Organic Chemistry Department
Babes-Bolyai University
Cluj-Napoca, 400028
ROMANIA

PhD Thesis

DESIGN, SYNTHESIS, STRUCTURAL ANALYSIS AND SUPRAMOLECULAR PROPERTIES OF SOME NEW MACROCYCLES AND CAGE MOLECULES

PhD Thesis Abstract

ADRIAN WOICZECHOWSKI-POP

Scientific advisor:
Prof. Dr. ION GROSU

Cluj-Napoca
29 September 2010

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ADRIAN WOICZECHOWSKI-POP

Jury:

Scientific advisor	Prof. Dr. Ion GROSU	Babeş-Bolyai University Cluj-Napoca, Romania
President	Conf. Dr. Eng. Luminița DAVID	Babeş-Bolyai University Cluj-Napoca, Romania
Reviewer	Prof. Dr. Yvan RAMONDENC	University of Rouen, France
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Cluj-Napoca
29 September 2010

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1. INTRODUCTION

Cryptands represent important building blocks in supramolecular chemistry field due to their properties to form complexes with different anions, cations or neutral organic compounds.[1]

Cage molecules or a well-defined system of cage molecules able to mime (perform mechanical-like movements) at small scale of real tools and machines used in daily life are important for the future development of science and technology.[2]

The work realized during this thesis is registered in this perspective.

The strategy conceived for the synthesis of cage molecules is illustrated in **Figure 1**. In the chosen strategy, two extended aromatic spacers and three *N*-containing aromatic bridge units are joined together by sixfold bond formation. These cage molecules are capable of binding a variety of organic guest molecules.

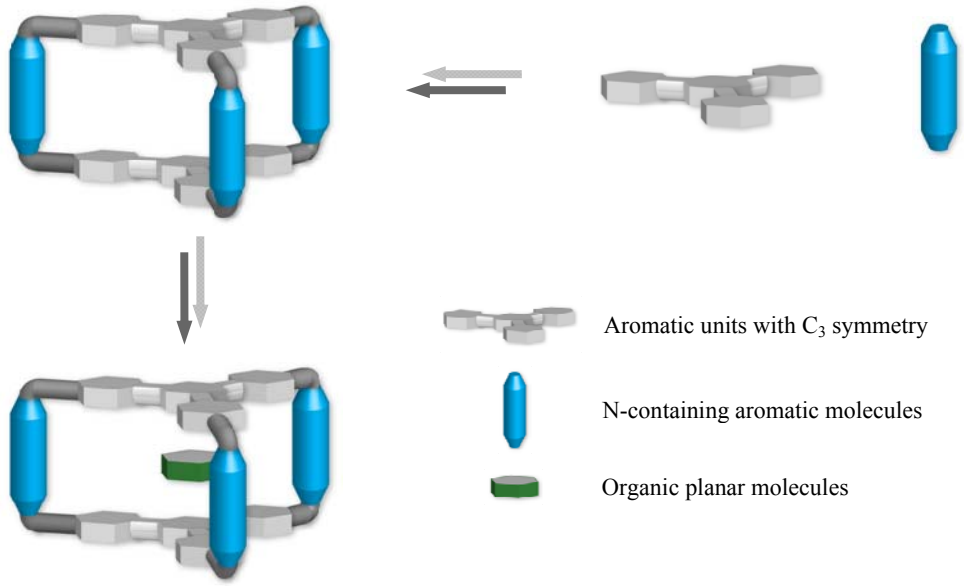


Figure 1. Cartoon representation of target macrocyclic compounds.

The first part of the thesis is assigned to the synthesis and supramolecular properties of some cage molecules based on trisphenylaryl units, presented in the literature.

The second part presents the synthesis and structural analysis of the precursors that are involved in different macrocyclization reactions. The precursors are one of the most important key in the synthesis of the desired cage molecules and those studies were

[1] (a) Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153; (b) Whitesides, G. M., Mathias, J. P., Seto, C. T. *Science* **1991**, *254*, 1312; (c) Lehn, J. M. *Supramolecular Chemistry Concepts and Perspectives*; VCH: NY, 1995; (d) Philp, D., Stoddart, J. F. *Angew. Chem. Int. Ed.* **1996**, *35*, 1154.

[2] (a) Batten, S. R., Robson, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1460; (b) Reinhoudt, D. N., Stoddart, J. F., Ungaro, R. *Chem. Eur. J.* **1998**, *4*, 1349; (c) de Mendoza, J. *Chem. Eur. J.* **1998**, *4*, 1373.

required. A part of these compounds are already described in the literature, but for some of them not all the analyses were effectuated, such as UV-Vis, fluorescence.

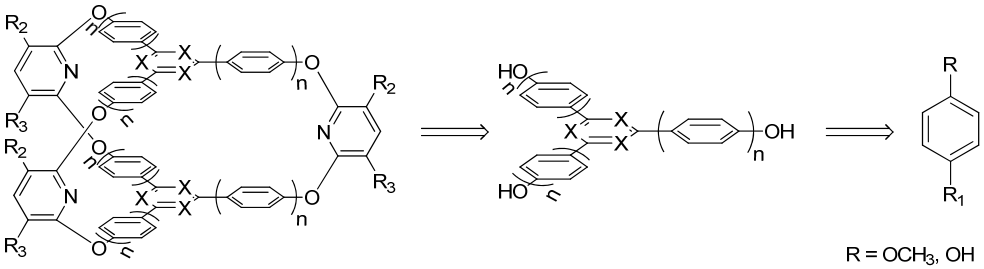
The most important part of the thesis, the synthesis, structural analysis and supramolecular properties of some new cage molecules with extended conjugation and C_3 symmetry is presented. X-ray analysis was used to characterize one cage molecule with the trisphenylbenzene units. Molecular modeling studies of two macrocycles are also described to confirm the possibility of these new compounds to form host-guest complexes.

The last part of the thesis consists in the experimental part, which presents details of the methodologies used for the synthesis of precursors and cage molecules, but also the complete structural analysis of the compounds.

3. OBJECTIVES

The purpose of the entitled work was *to obtain new macrocycles and cage molecules with special supramolecular properties*, which can be used as components to obtain *molecular machines* or other *molecular devices*.

A retrosynthetic scheme for the synthesis of the target cage molecules is presented in **Scheme 11**.



Scheme 11.

Complexation studies were planned to be made using different investigation methods, as *NMR spectroscopy*, *UV-Vis* and *fluorescence analysis*. *Molecular modeling studies* were employed in order to define the possibility of the cage molecules to bind organic molecules in the formed cavity.

Due to the selectivity of the determined size and shape of the cavity, the cage molecules are ideally suited to construct *nano-objects* and can have applications in *nanoscience*.

4. RESULTS AND DISCUSSIONS

4.1. SYNTHESIS AND ANALYSIS OF PRECURSORS FOR NEW CAGE MOLECULES

As it was stated before, our aim was to accomplish the synthesis of C_3 symmetric macrocyclic compounds. To obtain the expected macrocycles, different symmetrically trisubstituted aromatic building blocks were required, our strategy for the synthesis of cage molecules being illustrated in **Figure 1**. The building blocks consist in extended aromatic units which present planarity and favor the formation of π-π stacking interactions with different organic guest molecules. The general structure of the building blocks is drawn in **Figure 9**.

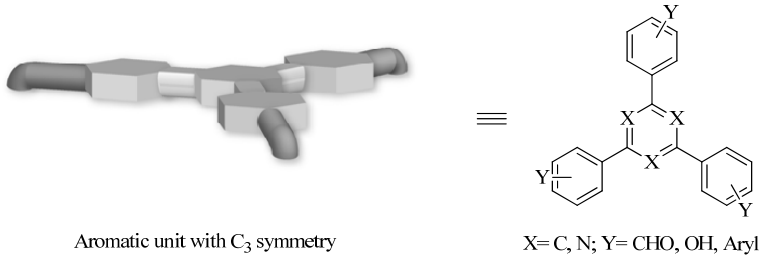
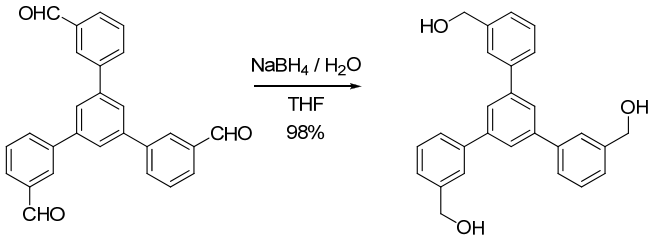


Figure 9. Cartoon representation of aromatic building blocks.

