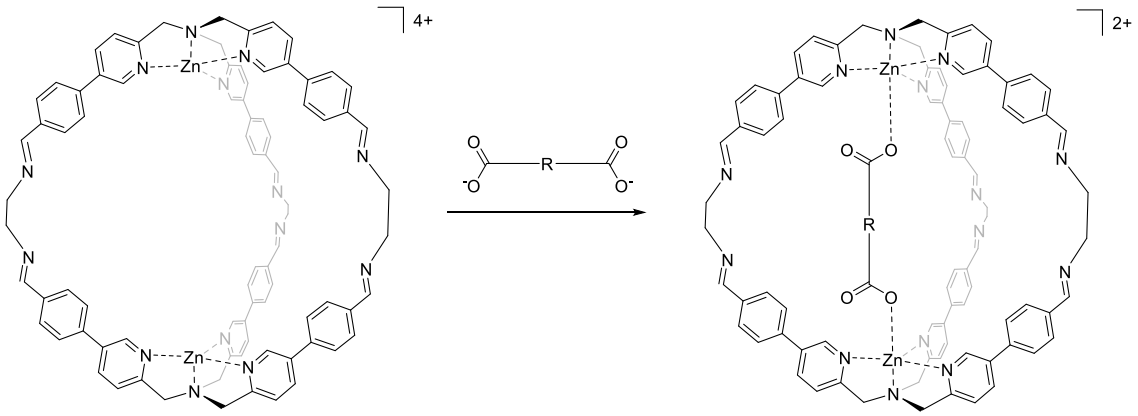


Figure 4: TPMA cage using ethylenediamine

1.5 APPLICATIONS OF THE TPMA CAGE

One of the main current applications of TPMA-complex cages regards its capability of encapsulate dicarboxylate anion.



Scheme 4: Encapsulation of dicarboxylic acid by TPMA supramolecular cage

The study of the binding constant of these complexes led to interesting results. The constant, in fact, depends both on the length of the dicarboxylic acid added to the solution of the cage and the diamine linker used to close the supramolecular cage.[13] A first study that was carried using only the cage synthetized with ethylenediamine as a linker. The focus of the study is a new set of H-NMR signals that are ascribable to the formation of the acid-cage complex.

The research used a series of dicarboxylic acids of various length, varying from succinic acid (C_4) to tetradecandioic acid (C_{14}), as a guest for the cage. The counterion used for cage salt is perchlorate, since is not able to act as a ligand and thus interfere with the encapsulation of the diacid.

The dependence of the binding constant to the length of the acid is found to be of a pseudo-gaussian type, centered on the C_8 acid.

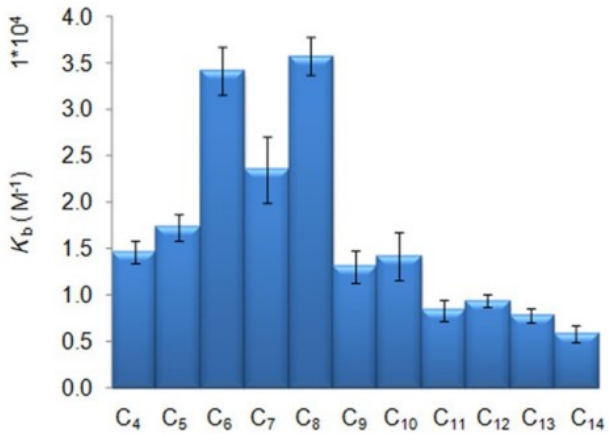


Figure 5: H-NMR binding constants (K2) for the inclusion of diacids C4-C14 in ethylenediamine linked cage

A second study was carried in order to determine the impact of different diamine linkers on the binding constant. In order to be able to gather more information at once, in this case was used a different method for calculating the rate constants, using a competition mechanism.

Instead of using H-NMR spectra, the cage in exam was put into a solution containing equal concentrations of the dicarboxylic acids. The use of ESI-MS allows the calculus of the relative ratio of the constant of all the acids at once, since the different complexes have different molecular mass.

It is possible to conclude that with the use of longer diamine linkers the pseudo-gaussian shift towards heavier dicarboxylic acids, as expected since the distance between the two coordination centers became wider. The selectivity of this confined space systems towards the complexation of diacids, depends largely on the chain length of the included guests.

Furthermore, more flexible linkers leads to a wider distribution of the preferential guests.

