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FACULTY OF CHEMISTRY AND CHEMICAL ENGINEERING ORGANIC

CHEMISTRY DEPARTMENT

Abstract

SYNTHESIS, STRUCTURAL ANALYSIS AND SUPRAMOLECULAR PROPERTIES OF SOME NEW MACROCYCLIC COMPOUNDS WITH HETEROAROMATIC UNITS

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Keywords:
Supramolecular Chemistry, phenothiazine, macrocycles, ESI-HRMS investigation.

1. INTRODUCTION

The concept of ''**Supramolecular Chemistry**'' was defined by Jean-Marie Lehn[1] as ''the chemistry beyond the molecule...the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by the association of two or more chemical species''. Supramolecular chemistry examines weak and reversible non-covalent interactions between molecules such as hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π-π interactions or electrostatic effects.[6,7] Concepts demonstrated by supramolecular chemistry[8] include molecular self-assembly,[9] molecular recognition,[10,11] host-guest chemistry,[12] mechanically interlocked molecular architectures[13] or dynamic covalent chemistry.[14]

Macrocycles are very useful in supramolecular chemistry and they provide whole cavities having different sizes which are able to completely surround gust molecules. Crown ethers are cyclic chemical compounds that consist of a ring containing several ether groups. The most common crown ethers are oligomers of ethylene oxide, the repeating unit being ethyleneoxy.

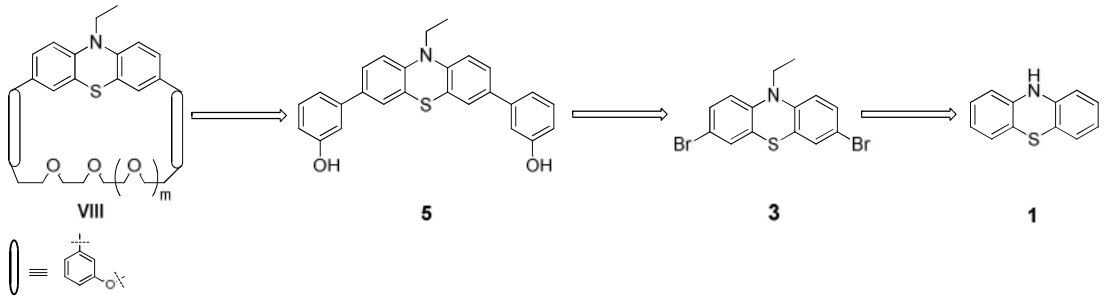
Phenothiazine molecules belong to a pharmaceutically important class of heterocyclic,[24] and due to their pharmacological efficiency can find applications as sedatives, tranquilizers, antiepileptics, antituberculotics, antipyretics, antitumor agents, bactericides and parasticides.[25] Another important aspect for phenothiazines derivatives is represented by their ability to have low reversible first oxidation potentials.[26,27]

As a consequence of the favorable electronic properties of phenothiazines make them suitable to applications as electrophore probes in supramolecular assemblies[32] for PET (**p**hoto-induced **e**lectron **t**ransfer) as sensor studies, and also as electron donor components in electrically conducting charge-transfer composites,[33] polymers,[34] and donor-acceptor arrangements[35] in material science investigations. Moreover, the electrochemical properties of phenotiazine derivatives are responsible for their physiological activities[39] andphenothiazines are also able to cleave DNA upon photochemical induction[40].

The prospect of integrating strongly coupled redox fragments like phenothiazines into conjugated chains could constitute so far a class of redox addressable molecular wires, in particular, for a redox manipulation of single molecules with nanoscopic scanning techniques.[41,42]

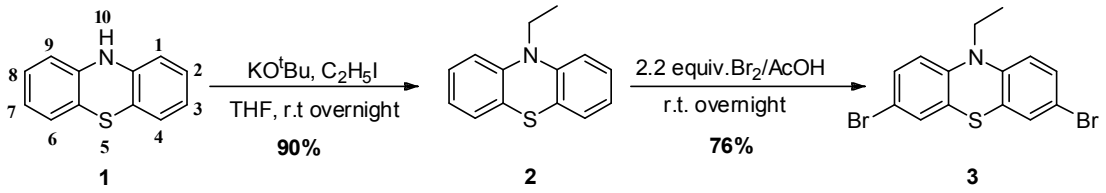
2. RESULTS AND DISCUSSIONS

The first part of the thesis is assigned to the synthesis, structural analysis and complexation studies of the new phenothiazine-coronands with polyethylenoxy chains. The strategy conceived for the synthesis of the macrocycles is illustrated in the scheme below (**Scheme 3**, type **VIII**).



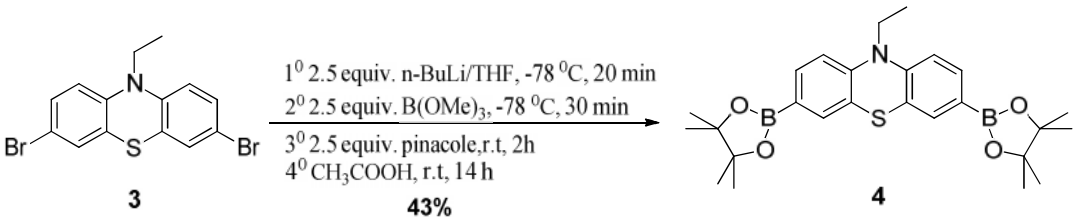
Scheme 3. Retrosynthetic strategy for the synthesis of macrocycles with phenothiazine core.

Thus, we first preformed the protection of NH group of phenothiazine. Compound **2** was obtained in excellent yield by deprotonation of 10*H*-phenothiazine **1** with potassium *tert*-butoxide used as a strong base, followed by the reaction with ethyl iodide (**Scheme 4**).[55]



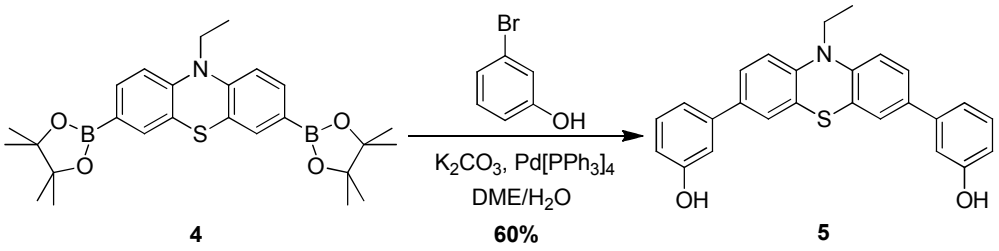
Scheme 4

The structure of compound **2** was confirmed by NMR spectroscopy (^{1}H and ^{13}C) and after purification on column chromatography the intermediate **2** was subjected to bromination reaction using 2.2 equivalents of bromine in acetic acid at room temperature.[56] Following a literature protocol[37b] compound **3** was transformed in one-pot reaction into boronate **4**. Double bromine-lithium exchange, followed by addition of the electrofile trimethylborate and transesterification with pinacol, yields the symmetrical bis-boronate **4** (**Scheme 5**).[57] The phenothiazine pinacolylboronic ester **4** was obtained, after purification, in correct yield (43%), as a white solid.



Scheme 5

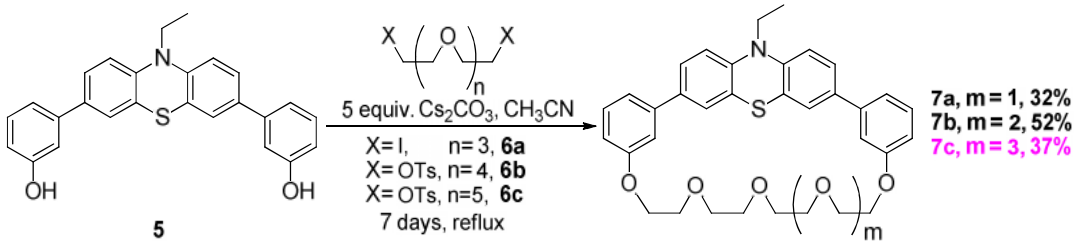
The key building block for our strategy emerging to target macrocycles is the diphenol **5**. With phenothiazine pinacolylboronic ester **4** in our hands, the Suzuki coupling appears to be the right method of choice to obtain **5**.[58] Thus, the boronate **4** was treated with 3-bromophenol in the presence of an excess of potassium carbonate, using DME/water (2:1) as solvents and in presence of catalytic amounts (8 mol %) of palladium (0) tetrakis(triphenylphosphine) (**Scheme 6**).