4.1.1. Compounds with tris(phenyl)benzene and tris(biphenyl)benzene units

The initial steps followed toward the formation of target cage molecules request the synthesis of some tris(phenyl) and tris(biphenyl)benzene derivatives.

Reduction with $NaBH_4$ in H_2O[3] of **6** leads to formation of compound **7** in almost quantitative yield (98%). Compound **7** has not been described yet in the literature. The structure of **7** was confirmed by NMR spectroscopy (**Scheme 14**).

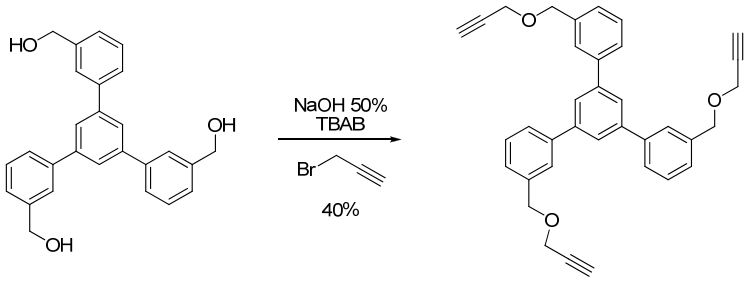


6 **7**

Scheme 14.

[3] Badjić, J. D., Cantrill, S. J., Stoddart, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2288.

Compound **7** was involved in a phase transfer reaction with propargyl bromide, reaction described in the literature, to obtain the new compound **8** in 40 % yield (**Scheme 15**).[4,5]



7 **8**

Scheme 15.

The characterization of compound **8** was possible by NMR spectroscopy. ^{1}H NMR spectrum of compound is presented in **Figure 21**.

The aromatic region of the ^{1}H NMR spectrum of compound **8** exhibits the expected number and pattern of resonances. Protons H_2 and $H_{2'}$ appear as singlets at 7.79 ppm and 7.70 ppm, respectively, while protons $H_{4'}$ and $H_{6'}$ shift as doublets downfield at 7.39 ppm (^{3}J = 7.5 Hz) and 7.64 ppm (^{3}J = 7.5 Hz). A triplet signal at 7.48 ppm (^{3}J = 7.5 Hz) can be assigned for protons $H_{5'}$.

The aliphatic region of the spectrum is simply, a singlet at 4.71 ppm appears for CH_2O protons, a doublet at 4.25 ppm (^{4}J = 2.5 Hz) for OCH_2 and a triplet at 2.50 ppm (^{4}J = 2.5 Hz) for CH protons.

[4] Chittaboina, S., Xie, F., Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331;
[5] (a)Wu, P., Feldman, A. K., Nugent, A. K., Hawker, C. J., Scheel, A., Voit, B., Pyun, J., Frechet, J. M. J., Sharpless, K. B., Fokin, V. V. *Angew. Chem. Int. Ed.* **2004**, *43*, 3928; (b) Saha, A., Ramakrishnan, S. *Macromolecules* **2009**, *42*, 4956.

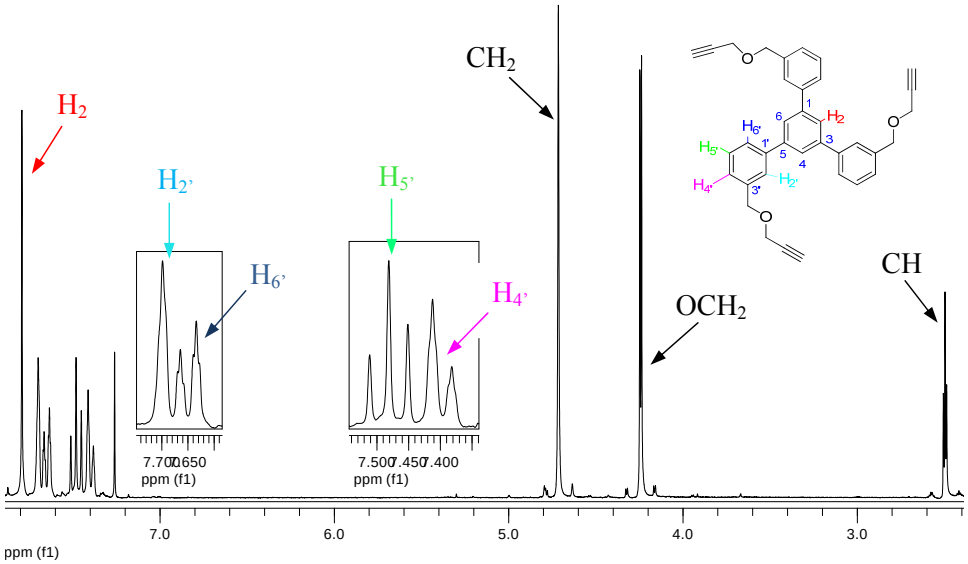
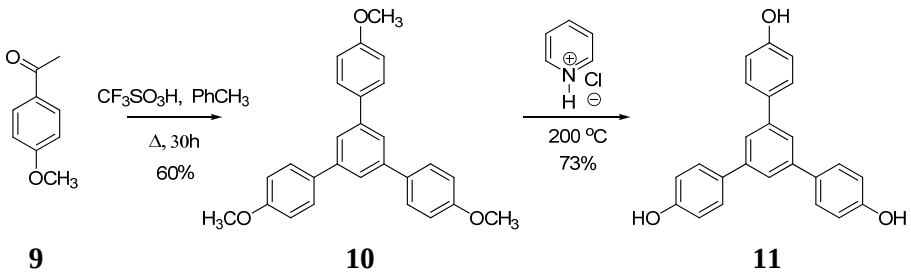


Figure 21. Fragment of ^{1}H NMR spectrum (250 MHz, $CDCl_3$) of **8**.

Compound **10** was obtained starting from commercial 4-methoxyacetophenone **9**, in toluene, using triflic acid as catalyst, in 60 % yield. Compound **11** was obtained from compound **10** in solution of pyridine hydrochloride at 200°C in 73% yield as light brown needles (**Scheme 16**).[6] The two compounds are known in the literature. For **11**, the UV-Vis and fluorescence studies are not yet described.

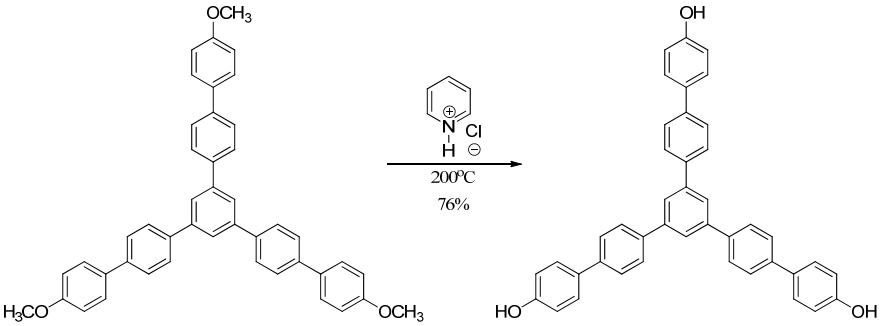


9 **10** **11**

Scheme 16.

Compound **14** was reacted with pyridine hydrochloride by a modified methodology from literature [7] to obtain derivative **15** in a good 76 % yield (**Scheme 18**). Although the compound has been already described, the full attribution of carbon atoms has not been presented. NMR spectroscopy was employed to characterize compound **15**.

[6] Constable, E. C., Housecroft, C. E., Neuburger, M., Poleschak, I., Zehnder, M. *Polyhedron* **2003**, *22*, 93.
[7] Mirokawa, A., Ono, K. *Polym. J.* **2000**, *32*, 255.



14 **15**

Scheme 18.

We have used the mass spectrometry for the analysis of compound **15**. The mass spectrum is shown in **Figure 34**, ionic species are detected at *m/z* 583 corresponding to $[M]^+$ and *m/z* 584 corresponding to $[M+H]^+$.