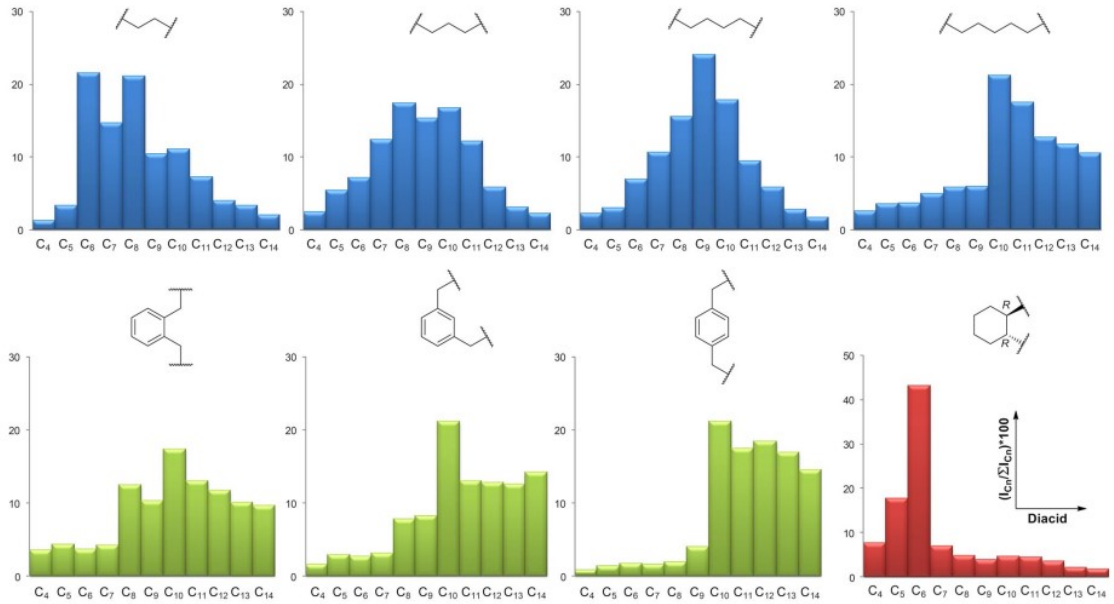
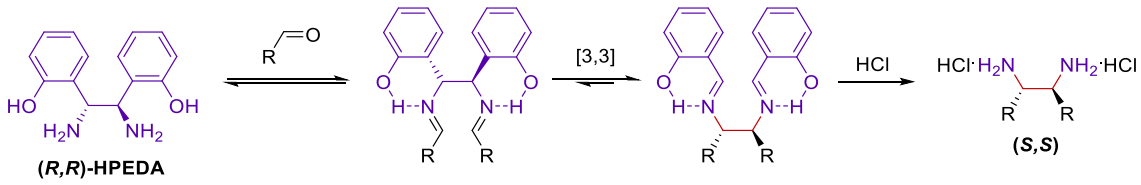


Figure 6:ESI-MS selectivity profiles for the different amine linkers.

1.6 DIAZA-COPE REARRANGEMENT

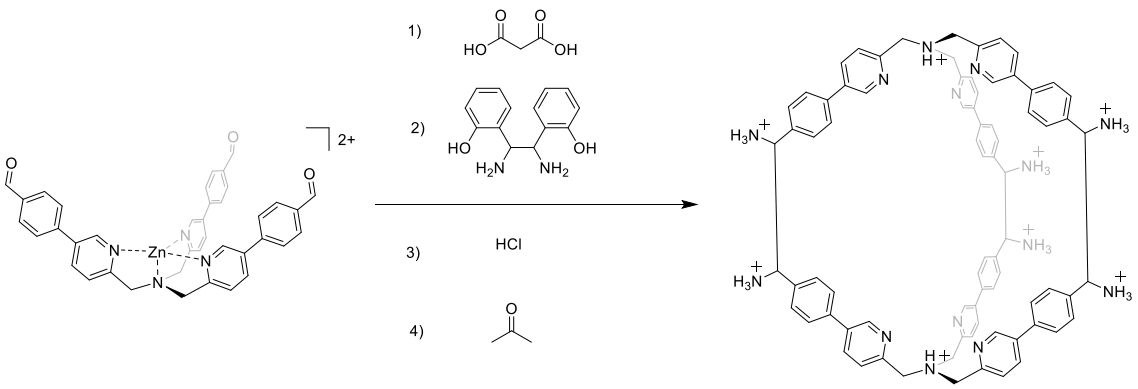
The presence of high amounts of water or an acid in the solution of the cage could lead to the hydrolysis of the iminic bond , thus limiting the possible use of imine-based supramolecular systems in water solution, thus reducing his usage for

molecular recognition and catalysis. The immediate way to stabilize the iminic bond, as explained before, is to reduce it to the corresponding amine with $NaBH_4$ or $NaBH(OAc)_3$. Initial attempts have been made using these reducing agents with the TPMA cage, but low conversion rates and difficulties to separate the product from the solution made it necessary to adopt a different strategy. The solution that was embraced is based on a [3,3]-sigmatropic rearrangement. Sigmatropic rearrangements are a powerful tool for the stereoselective formation of C-C bonds, widely used in organic chemistry synthesis. The focus was put on the Diaza-Cope rearrangement, which has largely been used in the formation of chiral enantiopure diamines.[14] In the afore-mentioned paper, the rearrangement allow to form a C-C bond stereospecifically, by starting from enantiopure 1,2-Bis(2-Hydroxyphenyl)ethylenediamine (R,R)-HPEDA and an aldehyde. The driving force of this reaction is the formation of a strong resonance-assisted hydrogen bond (RAHB) that shifts the equilibrium of the reaction towards the rearranged product that is released after hydrolysis.[15]