Scheme 6

2.1. Synthesis of Macrocycles

The compound **5** was subjected to a macrocyclization reaction with diiodurated (**6a**) or ditosylated (**6b-6c**) polyethyleneglycols in acetonitrile using the high dilution technique, and in presence of Cs_2CO_3 to afford macrocycles **7a**, **7b** and **7c** with different cavity sizes (**Scheme 7**)[59]. The ditosylated pentaethylene glycols **6b** and hexaethylene glycols **6c** were prepared by tosylation of the corresponding oligoethylene glycols.[60]



Scheme 7

The structure of the macrocycles **7** was confirmed by mass and NMR spectra and also by the solid state molecular structure measured by single crystal X-ray diffraction for the macrocycle **7b**, with five ethylenoxy units.[61] ^{1}H NMR spectrum of compound **7c** was recorded in CD_2Cl_2 and exhibits the expected signals (**Figure 11**).

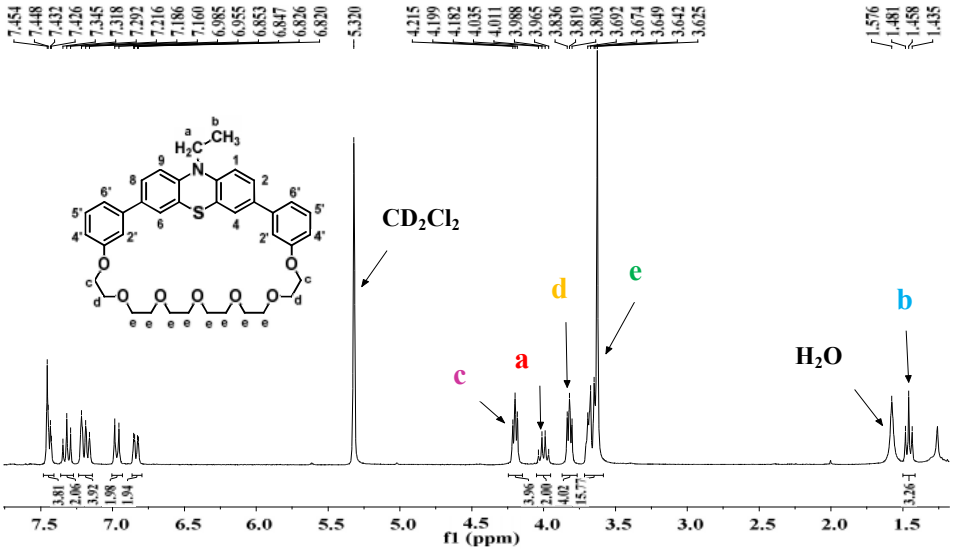


Figure 11. Fragment of ^{1}H-NMR spectrum of **7c** (CD_2Cl_2, 300 MHz, r.t.)

2.2. Complexation with Metal Cations

ESI (+)-HRMS investigations ware preformed in order to determine the affinity of **7a-c** for different alkali cations. A high affinity of **7a** for Li^+, **7b** for Na^+ and **7c** for K^+ was observed, accordingly to the macrocycles size cavity (**Figure 15**). The investigations were performed in acetonitrile solutions containing equimolecular amounts of macrocyclic *host* **7a**, **7b** or **7c** (1.5×10^{-4} M) and a mixture of LiCl, NaSCN, KSCN, Rb_2CO_3, Cs_2CO_3 (1.5×10^{-4} M), as well as samples containing the macrocycles **7a**, **7b** or **7c** and a single *guest* cation: (LiCl, NaSCN, KSCN, Rb_2CO_3, Cs_2CO_3 (1.5×10^{-4} M)).

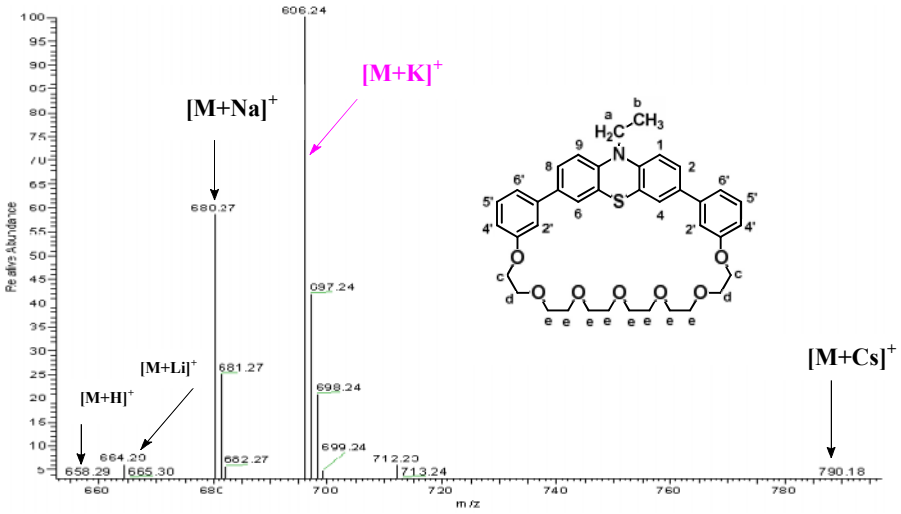


Figure 15. HRMS-ESI(+) spectrum of **7c** + cationic soup

2.3. Electronic Properties of the Macrocycles 7a-c

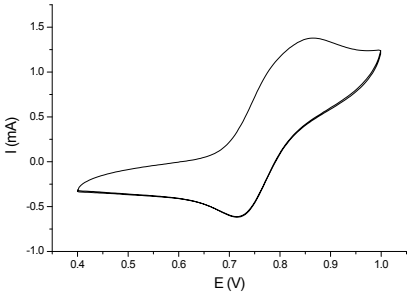
The electronic properties of macrocycles **7a–c** were investigated by UV-Vis spectrometry and cyclic voltammetry. Electrochemical data for the compounds **7a–c** were obtained by cyclic voltammetry at room temperature in the anodic region, and the redox potentials calculated against ferrocene are summarized in **Table 2**.

Table 2. Selected electronic properties of macrocycles**7a–c**

Compd.	Absorption $\lambda_{max, abs}$ (nm)*	$E_0^{0/+1}$ (mV)**
7a	276, 327	824
7b	280, 335	777
7c	280, 333	786

*Adsorbtion spectra were recorded at *r.t.* in CH_2Cl_2
**Cyclic voltammetry measurements were performed in CH_2Cl_2 at *rt*, v = 100 mV/s, electrolyte: $^nBu_4N^+PF_6^-$, Pt working electrode, Pt counter electrode and Ag/AgCl pseudo reference electrode.

Figure 16. Cyclic voltammogram of **7c** in CH_2Cl_2: *rt*, electrolyte= $^nBu_4N^+PF_6^-$, v = 100 mV/s, Pt as a working electrode, Ag/AgCl as a reference electrode, and Pt as a counter-electrode.



The reversible one-electron oxidation potential of phenothiazine derivatives **7a–c** are in the expected regions for the oxidation of phenothiazine derivatives and correspond to the formation of stable phenothiazine radical cations.

In comparison with N-methyl phenothiazine ($E_0^{0/+1}$= 767 mV),[25c] anodic shifts occur in the case of the synthesized macrocycles**7a–c**, probably due to the substitution of the phenothiazine core with the phenyl-ethylenoxy chains.

On the other side an increasing of the $E_0^{0/+1}$ was observed when the chain is either shortened from five to four or it is increased from five to six ethyleneoxy units. The chain with five ethyleneoxy units ensure a less sterically hindered structure of the macrocycle, while the increasing or the diminishing of the number of ethyleneoxide units determine a deformation of the aromatic part of the macrocycles and an increasing of the $E_0^{0/+1}$ values. A similar trend was observed for the variation of λ_{max} (in these cases a diminishing of the λ_{max} values) when the spectra of **7b** one side and of **7a**, **7c** on the other side were compared. The cyclic voltammetry of compound **7c** is represented in (**Figure 16**).