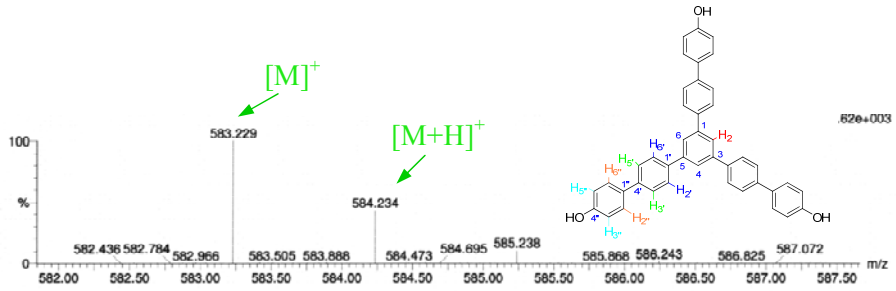
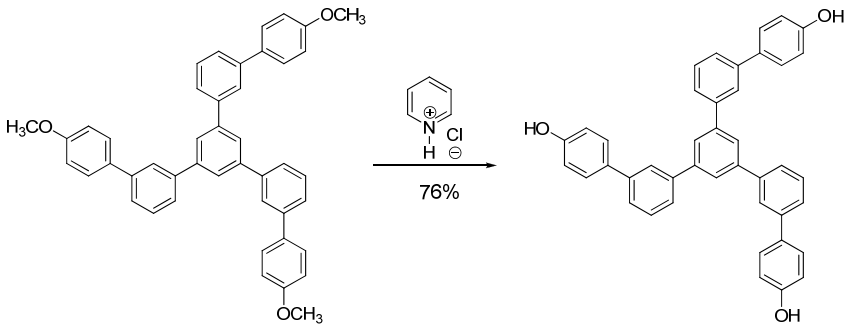


Figure 34. Mass spectrum of **15**.

Compound **17** was obtained from derivative **16** in reaction with pyridine hydrochloride at 200°C in 76% yield (**Scheme 20**) and it was not found in literature. The structure of the compound was analyzed by NMR spectroscopy and mass spectrometry.



16 **17**

Scheme 20.

The aromatic region of ^{1}H NMR spectrum of **17** (**Figure 38**) exhibits the expected number and pattern of resonances and their assignment was based on COSY experiments. OH protons are deshielded and appear as singlet at 9.57 ppm, while protons H_2 and $H_{2'}$ shift upfiled as singlets at 8.02 ppm and 8.00 ppm respectively. Protons $H_{6'}$ shift as a doublet at 7.79 ppm, with a coupling constant ^{3}J = 7.5 Hz, protons $H_{5'}$ appear at 7.54 ppm (^{3}J = 7.5 Hz) as a triplet and the doublet at 6.86 ppm is assigned for protons $H_{3''}$. Protons $H_{2''}$ and $H_{4'}$ are doublets and are overlapped and appear at 7.60 ppm.

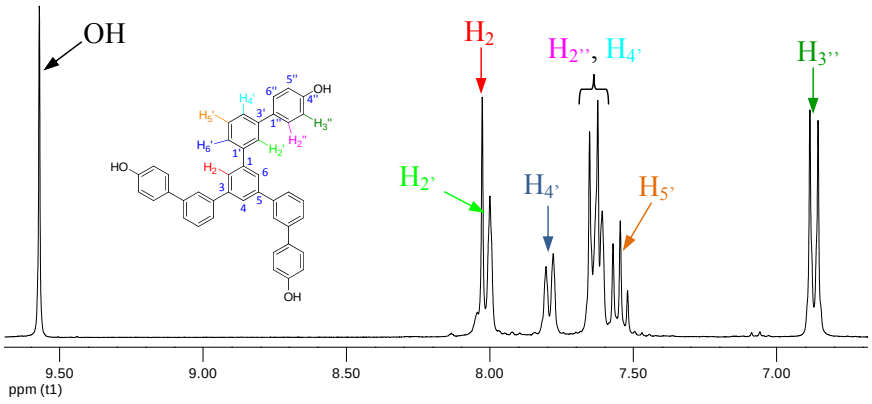
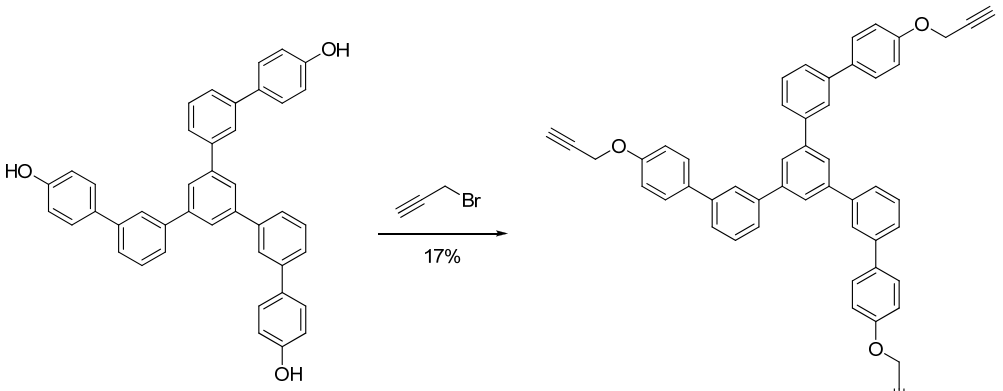


Figure 38. ^{1}H NMR fragment (300 MHz, DMSO-d_6) of compound **17**.

The synthesis of new compound **18** was performed by a reaction between triphenol **17** and propargyl bromide, in dichloromethane (**Scheme 21**).[8] The structure of compound **18** was confirmed by NMR studies.



17 **18**

Scheme 21.

4.1.2. Compounds based on 1,3,5-tris(phenyl)benzene units

Planarity represents an important factor in the synthesis of the target cage molecules. In this way, according to the literature, trisubstituted triazine derivatives with C_3 symmetry could be suitable for the formation of interesting supramolecular systems.

Recently, in literature data, some cage molecules were obtained by a „click" reaction.[9] This type of reaction involves a compound bearing terminal triple bond and a triazide derivative.

The new compound **24** was obtained in 81% yield from triazine derivative **23** by an adapted methodology,[10] using NaN_3 in dimethylsulfoxide (**Scheme 23**). The reaction key was represented by the synthesis of trisbrominated compound **23** which was obtained in low yields (22%) when triflic acid and dry chloroform were used (a modified synthetic methodology). The yields were significantly improved (from 22% to 69%) by changing the reaction conditions (triflic acid without solvent).[11]

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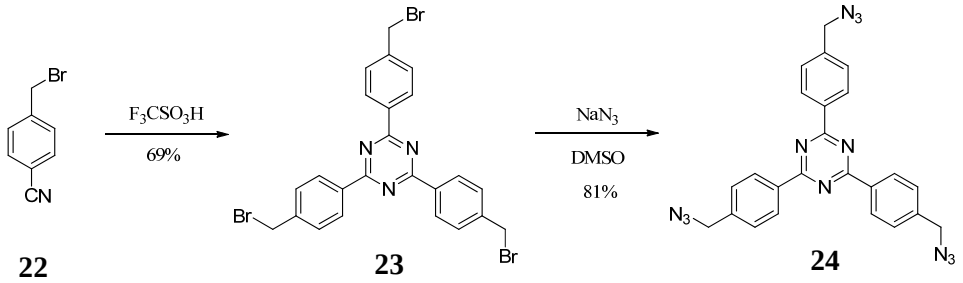
[8] (a) Bogdan, N. D., Matache, M., Meier, V. M., Dobrota, C. , Dumitru, I., Roiban, G. D., Funeriu, D. P. *Chem. Eur. J.* **2010**, *16*, 2170; (b) Wu, P., Feldman, A. K., Nugent, A. K., Hawker, C. J., Scheel, A., Voit, B., Pyun, J., Frechet, J. M. J., Sharpless, K. B., Fokin, V. V. *Angew. Chem. Int. Ed.* **2004**, *43*, 3928; (c) Saha, A., Ramakrishnan, S. *Macromolecules* **2009**, *42*, 4956; (d) Kim, S. H., Choi, H. S., Kim, J., Lee, S. J., Quang, D. T., Kim, J. S. *Org. Lett.* **2010**, *12*, 560.