Scheme 3: Diaza-Cope rearrangement

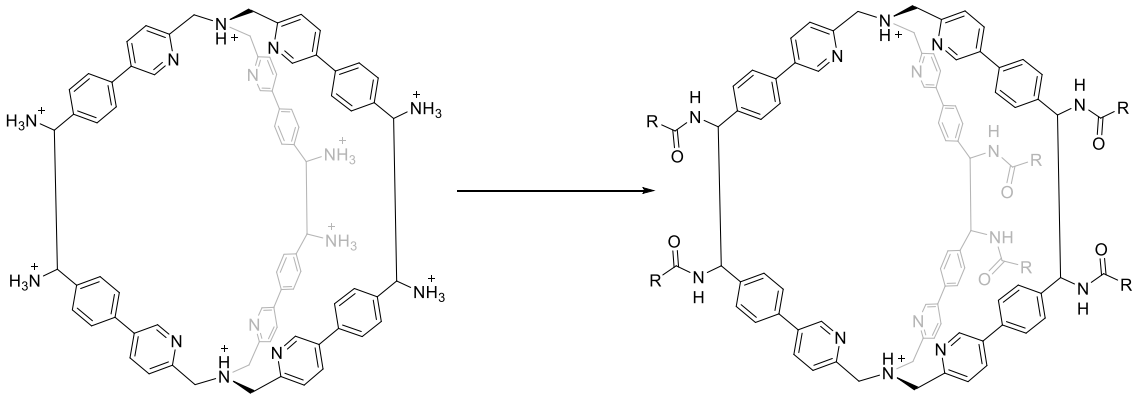
The TPMA cage was then synthetized by using (R,R)-HPEDA as a diamine linker and malonic acid as a ligand guest to facilitate the formation of the cage itself. Since the acid used was a dicarboxylic acid, it has been capable of coordinating the two metals of the two TPMA complexes needed to form the supramolecular cage. Malonic acid was preferred over heavier dicarboxylic acid because it can provide a complete rearrangement of the cage. Evidence of this can be found in the NMR spectra of the cages synthesized with different acids. The peaks in the cage synthesized with the malonic acid were sharper and more defined. HCl 37% was added to the solution of the synthetized cage to hydrolyze the imine bonds of the rearranged product. The addition of acetone led to the isolation of the ammonium salt of the cage in both high yield (> 80%) and purity. The addition of HCl also caused the decomplexation of the cage.



Scheme 4: Application of the Diaza-Cope rearrangement for the TPMA cage

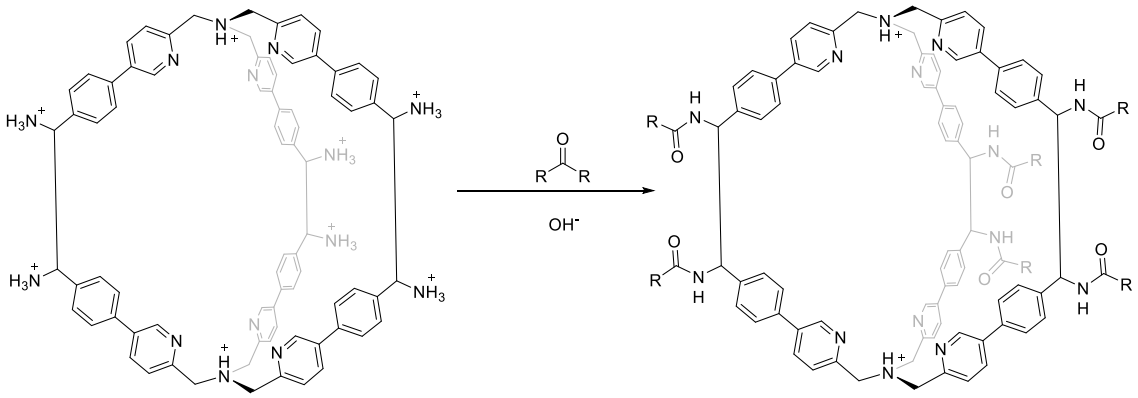
2 AIM OF THE THESIS

The TPMA cage that is formed using HPEDA and the Diaza-Cope rearrangement is very soluble in water. This is caused by the protonation of the amine groups, which happens in the last step of the synthesis. The protonation cause the formation of a formal +8 charge on the cage, witch result in a very polar molecule. The possibility of using such a complex molecule in polar solution can lead to interesting uses, but the downsides are a lack of solubility in almost every organic solvent and it makes much harder to purify the compound via column chromatography, since the affinity of the compound with the silica.
The aim of this thesis is to try to functionalize the TPMA aminic groups after its formation via formation of amides, in order to obtain a less polar molecule.



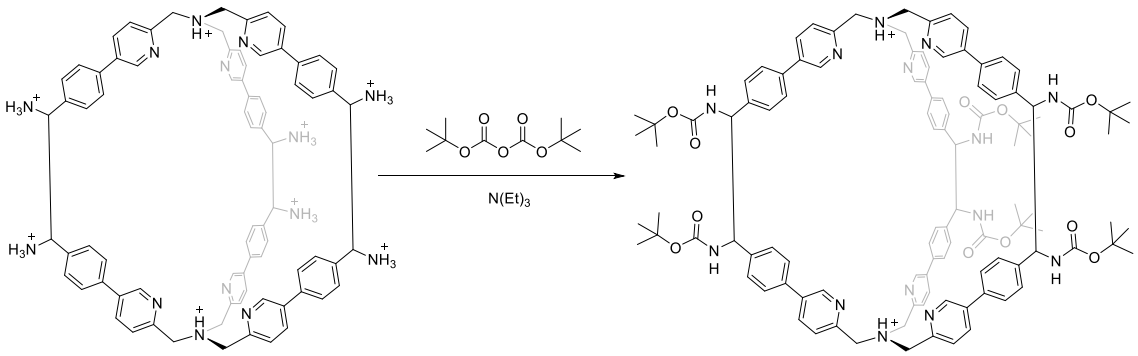
3 RESULTS AND DISCUSSION

The more straight forward way to functionalize an aminic group is to make it react with a carbonylic group, such as an anhydride, in order to form an amide.



For this reason the first attempts to the functionalization of the cage have been made using acetic anhydride and Di-*tert*-butyl dicarbonate (Boc_2O).