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II. Design, Synthesis and Structural Analysis of New Terpyridine Ligands Decorated with Nitrilotriacetic Acid

Keywords:
*Nitrilotriacetic acid (**NTA**), terpyridines, click chemistry, amide-bonds, His-tagged protein.*

1. INTRODUCTION

Terpyridine (2,2':6',2''-terpyridine or tpy) (**Figure 1**), is a oligoypyridine compound which contains three pyridine units attached by simple covalent bonds. The first parent terpyridine, named at that time tripyridyl, was synthesized in 1930 by G. Morgan and F. H. Burstall.[1] This type of compounds has a rich coordination chemistry due to high binding affinity toward a large variety of transition and rare earth metal cations, giving rise to diverse metallo-supramolecular assemblies with distinct photophysical, photochemical, electrochemical, catalytic and magnetic properties.[2] Due to its capacity to form complexes with different metal ions, terpyridine became a valuable *building block* used in coordinative chemistry.

The synthesis of coordination arrays, supramolecular-level structures of precise nuclearity and defined geometry has been reported.[19-21] These species are ordered inorganic architectures comprising one- or two-dimensional geometries of [m×n] nuclearity and presenting in sequence of increasing complexity basic geometries that may be termed *racks* [n]R, *ladders* [2n]L and *grids* [m×n],[22] where the nuclearity of the R, L, and G species is given by [n], [2n] and [m×n]. This heterocyclic compounds which containing the nitrogen atoms have found applications in: molecular biology,[27,28] photochemistry,[29] polymer science[30] or pharmaceutical research.[31]

Nitrilotriacetic acid (**NTA**) and its derivatives have found broad applications in the manipulation of hexahistidine (His6) tagged proteins such as in affinity chromatography,[32,33] crystallization on lipid template,[34] fluorescent labeling[35,36,37,38] and surface immobilization.[39] Nitrilotriacetic acid (NTA)-coordinated metals, such as Ni(II) Ni-NTA complexes avidly bind hexa-histidine–tagged macromolecules, including proteins and peptides. The advantages of the Ni-NTA-His6 interactions are reversibly and high selectivity.

In other words, the main objective of the second part of the thesis consists in the design and synthesis of new ***di-functional ligands*** endowed with metal-ions binding properties as result of combining the two entities depicted above: a *terpyridine moiety* and two *nitrilotriacetic acid* [**mono-NTA**] and [**tris-NTA**] pendant arms. This type of ligands could have synergistic complexant properties.

2. RESULTS AND DISCUSSIONS

Recent years have seen a surge of interest in the metal-ion directed construction of *discrete* molecular assemblies.[51-54] Metal-ion directed self-assembly of polydentate organic ligands like polypyridines, generates supramolecular architectures having various geometries (e. g. helicates, racks, ladders or grids)[22,16b] and high thermodynamic stability.[3f]

In other words, the main objective of the second part of the thesis consists in the design and synthesis of new di-functional ligands endowed with metal-ions binding properties based on a terpyridinic moiety and two nitrilotriacetic acid [**mono-NTA**] and [**tris-NTA**] pendant arms (**Figure 9**). The nitrilotriacetic acids (NTA) are known to interact with His-tagged protein with high affinity.

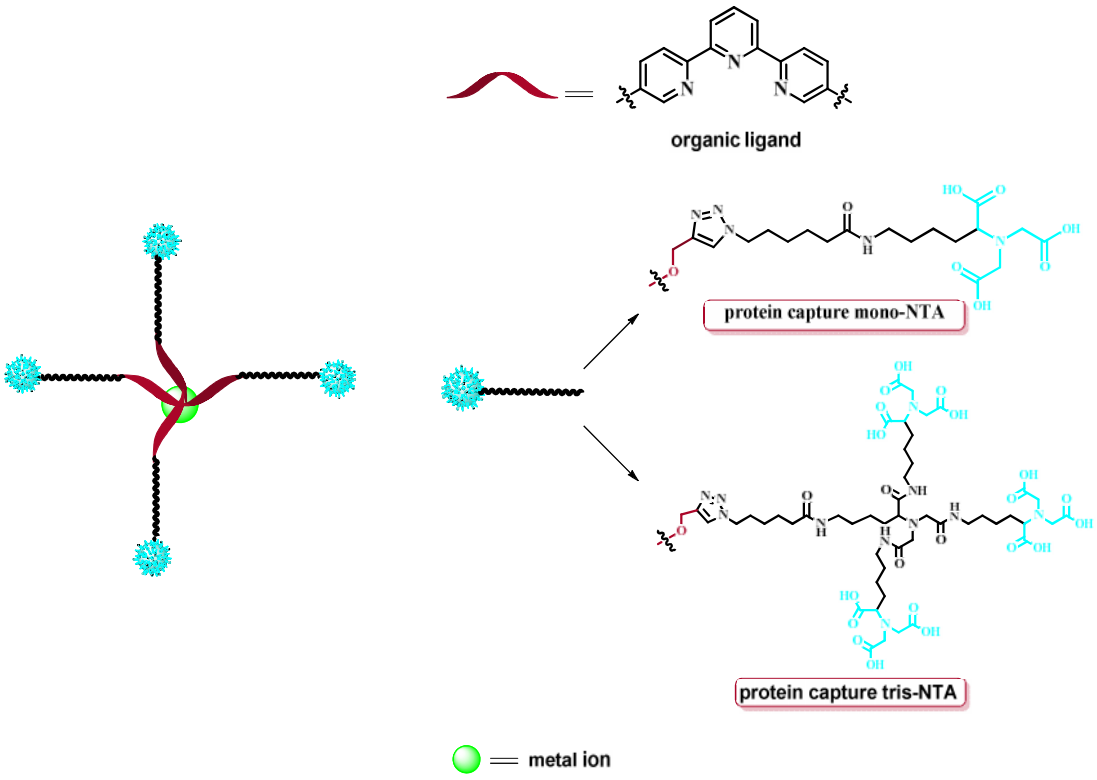


Figure 9. Schematic representation of the target compound.

Our strategy to prepare the target ligand-terpyridine core prolonged by two pendant arms having nitrilotriacetic acid function at extremities is shown in (**Figure 10**). It is easy to imagine a click chemistry-type reaction able to connect the terpyridine core with the pendant arms bearing NTA units. A literature survey unveils that in case of intermediates is easy to obtain terpyridine possessing triple bonds path (a), seven steps), azide intermediate possessing NTA unit path (b), four steps), and path (a) addition of path (b) give the target compound (**35**), in a two steps reactions (**Figure 10**).

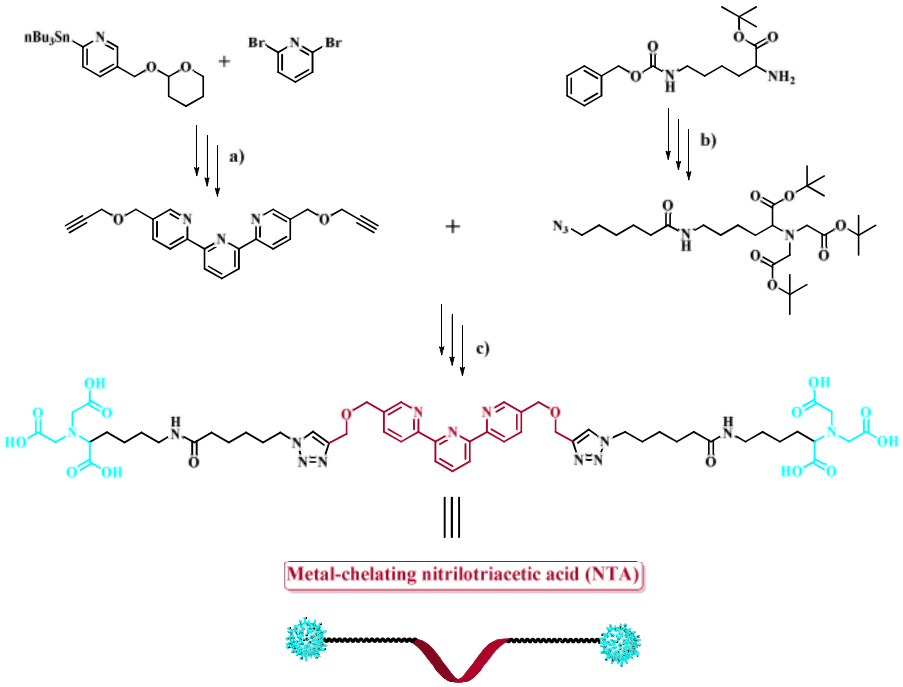


Figure 10. Envisioned strategy for the synthesis of the target compound containing metal-chelating nitrilotriacetic acid.