[9] (a) Brunet, E., Juanes, O., Jiménez, Rodríguez-Ubis, J. C. *Tetrahedron Lett.* **2009**, *50*, 5361; (b) Moni, L., Rossetti, S., Scoponi, M., Marra, A., Dondoni, A. *Chem. Commun.* **2010**, *46*, 475; (c) Ni, B. -B., Wang, C., Wu, H., Pei, J., Ma, Y. *Chem. Commun.* **2010**, *46*, 782; (d) Bogdan, N. D., Matache, M., Meier, V. M., Dobrota, C., Dumitru, I., Roiban, G. D., Funeriu, D. P. *Chem. Eur. J.* **2010**, *16*, 2170 ; (e) Morales-Sanfrutos, J., Ortega-Munoz, M., Lopez-Jaramillo, J., Hernandez-Mateo, F., Santoyo-Gonzalez, F. *J. Org. Chem.* **2008**, *73*, 7772; (f) Alonso, F., Moglie, Y., Radivoy, G., Yus, M. *Tetrahedron Lett.* **2009**, *50*, 2358.

[10] Sinha, J., Sahoo, R., Kumar, A. *Macromolecules* **2009**, *42*, 2015.

[11] Durot, S., Mobian, P., Collin, J. –P., Sauvage, J. –P. *Tetrahedron* **2008**, *64*, 8496.



Scheme 23.

^{1}H NMR spectrum of triazine derivative **24** is presented in **Figure 46**. All the signals are more shielded that in the case of compound **23**. An AB system can be also observed for the three phenyl groups on the triazine ring [8.54 ppm (^3J = 7.5 Hz) assigned for protons $H_{2'}$ and 7.36 ppm (^3J = 7.5 Hz) for protons $H_{3'}$. In aliphatic region of the spectrum, a singlet signal at 4.34 ppm appears for CH_2.

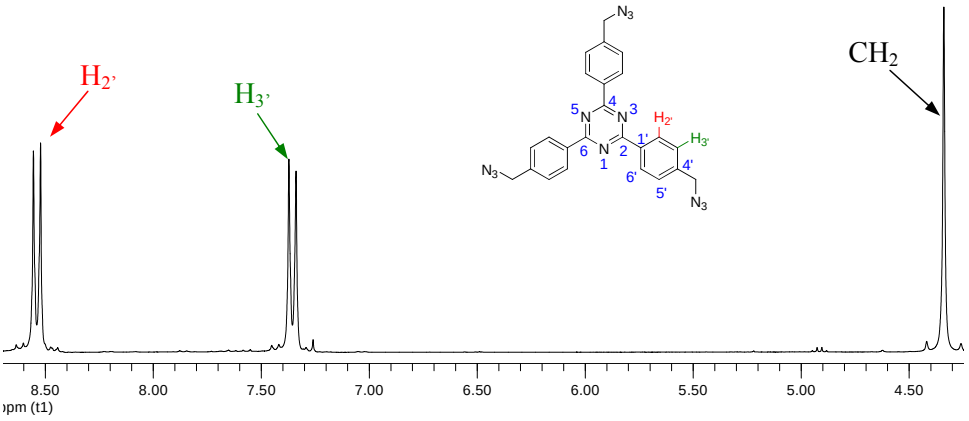
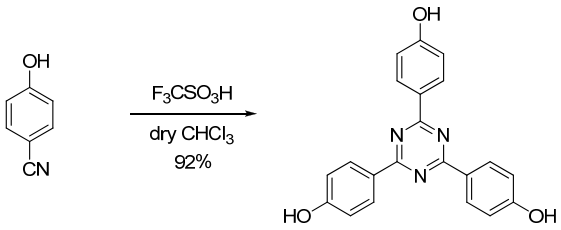


Figure 46. ^{1}H NMR fragment (250 MHz, $CDCl_3$) of compound **24**.

In order to obtain triphenolic derivative **26**, a trimerization reaction of commercially compound **25** using triflic acid in dry $CHCl_3$ at room temperature was employed (**Scheme 24**). Compound **26** is presented in literature,[12] but details concerning the experimental part and the structural analysis are not described. The simple purification by filtration gave the pure compound in 92% yield.

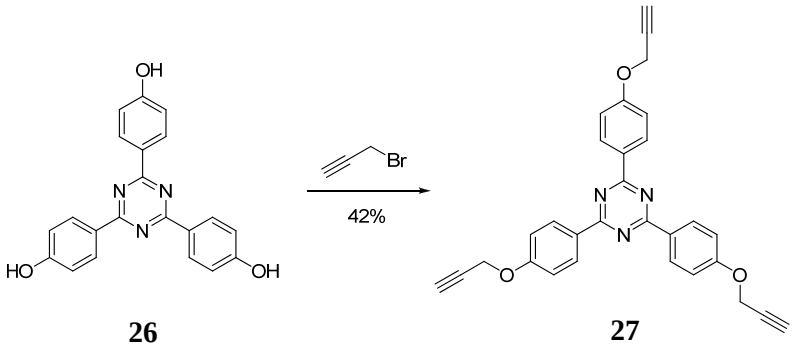
[12] Ranganathan, A., Heisen, B. C., Dix, I., Meyer, F. *Chem. Commun.* **2007**, 3637.



25 **26**

Scheme 24.

Compound **26** was involved in a reaction with propargyl bromide, using NaOH solution 50% in water and TBAB in CH_2Cl_2 to give the new derivative **27** in low yield (8%). The literature data furnished us another strategy for the synthesis of compounds with terminal acetylene groups.[13] In this way, the reaction was performed using K_2CO_3 as a base, toluene at reflux temperature (**Scheme 25**). The yield was substantially increased (42%).



26 **27**

Scheme 25.

Mono and bidimensional NMR spectroscopy studies confirmed the structure of molecule **27**. ^{1}H NMR (**Figure 51**) is in concordance with a symmetric structure, protons $H_{2'}$ and $H_{3'}$ being shifted as two doublets at 8.72 ppm (^3J = 7.5 Hz) and 7.13 ppm (^3J = 7.5 Hz), respectively. In aliphatic region of the spectrum, a doublet at 4.81 ppm (^4J = 2.5 Hz) is assigned for CH_2 protons and a triplet at 2.57 ppm (^4J = 2.5 Hz) appears for CH proton from the triple bond.

[13] (a) Berscheid, R., Nieger, M., Vöegtle, F. *J. Chem. Soc., Chem. Commun.* **1991**, 1364; (b) Morales-Sanfrutos, J., Ortega-Munoz, M., Lopez-Jaramillo, J., Hernandez-Mateo, F., Santoyo-Gonzalez, F. *J. Org. Chem.* **2008**, *73*, 7772.

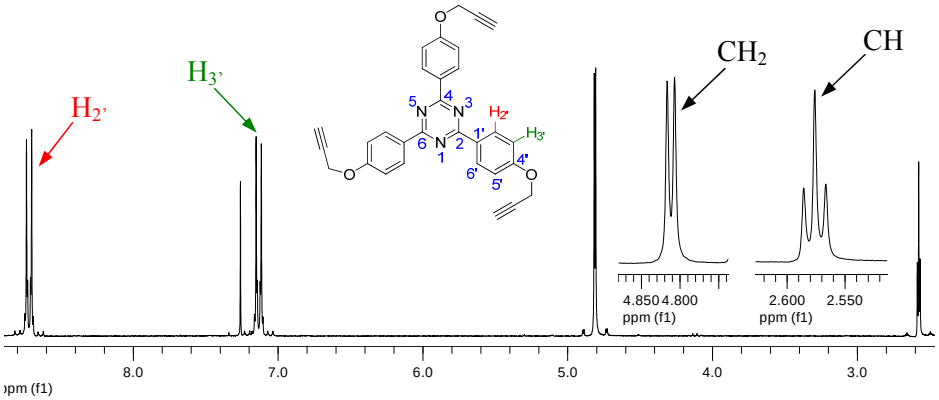


Figure 51. ^{1}H NMR fragment (250 MHz, $CDCl_3$) of compound **27**.