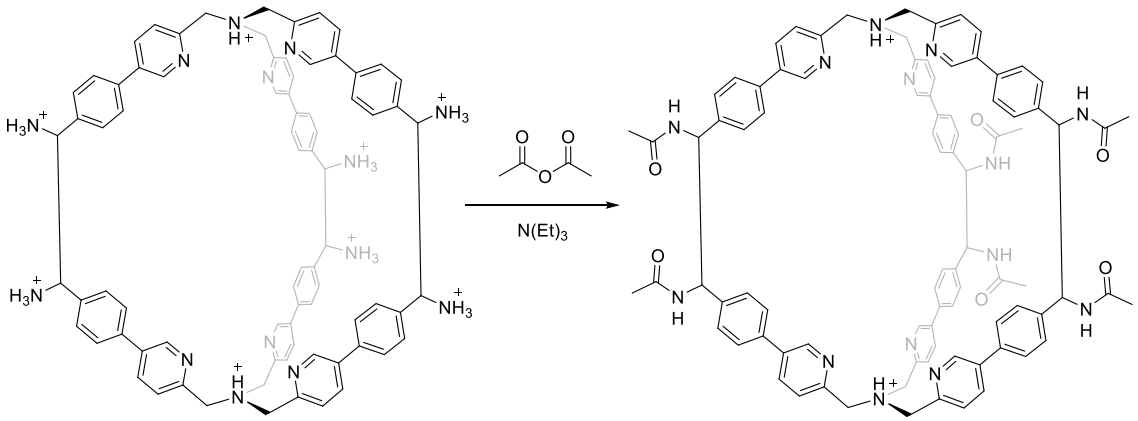
3.1 AMIDATION WITH Boc_2O



Since the cage was protonated and present as a salt with chloride as counter ion, Triethylamine ($N(Et)_3$) was used as a base. The reaction was carried out using dichloromethane .

Unfortunately, after analyzing the NMR spectrum, which shows no presence of the cage, it was possible to conclude that the reaction didn't occur. The reason may be found in the difficulty for the cage to dissolve and deprotonate in such solvent.

3.2 AMIDATION WITH ACETIC ANHYDRIDE



Given the bad results obtained with Boc_2O, attempts were made using acetic anhydride. The first two reactions were carried out using water as a solvent and without the use of any solvent (neat reaction).

The use of a polar solvent, such water, should increase the reactivity of the cage, since the ionic form in which is present should be more soluble in such medium.

Even in this attempts, though, the results were negative.

There was no sign of the functionalized cage in the H-NMR spectra that were recorded.

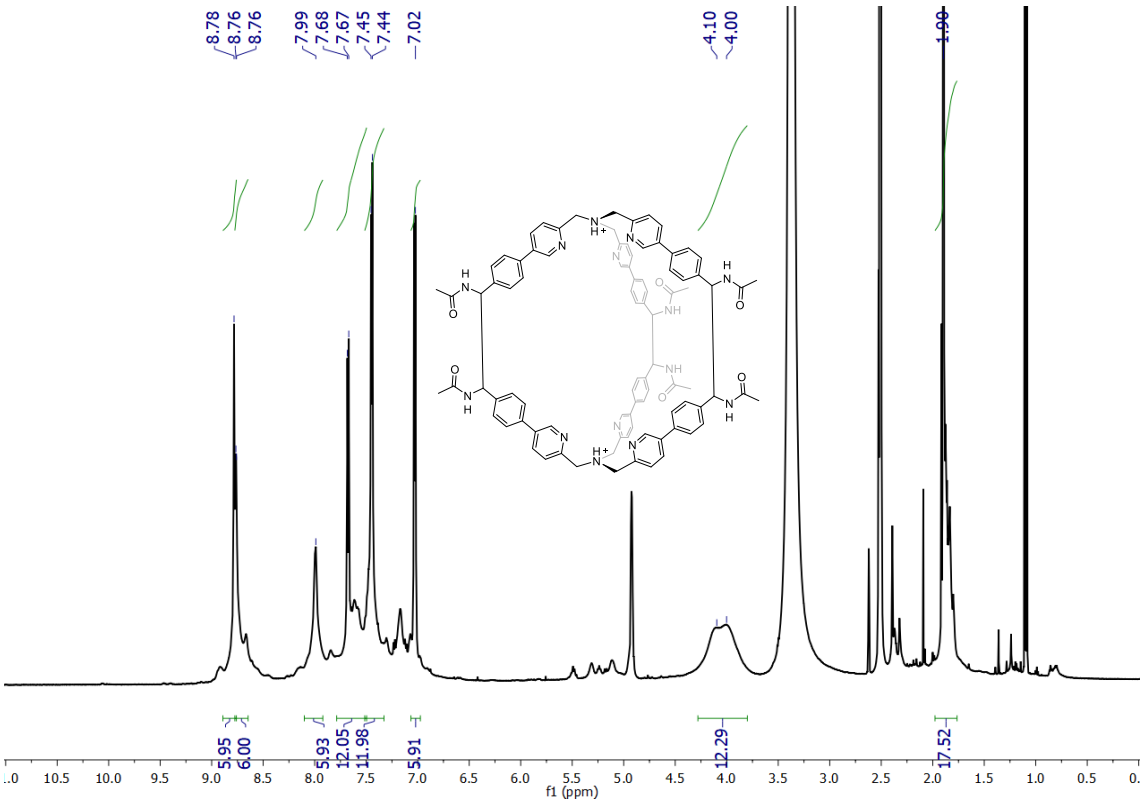
3.2.1 USE OF PYRIDINE AS A SOLVENT

Since the previous attempts' results were negative, the focus of this research shifted to found a solvent in which the reaction could took place. The first solvents that were tested were dimethylformamide and pyridine. While dimethylformamide didn't bring any interesting result, pyridine was a much more promising choice. It is, in fact, a solvent which is capable of both dissolve partially the cage and deprotonate it, given its basic nature.