As depicted above, the strategy to synthesize the target ligand is based on the obtaining of two key intermediates:

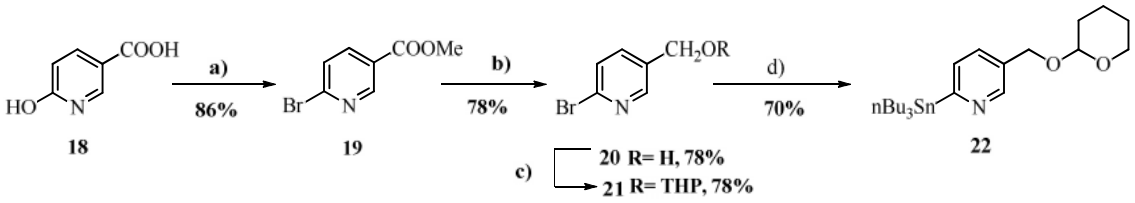
- Synthesis of terpyridine *building block* – path a)
- Synthesis of the *synthon* bearing NTA functionalities – path b)
- Coupling the two intermediates into the final ligand – path c)

2.1. Synthesis of the Terpyridine Intermediates (25) and (37)

Path a

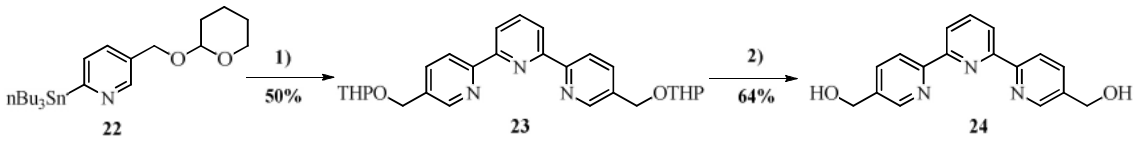
The strategy to synthesize the ligand decorated with a triple bond consists in a multi-step reaction. Starting from commercially available hydroxynicotinic acid and using *Stille* coupling reaction as key step of synthesis was obtained the terpyridine unit **24** (**Scheme 6**).[55] Therefore, hydroxynicotinic acid **18** was transformed into **19**, by heating (approximately 170 ^{0}C) and melting **18** with $POBr_3$ in absence of any solvent. After the reaction was quenched by addition of methanol, the compound **19** was isolated in very good yield.

The ester thus obtained, was subjected to reduction using $NaBH_4$ in absolut ethanol at room temperature. Then, the alcohol **20** was protected with 3,4-dihydro-1*H*-pyran (D*H*P) in presence of *p*-toluenesulfonic acid as catalyst in chloroform, in good yield. The compound **21** was further subjected to a lithiation reaction (*n*-BuLi in dry THF), for a bromine-lithium exchange, followed by addition of tributyltin chloride as electrophile (**Scheme 5**).[55]



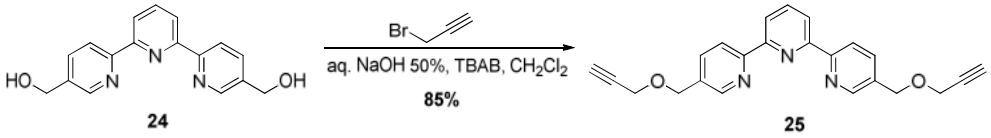
Scheme 5. Reagents and conditions: a) 1) $POBr_3$, 170 ^{0}C, 2) MeOH; b) $NaBH_4$, EtOH, r.t., overnight; c)DHP, PTSA, $CHCl_3$, r.t., overnight; d) THF, *n*-BuLi, -78 ^{0}C, $(n\text{Bu})_3\text{SnCl}$.

Synthesis of compound **24** involves in a first step the obtaining of the intermediate **23** by a Stille cross-coupling reaction between compounds **22** and 2,6- dibromopyridine in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium (0) in dry toluene under inert atmosphere, in order to obtain the terpyridine skeleton as previous described (**Scheme 6**).[56,55] Then the compound 5,5"-bis{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}-2,2'-6',2"-terpyridine (**23**) was subjected to deprotection of the tetrahydropyranyl group in acidic conditions to obtain the intermediate **24** in good yields (**Scheme 6**).[55]



Scheme 6. Reagents and conditions: 1) 2,6-dibromopyridine, $Pd(PPh_3)_4$, toluene, reflux overnight; 2) HCl, MeOH, reflux overnight.

Starting from key intermediate **24**, the synthesis in very good yields of the terminal alkyne **25** was possible by its reaction, with propargyl bromide, in dichloromethane and 50% aq. sol. of NaOH as solvents in presence of tetra-*n*-butyl ammonium bromide (TBAB)-as phase-transfer catalyst (**Scheme 7**).[55]



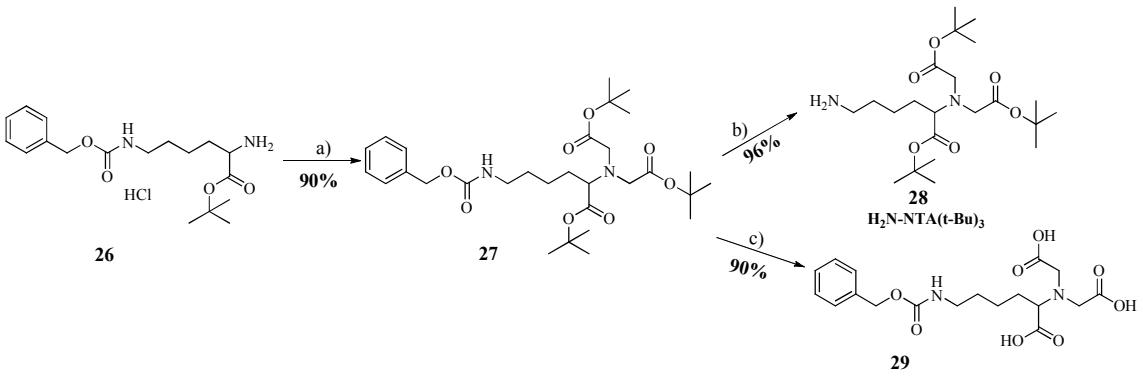
Scheme 7

2.2. Synthesis of Azide Decorated mono-NTA Units (33)

Path b

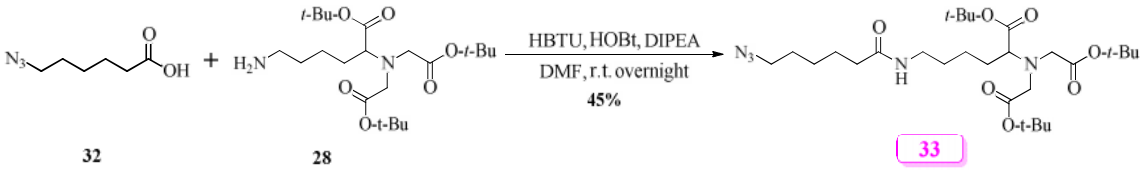
Starting from protected lysine (**26**), we synthesized the mono-NTA synthon functionalized with an amine group (**28**). The synthetic steps for building NH_2-NTA(*t*-Bu)$_3$ is presented in **Scheme 8**.[45] Thus carboxy and side chain protected $_L$-lysine (**26)** was functionalized by a double alkylation reaction with bromoacetic acid *tert-butyl* ester in presence of DIPEA and heating the reaction mixture overnight at 55 °C in DMF, when *t-butyl* ester-protected NTA synthon (**27**) is delivered in a very good yield.[45]

Then the compound (**27**) was deprotected using trifluoroacetic acid in CH_2Cl_2 to obtain the NTA tether (**29**) in quantitative yield.[57] Finally the key intermediate **28** was obtained after the removal of carbamate group (CBz) by hydrogenation using Pd/C (10%) (**Scheme 8)**.[58] Then the amine so obtained was used for further coupling reactions in order to be attached to our central motive (terpyridine derivative).