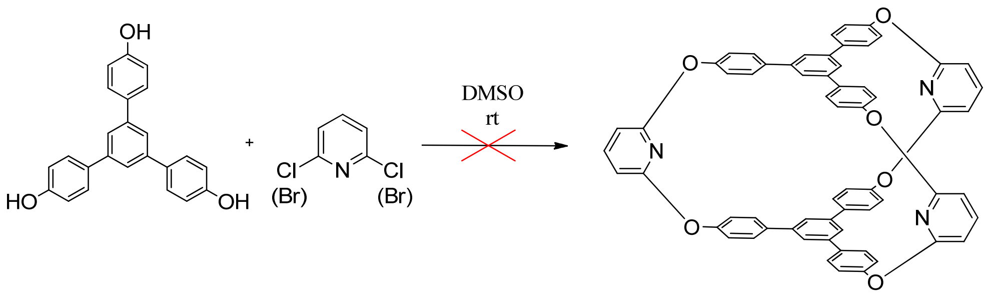
4.2. CAGE MOLECULES CONTAINING TRIS(PHENYL)BENZENE UNITS

With our C_3 aromatic units in hands, we next investigated synthetic methodologies for their use in cage macrocyclic preparation. For this, we adopted an intermolecular condensation as described in objectives.

4.2.1. The synthesis and structural analysis

Our intents to prepare macrocycle **38** (**Scheme 31**) were based on literature studies.[14] The macrocyclisation reaction was made in DMSO, at room temperature, using as starting materials compound **11** and the commercial dichloro- (**37a**) or dibromopyridine (**37b**) and cesium carbonate as a base. In both cases, the target compounds were not obtained, only the starting materials being found at the end of the reaction. Another idea was to change the base, using a stronger one. In this way, triethylamine was used, the temperature being rise at 80^{o}C. The expected compound could not be obtained, starting materials being recuperated.

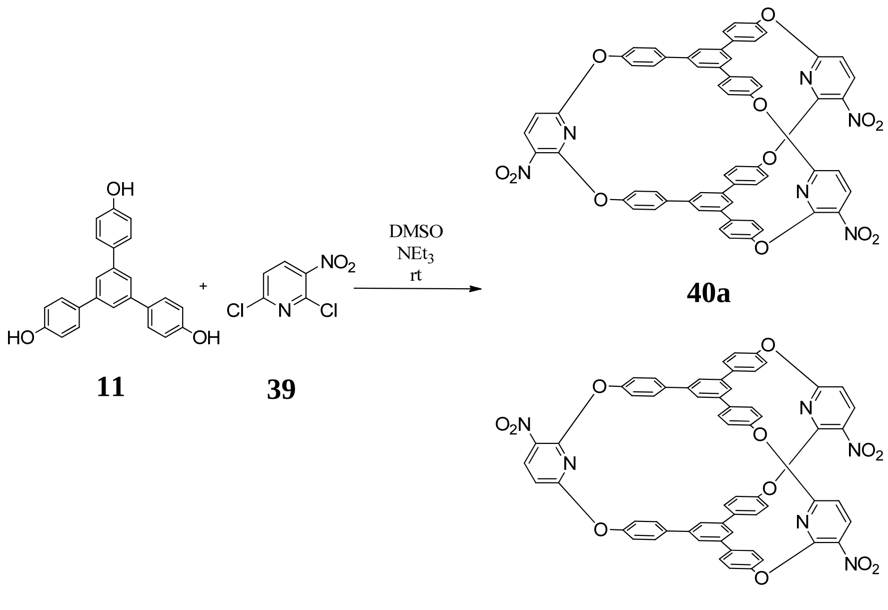
[14] Katz, J. L., Selby, K. J., Conry, R. R. *Org. Lett.* **2005**, *7*, 3505



11 **37a, b** **38**

Scheme 2.

The synthesis of cage molecules **40a** and **40b** was performed using as starting materials the commercial compound 2,6-dichloro-3-nitropyridine **39** and the compound **9** (**Scheme 32**). The isolation of the two formed isomers was not possible.

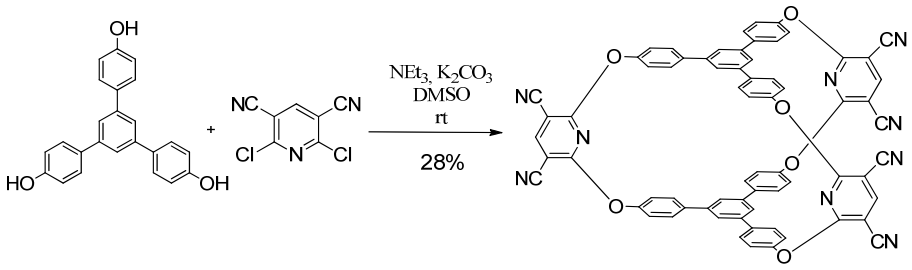


11 **39**

40b

Scheme 32.

In the case of using 2,6-dichloro-3,5-dicyanopyridine **41** instead of dichloropyridine, the new cage molecule **42** is obtained in 28% yield (**Scheme 33**). The reaction was achieved by using triethylamine as a base and potassium carbonate as “template” in DMSO at 80°C.



11 **41** **42**

Scheme 33.

The drawn structure of cage molecule **42** is proved by NMR spectroscopy, mass spectrometry and X-Ray diffraction studies. Also, UV-Vis and fluorescence spectra were employed for characterization of the macrocycle **42**.

The aromatic region of the ^{1}H NMR spectra of the macrocycle **42** exhibits the expected number and pattern of resonances (**Figure 58**). A singlet at 9.11 ppm is assigned for the proton H_9 from pyridine ring. Protons H_4 shift as doublets at 7.75 ppm (^{3}J = 8.4 Hz) while protons H_5 shift as doublets downfield at 7.15 ppm (^{3}J = 8.4 Hz). The H_1 protons shift at 7.66 ppm as a singlet.

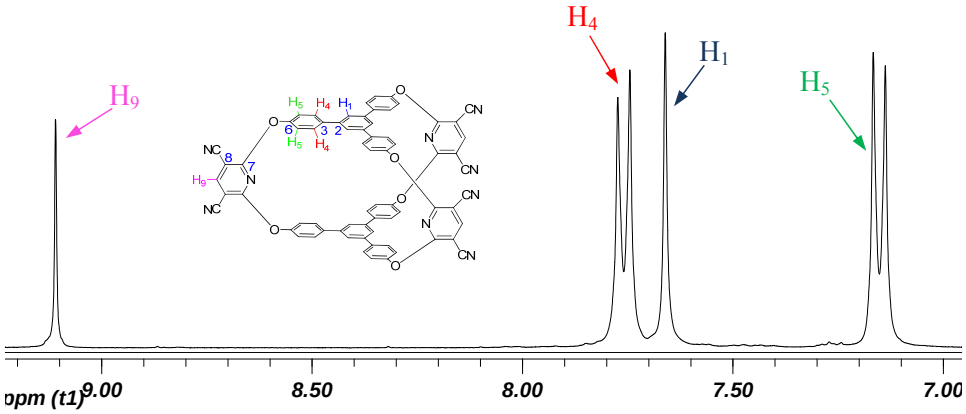


Figure 58. ^{1}H NMR fragment (300 MHz, DMSO-d_6) of macrocycle **42**.

^{13}C NMR was employed for a characterization of product **42** (**Figure 59**). Six singlet resonances for quaternary carbons are highlighted: δ (ppm): 89.14 (C_8), 113.00 (CN), 136.84 (C_2), 139.07 (C_3), 150.23 (C_6) and 164.00 (C_7). A set of four signals for tertiary carbons can also be evidenced: δ (ppm): 121.26 (C_5), 127.06 (C_4), 122.36 (C_1) and 150.85 (C_9).