The use of pyridine was successful, in fact the functionalized cage was successfully synthetized. The high reactivity found in this particular case can be caused by an active role of the solvent in the reaction as a catalyst.

This was only been hypothesized and was not proven by any experiment. More data will be collect in the future in order to test this guess.

3.2.3 ANALYSIS OF H-NMR SPECTRUM



Spectrum 2: H-NMR (600 MHz, $CDCl_3$) for the supramolecular cage functionalized with acetic anhydride

The H-NMR analysis of the product identifies it as the desired molecule. The presence of many subproducts, however, make it harder to analyze.

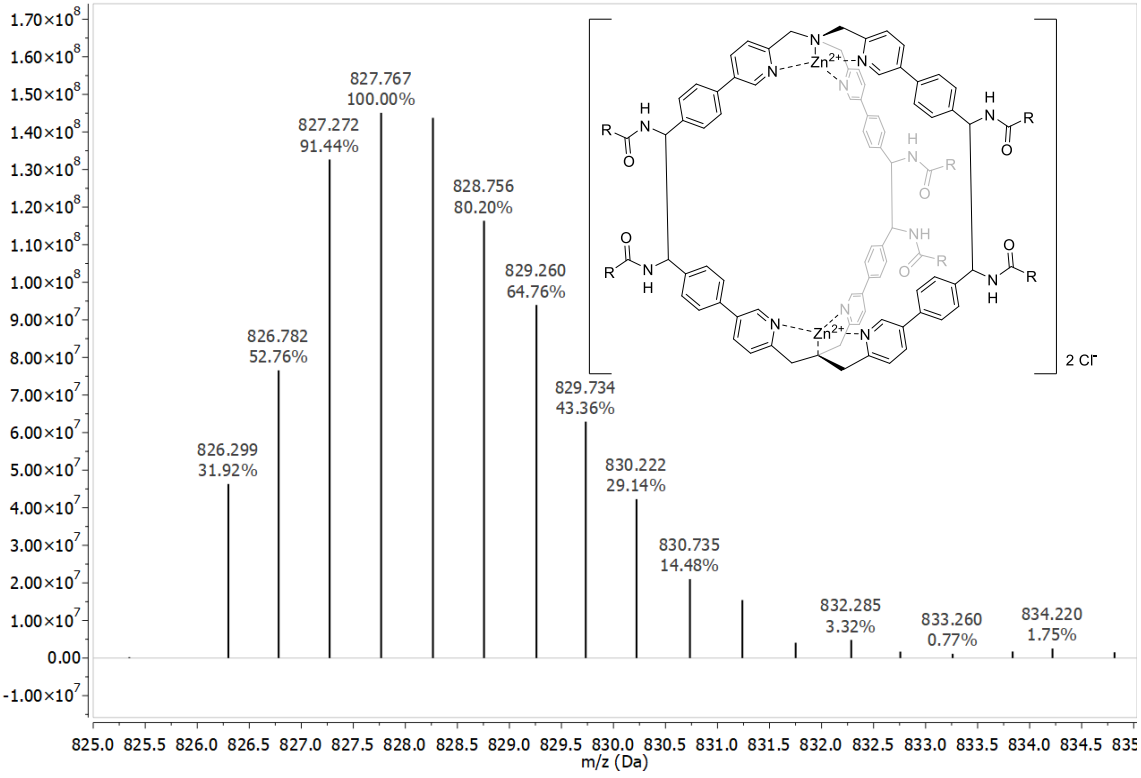
The main differences compared to the one of the reagent are the presence of an 18 proton singlet peak, situated at 1.90 ppm, ascribable to the methyl group that was added to the cage, and the peak at 8.78 ppm, assignable to the amidic group.

The low purity of the product is something to improve on, and future research works will be carried in order to archive such goal.

3.2.2 ANALYSIS OF ESI-MS SPECTRUM

The product was finally analyzed using ESI-MS technique.

The initial attempt of analysis did not bring any useful result, due to the poor ionization of the cage. For this reason, Zinc Chloride was added in order to obtain the complexation of the cage and lead to the metal-organic structure. In the molecular peak, which is reported in spectrum 3, can be noticed an isotopic pattern that is typical the zinc complex. The distance between the isotopic peaks, which is half of an atomic mass unit, identifies the ion as a double charge ion.



Spectrum 1: ESI-MS molecular peaks identified for the complexed functionalized cage. Cl^- as counterion.

The ESI-MS spectrum confirmed the presence of the cage with six amide groups. No other useful peaks were found in the mass spectrum of the product.

3.3 USE OF OTHER ANHYDRIDES

After the good results obtained using acetic anhydride as functionalizing agent, other experiment were carried using other anhydrides.

The use of bigger anhydrides, in facts, would improve the solubility of the cage in apolar solvents, since the aliphatic chains of the molecule force the molecules apart one from another, thus reducing the strength of the ionic interactions.

The reaction was tested using stearic anhydride, esanoic anhydride, that was synthetized starting from esanoic acid, and benzoyl chloride, using the same operative condition as from the successful reaction with acetic anhydride.