Scheme 8. Reagents and conditions: a) tert-butylbromoacetate/ DIPEA/ DMF, 55 ^{0}C, 36 h; b) MeOH/ 10% Pd/C/H_2, r.t., overnight; (c) TFA/DCM, 23 h, r.t.

The compound **33** was synthesized in good yields, by the reaction of 6-azidohexanoic acid **32** with amine derivative **28**, in presence of the coupling reagents HBTU and HOBt, using DIPEA as base (**Scheme 11**). The reaction took place overnight in DMF at room temperature. The structure of the compound **33** was confirmed by NMR spectroscopy and mass spectrometry.



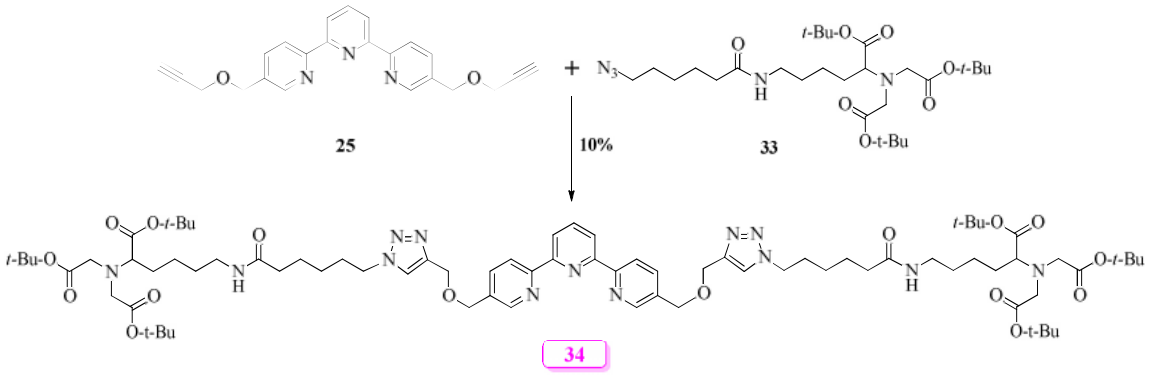
Scheme 11

2.3. Synthesis of the Target Ligand (35)

Path c

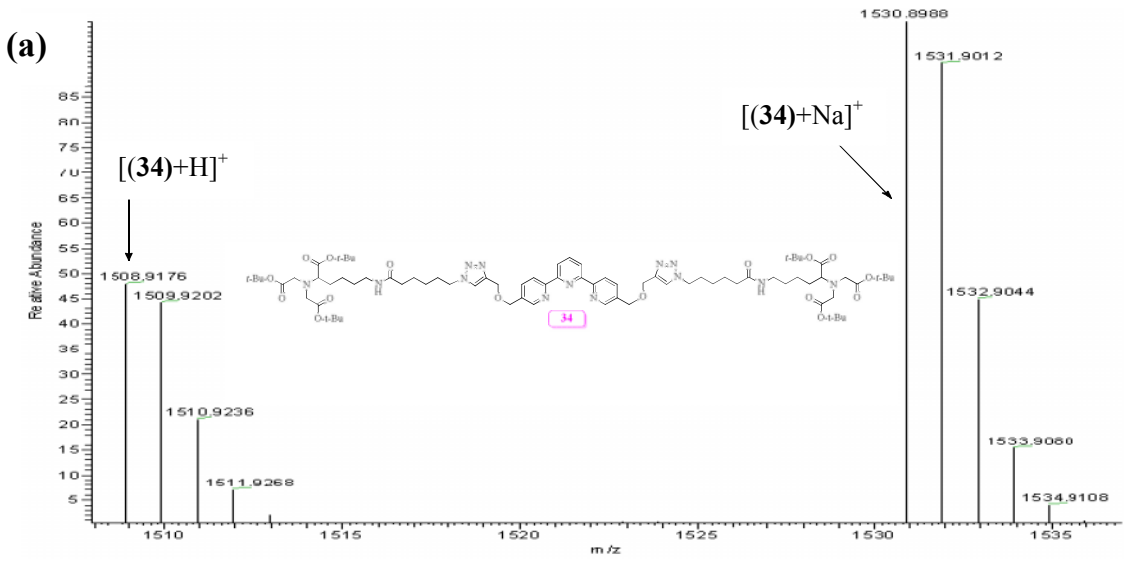
The synthesis of derivative **34** was possible by the reaction of derivative **33** with alkyne **25** using the click chemistry conditions.[61,62] The reaction took place in degassed acetonitrile, using $[Cu(CH_3CN)_4]PF_6$, [tetrakis(acetonitrile)-copper(I) hexafluorophosphate] as catalyst under inert atmosphere. Compound **25** was first stirred for 30 min with one equivalent of the Cu (I) salt to form Cu(I) complex of **25**, followed by the addition of the azide mono-NTA **33**, and an extra 0.5 equivalents of copper (I) ions and the reaction was

allowed to stir overnight at 60 ^{0}C. The desired compound was obtained in low yield (10%) (**Scheme 12**).



Scheme 12. Click reaction between affinity label **33** and the terpyridine alkyne **25**. Reagents and conditions: $[Cu(CH_3CN)_4]PF_6$, acetonitrile, 60 ^{0}C, overnight.

HRMS (ESI$^+$) spectrum of ligand **34** displays the $[M+H]^+$ molecular ion peak at m/z= 1508.9176, and the base peak at m/z= 1530.8988 corresponding to the $[M+Na]^+$ (**Figure 20 a**). We could also indentify peaks corresponding to lower mass fragments at m/z= 1396.7849 for $[M-2tBu]^+$, at m/z= 1340.7228 for $[M-3tBu]^+$ and also at m/z= 1284.6605 $[M-4tBu]^+$ due to successive loss of the *tert*-butyl groups (**Figure 20 b**).



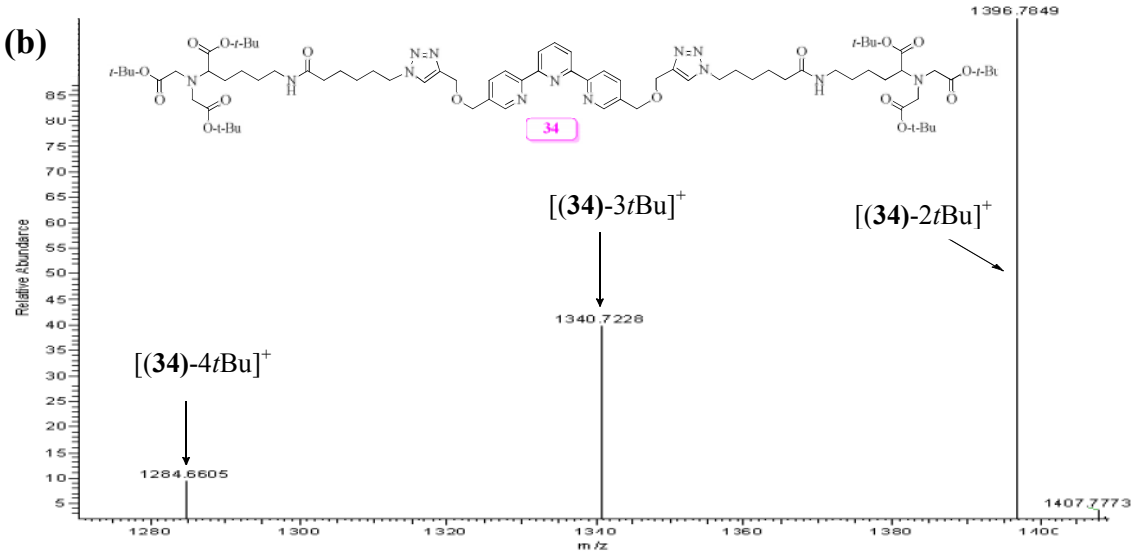
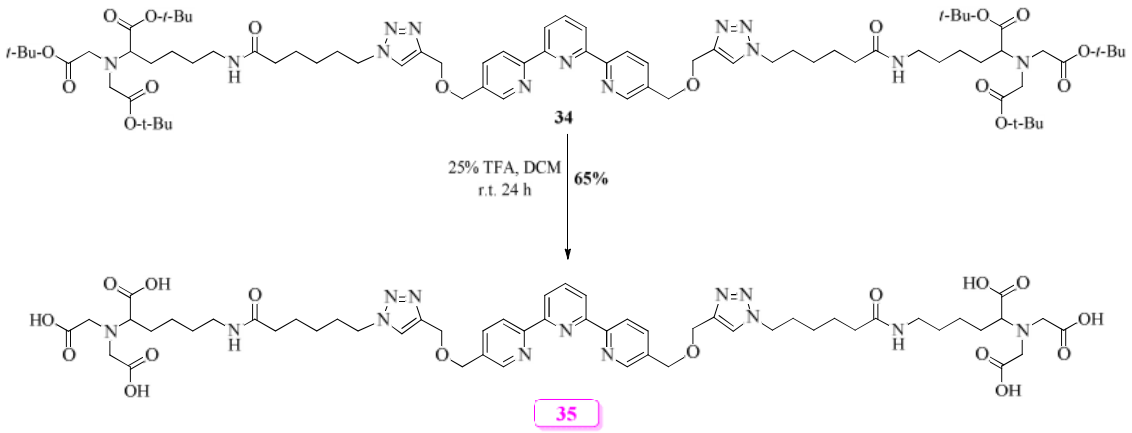