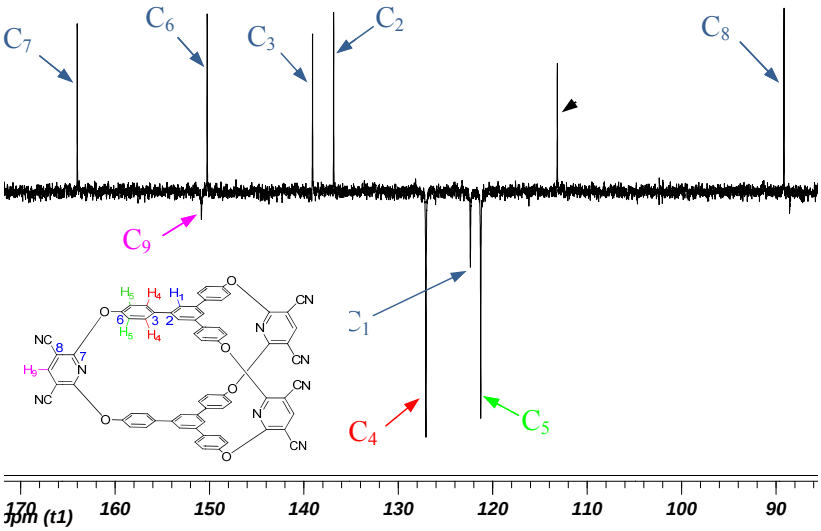


Figure 59. ^{13}C APT spectrum (75 MHz, DMSO-d_6) of **42**.

Mass spectrum of cage molecule **42** is in agreement with assigned structure. The molecular peak appears as ionic species: at *m/z* 1120 as [M+Cl$^-$], at *m/z* 1114.5 as [M+OCH$_3^-$], at *m/z* 1100 as [M+HO$^-$] and at *m/z* 960.5 as [M-Py derivative] (**Figure 62**).

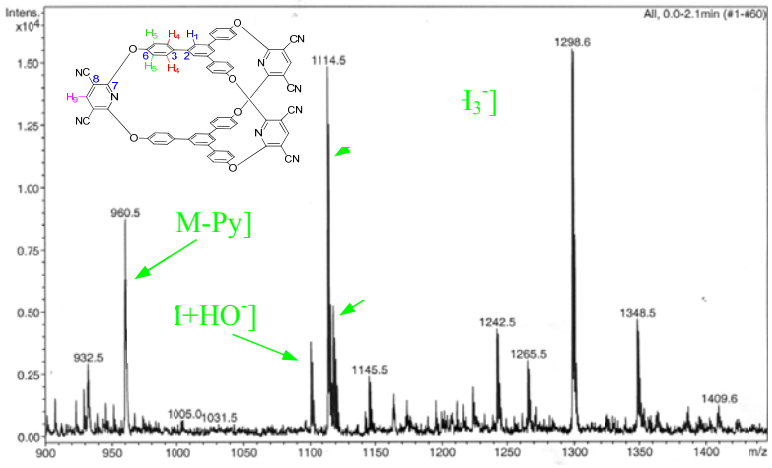


Figure 62. Mass spectrum of molecule **42**.

Slow evaporation from ethylacetate solution of **42** afforded colourless single crystals suitable for X-Ray diffraction. DIAMOND diagram showing the molecular structure of compound **42** is presented in **Figure 63**. The two trisphenylbenzene units are not planar, a

helicoidal form being observed. The spacing of the capping **A** type benzene rings from the trisphenylbenzene units is 3.963 Å, this distance being shorter than distance between the centroids of **B** type benzene rings (4.211 Å). The nitrogen atoms point directly into the cavity.

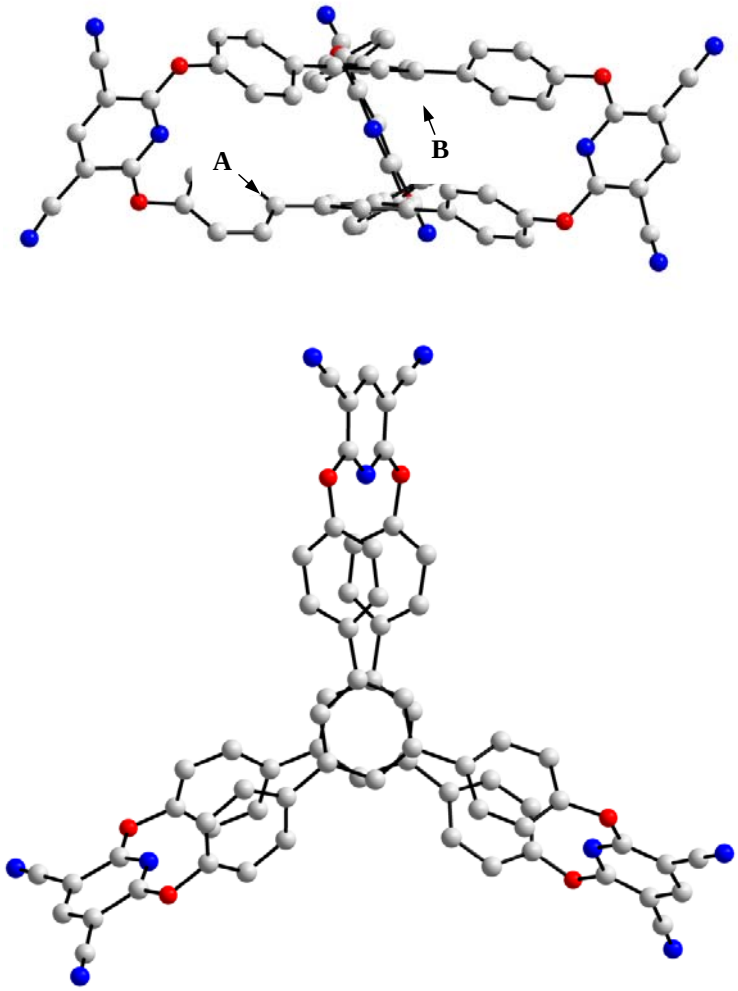
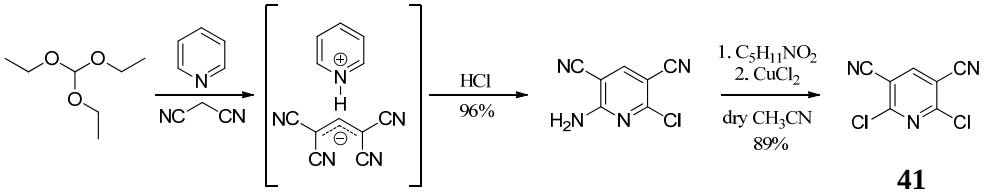


Figure 63. X-ray crystal structure of cage molecule **42** (Hydrogen atoms are removed for clarity).

In order to obtain the title cryptand **42**, the pyridine derivative **41** was synthesized (**Scheme 34**). The synthesis of the title compound is known in the literature, but, electron withdrawing CN groups, the acidic proton in position 4 and chlorine atoms, besides the *N* atom of the heterocycle ring, may induce interesting interactions in the lattice and support the interest for the single crystal X-ray investigations.[15]



Scheme 34.

Single crystal studies compound **41** was studied by X-Ray diffraction analysis. The single crystal was possible by slow evaporation of dichloromethane.

Molecule of **41** is planar, only the nitrogen atoms from the CN groups being slightly deviated from the plane defined by the pyridine ring [0.061(4) and 0.025(4) Å] and are situated on the same side of the plane.

The molecules are connected in chains by C—H···N interactions (C3—H3···N1^{i} = 2.54 Å) along *b* axis. The consecutive pyridine rings from the aggregates are not coplanar and are tilted one in regard to another with an angle of 56.5(1)°. The aggregates are linked in layers along the *ab* plane by C—Cl···N interactions [3.241(4) Å and 3,281(5) Å, respectively] (**Figure 65**).

[15] Woiczechowski-Pop, A., Varga, R. A., Terec, A., Grosu, I. *Acta Cryst. E, submitted.*

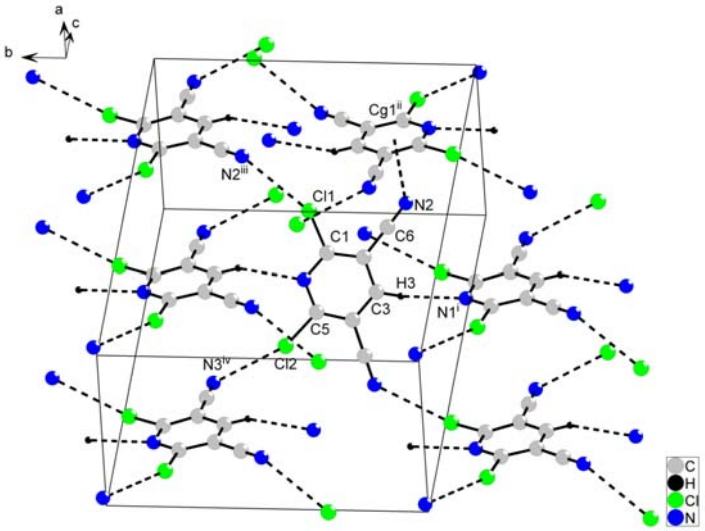


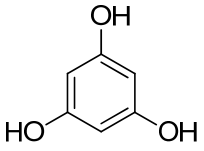
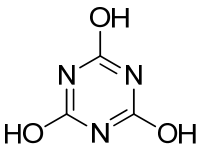
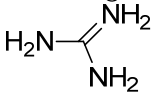
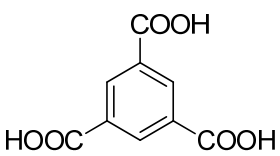
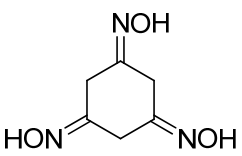
Figure 65. Intermolecular interactions (represented with dashed lines) in the crystal structure of **41**.