The reaction using stearic anhydride didn’t led to any useful result since the anhydride wasn’t soluble in pyridine.

Unfortunately, the NMR analysis of the products of the other reactions showed no results too. The cage didn’t react in these condition.

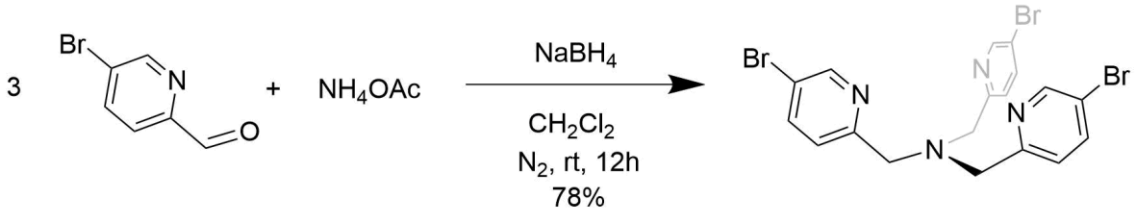
4 EXPERIMENTAL SECTION

4.1 GENERAL METHODS

NMR spectra were recorded at 301 K in Bruker Avance 300 MHz instruments. The NMR data were processed using Bruker Topspin 3.5 pl2 and MestReNova 12.0.2. Low resolution electrospray ionization mass spectrometry LRMS (ESI-MS) experiments ESI-MS spectra have been acquired with an Agilent Technology LC/MSD Trap SL, interfaced to an Agilent 1100 binary pump. The samples were preventively diluted in acetonitrile and then injected via direct infusion with a syringe pump at a rate of 0.3 ml/min. The following settings have been used: Nebulizer = 15 psi, Dry gas = 5 L/min, Dry Temp = 325°C. Detector potential = 2500 volts. The ESI-MS data were processed using MestReNova 10.0.2. Chemicals were purchased from Aldrich, TCI or Arcos and used without further purification.

4.2 SYNTHESIS OF TPMA CAGE

4.2.1 SYNTHESIS OF TRIS(5-BROMOPYRIDIL)-METHYLAMINE

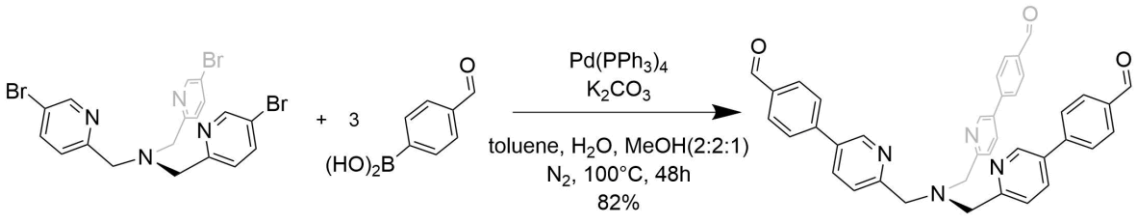


In a 250 ml double neck flask, anhydrous NH_4OAc (1.38 g, 17.9 mmol) and 5-bromo-2-pyridinecarboxaldehyde (10.00 g, 53.7 mmol) were dissolved in dry CH_2Cl_2 (170 mL) under N_2 and left under stirring for 1 hour. Three aliquots of $NaBH(OAc)_3$ (3.80 g, 17.9 mmol) were added waiting one hour between each addition. After that the reaction was stirred for 12 hours at room temperature. The solvent was removed under reduced pressure. The resulting white solid was dissolved in AcOEt and the solution extracted with 0.1 M solution of KOH (3x100 ml). The organic phases were dried on anhydrous MgSO4 and the solvent was

removed under reduced pressure. The resulting solid was precipitated by crystallization from THF/hexane to yield a white solid (7.43 g, 79%).

1H NMR (200 MHz, CDCl3) δ (ppm): 8.60 (d, 3H, J = 2.0 Hz, ArH), 7.78 (dd, 3H, J = 2.0 Hz, J = 8.0 Hz, ArH), 7.41 (d, 3H, J = 8.0 Hz, ArH), 3.81 (s, 6H, CH2).

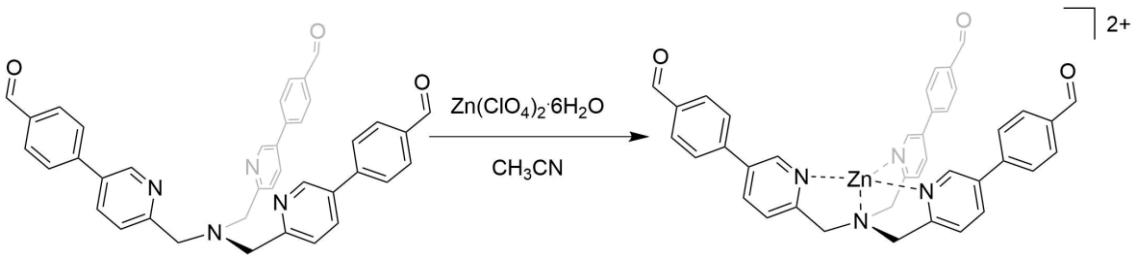
4.2.2 SYNTHESIS OF THE LIGAND



In a Schlenk apparatus a mixture of tris(5-bromopyridil)-methylamine previously synthetized (3.00 g, 5.69 mmol), 4-formylphenylboronic acid (3.84 g, 25.6 mmol), $Pd(PPh_3)_4$ (65 mg, 0,0057 mmol, 1 mol%) and K_2CO_3 (5.51 g, 39.8 mmol) was dissolved in 60 ml of H_2O/toluene/CH_3OH (1:1:0.5). The mixture was stirred under N_2 for 48 hours at 100°C. The solvent was removed under reduced pressure. The resulting yellow oil was dissolved in $CHCl_3$ and the solution extracted with H_2O (3x50 mL). The organic phases were dried on anhydrous $MgSO_4$, filtered on celite and then the solvent was removed under reduced pressure. The resulting solid was precipitated by crystallization from THF/hexane to yield a pale yellow solid (2.89 g, 82%).