Figure 20. HRMS ESI (+) spectrum of compound **34**: (**a**) m/z values of $[M+H]^+$; $[M+Na]^+$; ions; (**b**) The peaks corresponding to lower mass fragments due to successive loss of the tert-butyl groups.

The final step, in order to obtain the target ligand consists in deprotection of **34** in acidic condition (25% TFA) in DCM lead to the formation compound **35** (**Scheme 13**).



Scheme 13

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III. Applications of Dynamic Constitutional Chemistry in the Synthesis of New Cryptands

Keywords:

Dynamic Combinatorial Chemistry (DCC), Dynamic Combinatorial Libraries (DCLs), High Resolution Mass Spectrometry (HRMS).

1. INTRODUCTION

1.1. General Remarks on Dynamic Constitutional Chemistry

Combinatorial chemistry (CC) can be seen as the process of diversity generation and it is now widely used to design biologically active compounds, new receptors and catalysts.[1] The combination between CC with supramolecular chemistry self-assembly directed by molecular recognition) lead to a new research field named dynamic combinatorial chemistry (DCC),[2] in which the *building blocks* are connected to each other by means of reversible linkages.[3] This concept was introduced in the mid-1990s by the research groups of Sanders[4] Lehn[5,2b] and others.[6,7,2e] DCC was implemented in three main areas:

- identification of bioactive compounds for biological receptors
- identification of synthetic receptors
- the development of dynamic polymers.

Dynamic Combinatorial Chemistry (DCC)[38] exploits the reversibility reactions. Multicomponent systems composed of amines and carbonyl compounds. The resulting mixtures are called dynamic combinatorial libraries (DCLs).

Combinatorial libraries play an important role in creation of large libraries of structurally diverse compounds and also in modern drug development.[39] Dynamic combinatorial libraries (DCLs) have been used to produce new synthetic receptors,[40] interlocked structures,[41] ligands for biomolecules,[42] sensors[43] and catalysts.[44]

A dynamic combinatorial library (DCL) is a thermodynamically controlled mixture of interconnecting species that can respond to various stimuli: pH, temperature or electric field. In dynamic combinatorial chemistry, simple molecular units (*building blocks*) are held together by non-covalent or reversible covalent bonds, generating a complex mixture of products which continuously interconvert: the composition of the mixture at thermodynamically controlled and its referred to as a dynamic combinatorial library.[45]

2. RESULTS AND DISCUSSIONS

2.1. Synthesis of New Cryptands under Thermodynamic Control- Dynamic Combinatorial Libraries (DCLs)

The third part of the thesis describes the synthesis and the structural characterization of new cryptands obtained by condensation of trialdehyde (**4**) with different diamines (i.e. *ortho*-,*meta*- and *para*-xylenediamnes **A**, **B**, **C**), under thermodynamic control. The set of substrates chosen to study the formation and dynamic behavior of such libraries is presented in **Figure 4**.

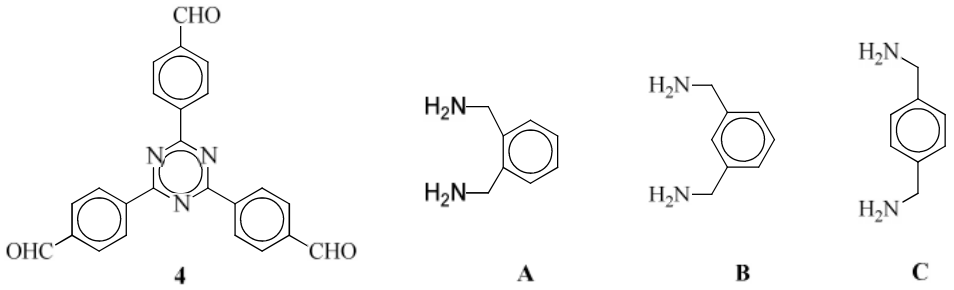
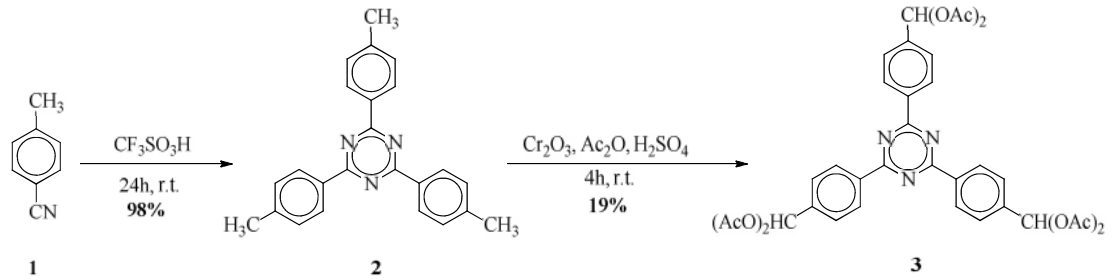


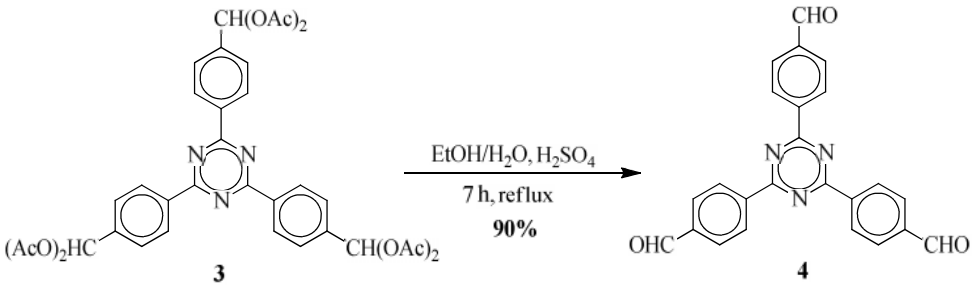
Figure 4. *Building blocks* for the generation of imines libraries

The first step towards the formation of the trialdehyde **4** required the synthesis of C_3 symmetrically derivative **2**. Therefore, 2,4,6-tri-tolyl-1,3,5-triazine **2** was synthesized in very good yields (98%) by trimerization of commercially available *p*-tolunitrile **1** in acidic conditions (triflic acid) and appear as a white solid. Compound **2** was then subjected to oxidation reaction, using chromium trioxide in acetic anhydride, at room temperature to obtain the compound **3** in rather low yields (**Scheme 1**).[60]



Scheme 1

4,4 '4"-(1,3,5-triazine-2,4,6-triyle) tribenzaldehyde **4** was synthesized in very good yields (90%) by hydrolysis of derivative **3** in presence of ethanol/water mixture and sulfuric acid (**Scheme 2**).[60]