4.2.2. Molecular modeling studies

In the order to shed light on the structure and supramolecular properties of the cage molecule **42**, we have performed theoretical calculations using different aromatic guest molecules. The results were obtained using quantic chemistry package Gaussian 03 by applying DFT, B3LYP, BHandHLYP method.

A series of complexation studies were made using as *host* molecule the cryptand **42**, and as *guests* different inclusion products. In the table below guest molecules are shown.

Table 1. Guest molecules used in molecular modeling study.

Guest molecules		
		
		

Molecules used in these studies allowed us to design a macro- or supramolecular structure with extended cavities with two parallel units. The formed cavities can be used as molecular filters or molecular trap, for different neutral molecules. Based on molecular modeling studies we are able to predict if the formed cavity has the proper structure.

Geometrical optimization of cryptand shows that the two parallel aromatic units are not planar, but one is gliding against the other.

4.2.3. UV-Vis and fluorescence studies

In order to study the supramolecular properties of the cage molecule **42**, UV-Vis and fluorescence analyses were achieved.

As it can be seen from the spectrum (**Figure 75**), the maximum absorption band is located at 274 nm. The absorption in the UV region was due to the aromatic structure.

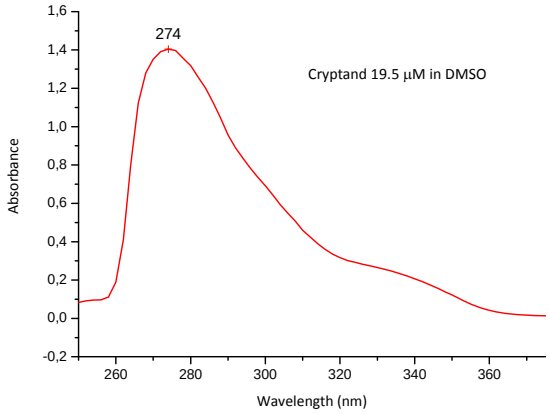


Figure 75. UV-Vis spectrum of compound **42** in DMSO (19.5 µM).

The light-emitting properties of the macrocycle have been also investigated. As it can be seen in **Figure 77**, the maximum emission band was at 380 nm (19.5 µM in DMSO).

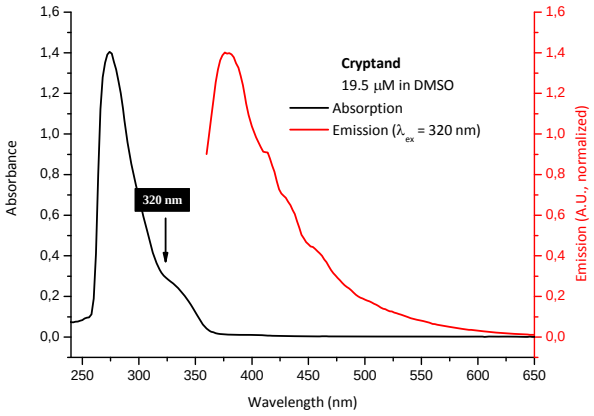


Figure 77. Fluorescence spectrum of cage molecule **42** in DMSO (19.5 µM).

Complexation properties of cage molecule **42** were further studied. In this way, according to molecular modeling studies, some guest molecules were used. The forming of host-guest complex was studied using fluorescence investigations.

The first complexation studies were performed using guanidinethiocyanate as a guest molecule. **Figure 80** shows the maxima emission bands for cage molecule **42** and for cryptand **42**/guanidinethiocyanate complex system. No significant effect can be observed for the complex, maximum band of emission being around 378 nm. To conclude, the complex is not formed or instable due to the absence of the hydrogen bonds between macrocycle **42** and guest molecule.

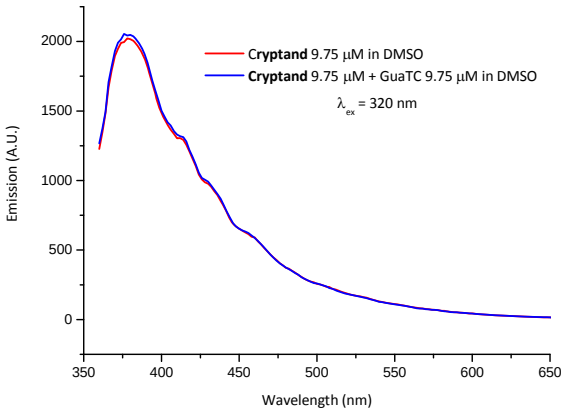


Figure 80. Overlapped fluorescence spectra of compound **42** and cryptand **42**/guanidinethiocyanate complex system.

Another molecule used as guest for analysis of complexation properties of **42** was 4,4'-dimethoxytrityl chloride (**Figure 82**). The UV-Vis spectrum shows that some modifications cannot be observed for the complex regarding the studied cage molecule. In time, the emission band for the guest molecule diminishes. A significant effect can be seen after one day, when the maximum emission band for 4,4'-dimethoxytrityl chloride cannot be observed.

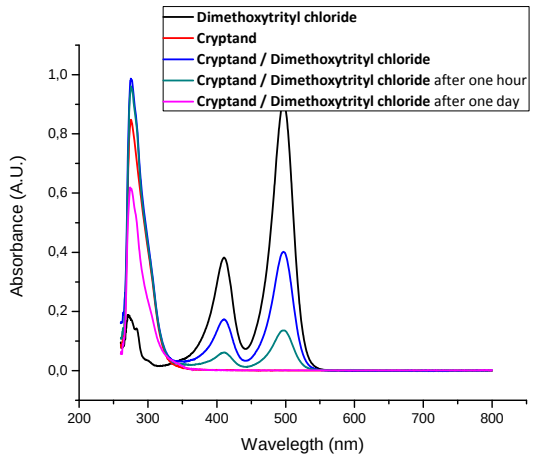
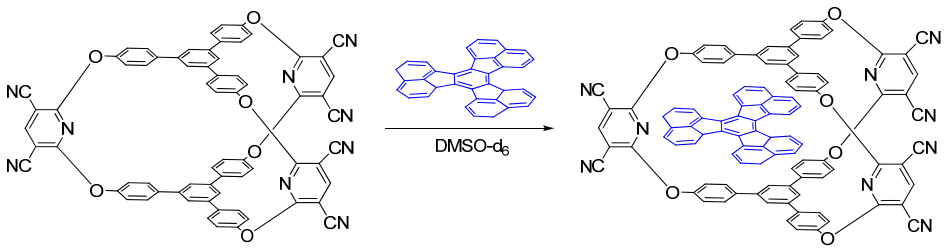


Figure 82. Overlapped UV-Vis spectra of **42**, dimethoxytrityl chloride and **42**/dimethoxytrityl chloride.

4.2.4. NMR studies

NMR studies were used to determine the complexation properties of cage molecule **42**.

First attempt was the reaction between macrocycle **42** and commercially decacyclene **31**, using DSMO-d_6 as solvent (**Scheme 35**) to obtain the complex species **43**. No crystals were obtained for X-Ray diffraction studies.



42 **43**

Scheme 35.

^{1}NMR spectrum of complex **43** is presented in **Figure 83**. No change can be detected with respect at the values of resonance signals comparatively with cage molecule **43** and decacyclene. Further studies are required to define the formation of the supramolecular complex **43**.