1H NMR (200 MHz, CDCl3) δ (ppm): 10.11 (s, 3H, CHO), 8.89 (d, 3H, J = 2.0 Hz, PyrH), 8.02 (dd, 3H, J = 8.0 Hz, J= 2.0 Hz, PyrH), 7.97 (d, 6H, J = 8.25 Hz, ArH), 7.83 (d, 6H, J = 8.25 Hz, ArH), 7.72 (d, 3H, J = 8.0 Hz, PyrH), 4.09 (s, 6H, CH2).

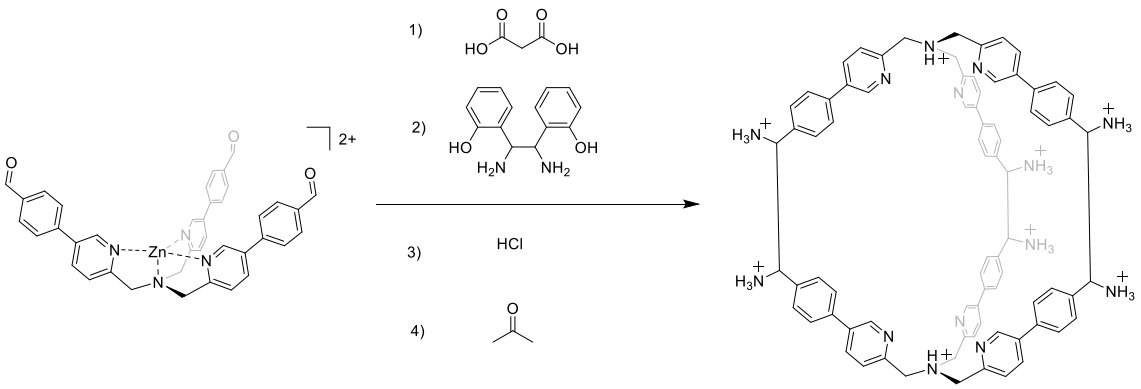
4.2.3 SYNTHESIS OF THE COMPLEX TPMA-Zn



To a suspension of the ligand (100 mg, 0.17 mmol) in acetonitrile (15 ml), was added zinc (II) perchlorate hexahydrate (40.5 mg, 0.17 mmol). The solution was stirred at room temperature for 1 hour. At the end of the reaction diethyl ether (25 ml) was added obtaining quantitatively a crystalline solid, then centrifuged and dried. The complex results as a pale yellow solid (128 mg, 90%).

1H NMR (300 MHz, CD3CN) δ (ppm): 10.09 (s, 3H, CHO), 8.82 (d, 3H, J= 2.0 Hz, PyrH), 8.44 (dd, 3H, J=8.0 Hz, J=2.0 Hz PyrH), 8.07 (d, 6H, J=8.0 Hz, ArH), 7.94 (d, 6H, J=8.0 Hz, ArH), 7.75 (d, 3H, J=8.0 Hz, PyrH), 4.40 (s, 6H,CH2).

4.2.4 SYNTHESIS OF THE TPMA CAGE

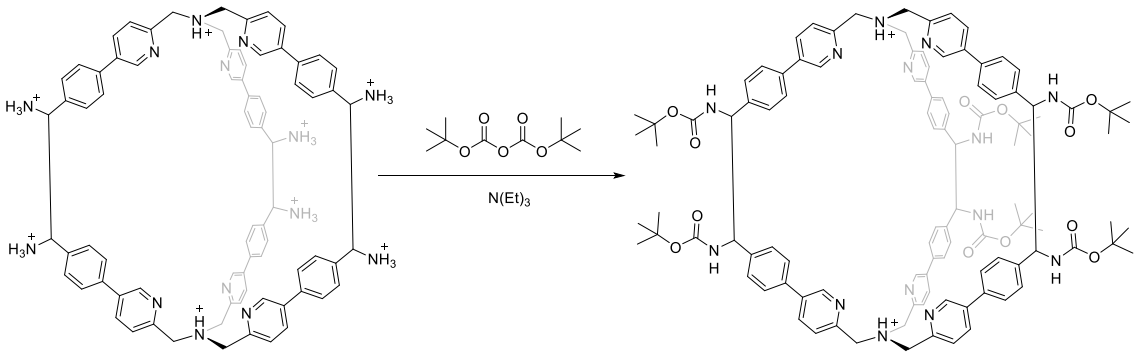


To 30 ml (60 µmol) of a solution 0.002 M of the TPMA complex in CH_3CN were added 3 ml (30 µmol) of a solution 0.01 M of malonic acid in CH_3CN and 7.5 ml (150 µmol) of a solution 0.02 M of 1,2-diphenylethylenediamine in CH_3CN/DMSO. The mixture was left reacting for 12 hours at room temperature. After having removed CH_3CN by evaporation, the product, still dissolved in DMSO, was treated with 3 ml of concentrated HCl 37% and stirred for 1 hour. Then, 50 mL of acetone were added to the solution, leading to the quantitative precipitation of a crystalline solid, which was subsequently centrifuged, dried and checked via H-NMR. The product results as a pale yellow solid (80.8 mg, 90% yield).