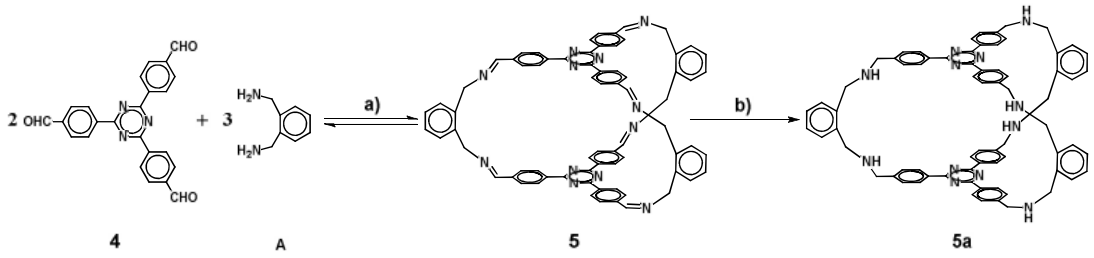


Scheme 2

With compound **4** and various diamines (i.e. *ortho*-, *meta*-, and *para*-xylenediamines) (**A**, **B**, **C**-commercially available) in our hands we generate a CDLs, using the imination reaction. Different reaction conditions were used, by means of changing reaction parameters: solvent, temperature, concentration of the reagents and equilibrium time. The optimal reaction conditions proved to be at the reflux in dichloromethane/methanol because in this way the reactions maintain their homogeneity. All the reactions were monitored at different time points by HPLC-MS, observing different responses from the libraries.

The reaction mixture could be analyzed only after the reduction with sodium borohydride due to the instability of the formed imines. The thermodynamic control for the composition of combinatorial libraries can give the remarkable results and provides the most compelling demonstration of the potential of reversible covalent chemistry. The composition of the library is determined by the thermodynamic stability of the library members.

Reaction of **4** with *ortho*-xylenediamine (**A**) gave almost exclusively, after the establishment of the equilibrium, the imine derivative **5** which was then converted into corresponding amine **5a** applying a fast reduction protocol (**Scheme 3**).[61] The reaction was performed in dichloromethane/methanol at reflux in presence of molecular sieves. The cryptand **5a** was purified by successive washes with diethyl ether. HPLC-MS was used as a method for qualitative determination of the composition of imines libraries and the estimation of the equilibration time. The cryptand **5a** was obtained in quantitative yield Thus, in HPLC-MS we observed formation (**5a**) as a major compound after 18 hours and the thermodynamic equilibrium was reached after **2** days.



Scheme 3. Reagents and conditions: a) dry DCM/MeOH, molecular sieves, **2**days; b) $NaBH_4$, DCM/MeOH, r.t. 2 h

The structure of compound **5a** was confirmed by NMR spectroscopy and mass spectrometry. The ^{1}HNMR for the compound **5a** is depicted in **Figure 8** and presents the signals in accordance with the proposed structure.

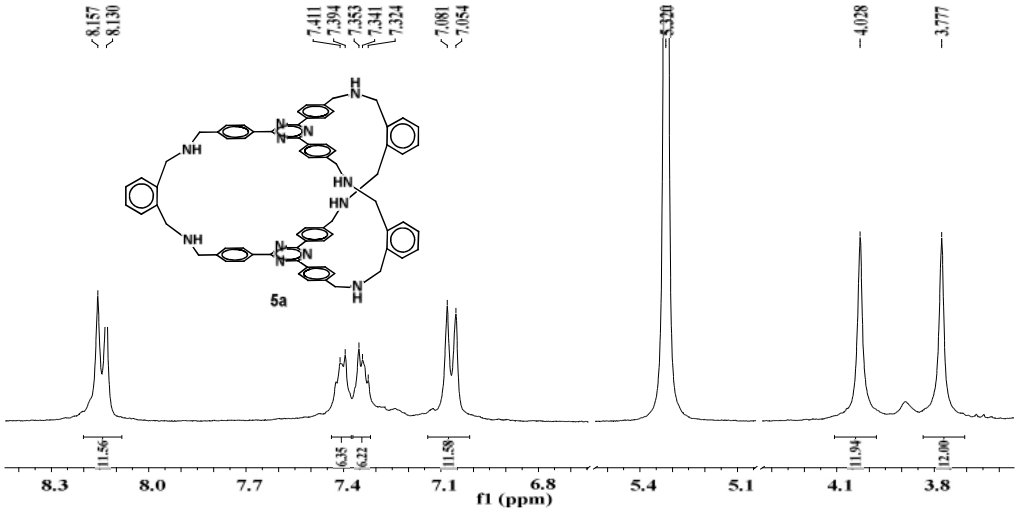
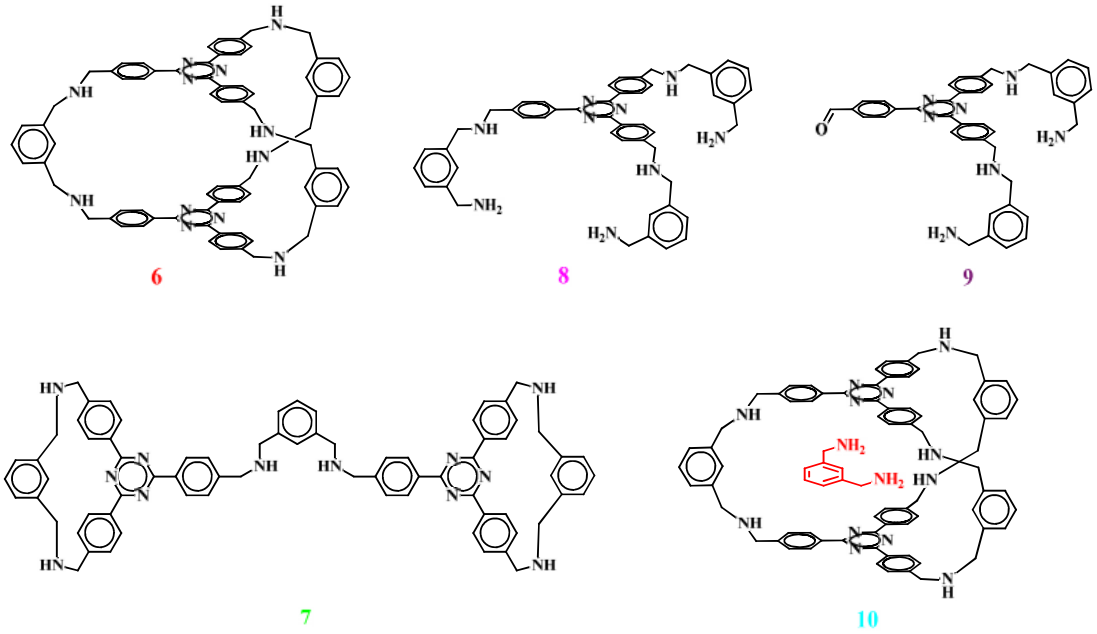


Figure 8.^{1}H NMR fragments of **5a** (CD_2Cl_2, 300 MHz, r.t.)

Dynamic constitutional libraries generated from the trialdehyde (**4**) and *meta*-xylenediamine (**B**) (in the same conditions: dry DCM, molecular sieves) yielded at equilibrium (after 20 days) a mixture of compounds **6**, **8** and bis-macrocyle **7** as major compounds (**Figure 10c, Scheme 4**).



Scheme 4. Components of the library generated from the trialdehyde **4** and *meta*-xylenediamine (1:1.5 ratio DCM, reflux)

The ^{1}H NMR spectrum of **6** is presented in **Figure 11**. The structure of **6** will be further investigated by variable NMR spectroscopy.