1H-NMR (400 MHz, D_2O) δ (ppm): 8.74 (d, J = 2.2 Hz, 6H, PyrH), 8.28 (dd, J = 8.3, 2.2 Hz, 6H, PyrH), 7.72 (d, J = 8.3 Hz, 6H, PyrH), 7.49 (d, J = 8.1 Hz, 12H, ArH), 7.38 (d, J = 8.1 Hz, 12H, ArH), 5.26 (s, 12H, CH_2 ammine TPMA), 4.40 – 4.22 (m, 12H, CH_2 TPMA)

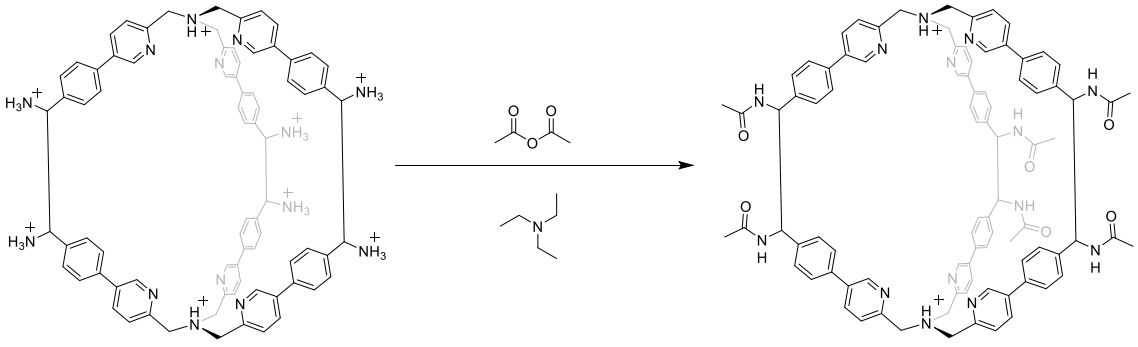
4.3 FUNCTIONALIZATION OF THE CAGE

4.3.1 AMIDATION WITH Boc_2O



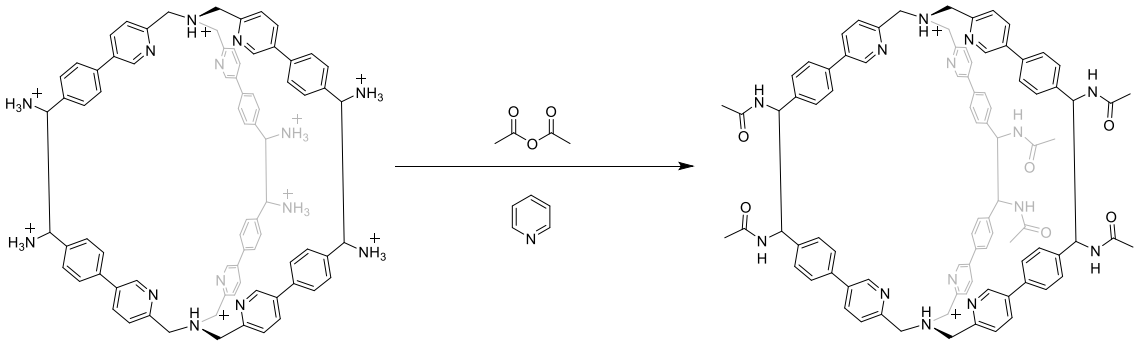
10 μg of the TPMA cage were mixed with 10 μL of triethylamine and 10 μL of Boc_2O in 3 ml of dichloromethane. The reaction was left stirring at room temperature for 12 hours. The solvent was removed under reduced pressure. The reaction was checked via NMR but the result was negative.

4.3.2 AMIDATION WITH ACETIC ANHYDRIDE (NEAT)



10 μg of the TPMA cage were mixed with 10 μL of triethylamine and three drops of acetic anhydride without the use of any solvent. The reaction was left stirring at room temperature for 12 hours. The product was isolated by adding water to the solution and via extraction with ethyl acetate. The reaction was checked via NMR but the result was negative.

4.3.3 AMIDATION WITH ACETIC ANHYDRIDE IN PYRIDINE



10 μg of the TPMA cage were mixed with 1,5 ml of pyridine. After the formation of a suspension the solution was put into a water/ice cooling bath and were added 1 ml of acetic anhydride to the solution (in large excess). The reaction was left stirring for 12 hours.

With the addition of acetonitrile was noted the formation of a pale yellow precipitate. The product was purified via centrifugation with three aliquotes of acetonitrile and three aliquotes of diethyl ether. The product was checked via H-NMR and ESI-MS.

(ESI-MS) (m/z): calculated for $[C_{90}H_{87}N_{14}O_6Zn_2+2ClO_4^-]^{2+}$ = 829.3; found = 827.8.

1H-NMR (600 MHz, CD_3Cl) δ (ppm): 8.78 (s, 6H, NH), 8.76 (d, 2.2 Hz, 6H, PyrH), 7.99 (s, 6H, PyrH), 7.68 (d, J = 8.1 Hz, 12H, ArH), 7.45 (d, J = 8.1 Hz, 12H, ArH), 7.02 (s, 6H, PyrH), 4.10 (d, 12H, CH_2 TPMA), 1.90 (s, 18H, CH_3)

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