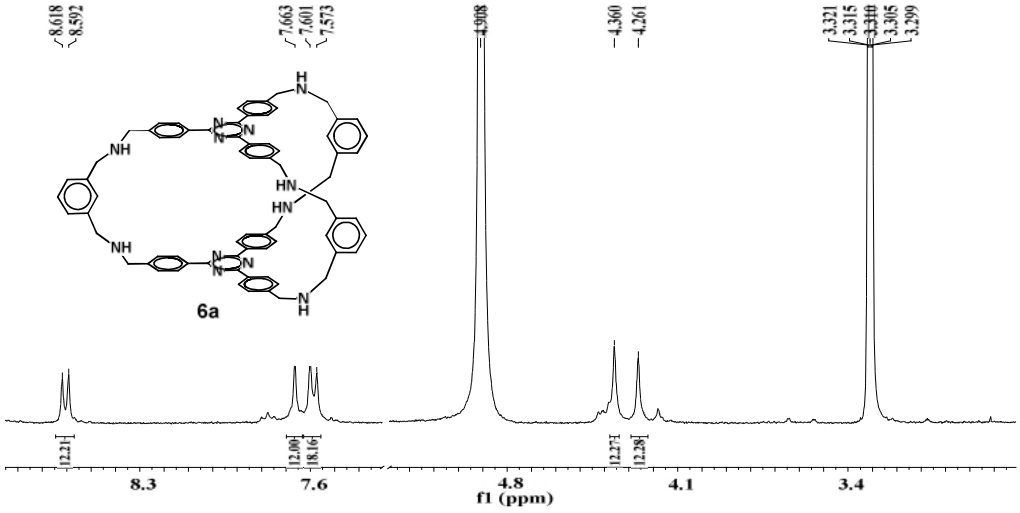


Figure 11. Fragment of ^{1}H NMR spectrum of **6** (CD_3OD, 300 MHz, r.t.)

After the reduction step, compound **6** was isolated and pufiried by preparative HPLC. The HPLC chromatogram of the purified cryptand **6** is presented in **Figure 12**.

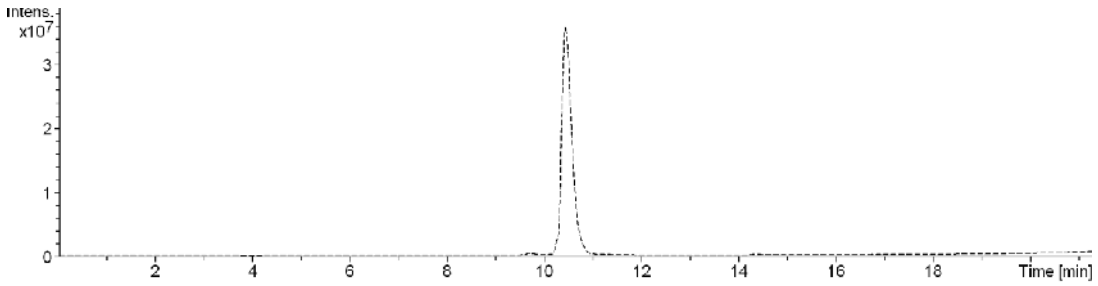


Figure 12. HPLC chromatogram of the cryptand **6**

Mass spectrometry APCI positive mode was used to confirm the obtaining of compound **6** (**Figure 13**). The base peak of the spectrum at m/z 1100.1 corresponds to the protonated species $[M+H]^+$.

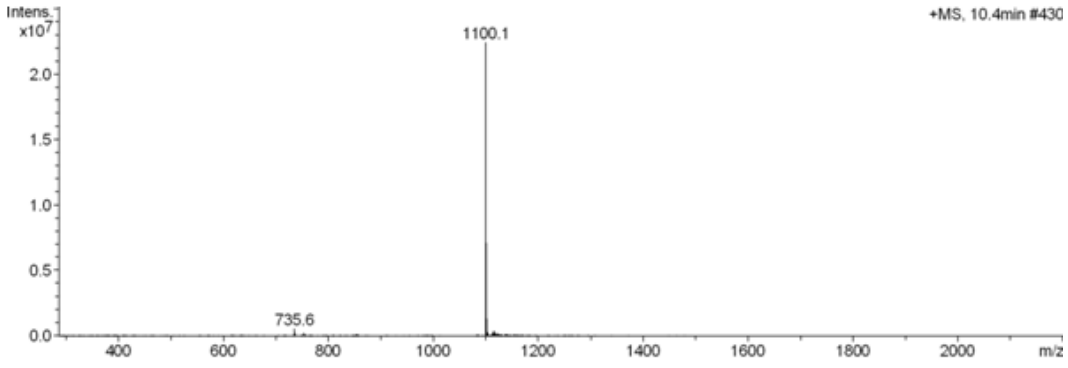


Figure 13. APCI (+) mass spectrum of compound **6**

The reaction between **4** and *para*-xylenediamine performed in DCM was monitored in HPLC-MS during four days, and the CDLs contains the compounds **11**, **12** and **13** (**Figure 14**).

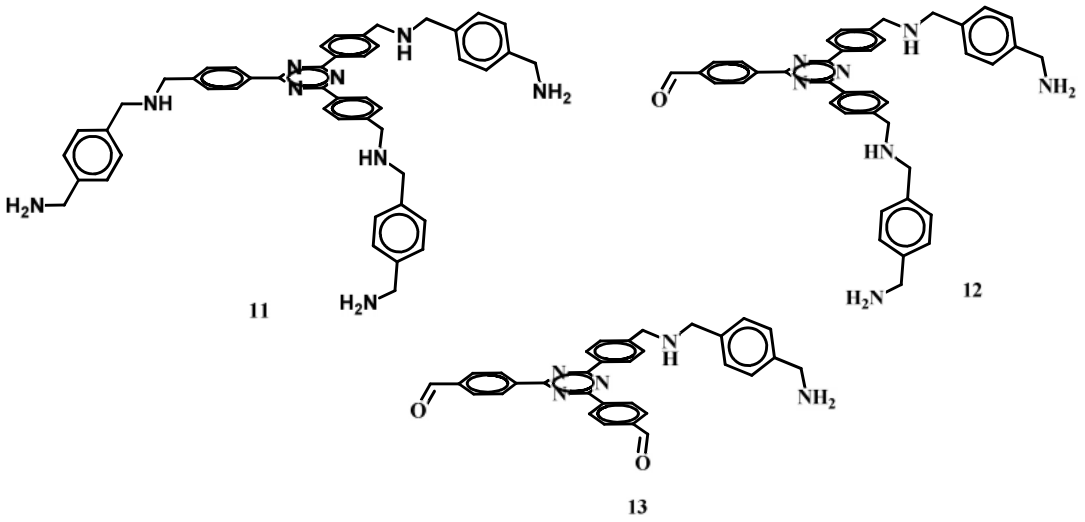


Figure 14. Components of the library generated from the trialdehyde **4** and *para*-xylenediamine (1:1.5 ratio DCM, reflux), after 4 days.

Unfortunately after four days the expected compounds were not observed in the library, because some components of the libraries precipitated out of the reaction mixture and the thermodynamic equilibrium could not be reached.

2.2. Complexation Studies

Next we set to study the complexation ability of the synthesized cryptands. electrospray ionization mass spectrometry (ES-MS) was use to characterize the complexation of **6** with different neutral molecules. The guests examined were: le 2,4,6-tri-*p*-tolyl-1,3,5-triazine (**2**), le 2,4,6-tris(4-bromophenyl)-1,3,5-triazine (**14**) and 2,2",3,3",4,4",5,5",6,6"-decafluoro-5'-(perfluorophenyl)-1,1':3',1"-terphenyl (**15**) **Figure 15**.

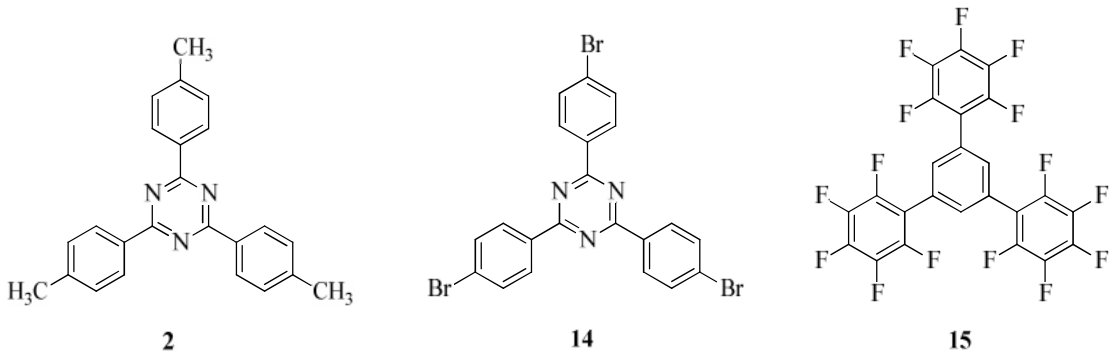


Figure 15. Guests molecules

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