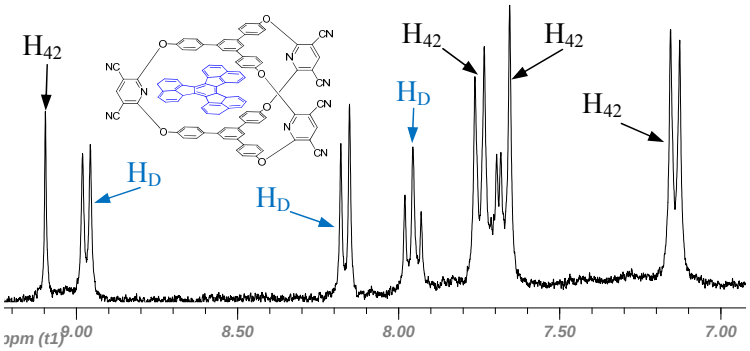
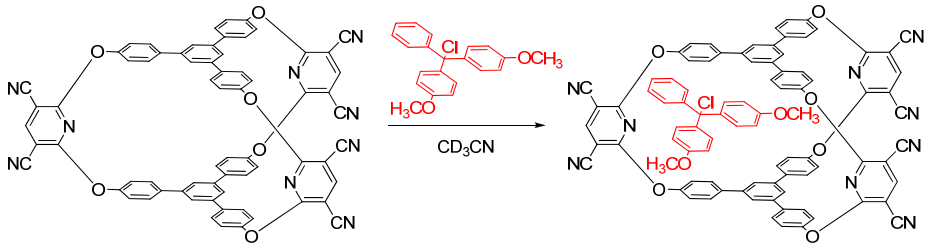


Figure 83. ^{1}H NMR fragment (300 MHz, DMSO-d_6) of complex **43**.

Compound **42** was reacted with 4,4'-dimethoxytrityl chloride **45** in acetonitril-d_3 at room temperature to obtain the complex **46** (**Scheme 37**). Compound **45** was chosen as a guest molecule due to the possibility to form trityl cation in acetonitril.



42 **46**

Scheme 37.

^{1}H NMR presented in **Figure 85** does not furnish sufficient information concerning the formation of the complex by the association between cryptand **42** and dimtethoxytrityl chloride. Further investigations (changing the reaction conditions) will be carried out.

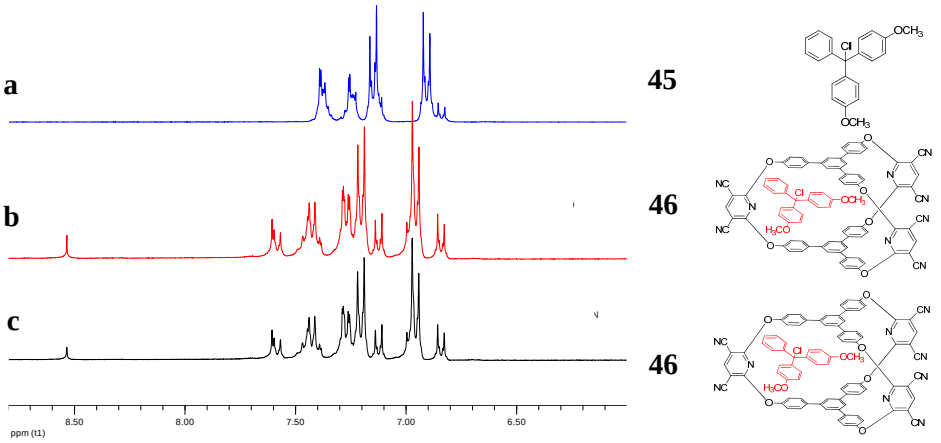


Figure 85. ^{1}H NMR fragments (CD_3CN) of a) 4,4'-dimethoxytrityl chloride **45**, b) **46** after one hour, c) **46** after one day.

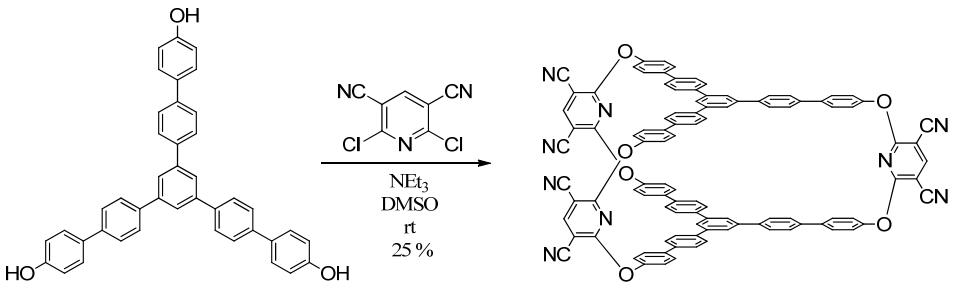
The results obtained are not sufficient to confirm the formation of a supramolecular complex between macrocycle **42** and different organic molecules. Further studies are required, involving either the change of reaction conditions or the use of other host planar organic molecules.

4.3. CAGE MOLECULES CONTAINING TRIS(BIPHENYL)BENZENE UNITS

4.3.1. Synthesis and structural analysis

Compound **15** was reacted with 2,6-dichloro-3,5-dicyanopyridine **41** and macrocyle **48** was obtained (**Scheme 39**). Using cesium carbonate as a base, the target compound was not obtained, only the starting materials being recovered. The synthesis was made in DMSO at 80^{o}C, using different stronger bases (triethylamine, diisopropylethylamine and DBU). In all cases the yield was almost the same (25%).

To conclude, as in the case presented before, the base has also an important role in macrocyclization reaction.



15 **48**

Scheme 39.

In aromatic region of cage molecule **48** a singlet at 9.11 ppm is assigned for $H_{4''}$, a singlet at 7.65 ppm corresponds to H_2. Protons $H_{3''}$ and $H_{3'}$ shift as doublets at 7.42 ppm (^3J = 8.1 Hz), 7.14 ppm (^3J = 8.7 Hz) respectively. Two doublets are overlapped between 7.56 and 7.59 ppm and are assigned for protons $H_{2'}$ and $H_{2''}$ (**Figure 86**).

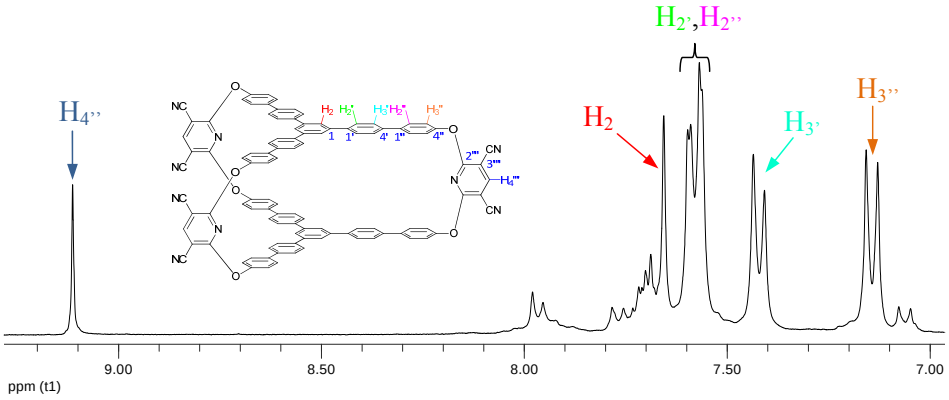
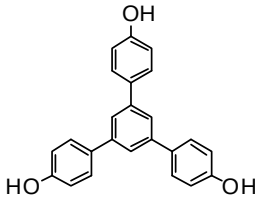
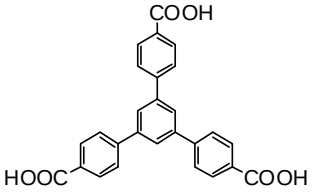
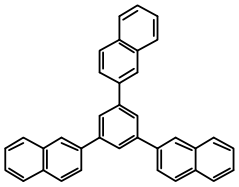
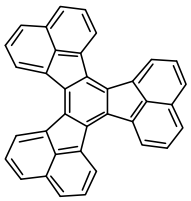


Figure 86. ^{1}H NMR fragment (300 MHz, DMSO-d_6) of **48**.

4.3.2. Molecular modeling studies

In order to perform optimization process, the geometry of molecule **48** it was considered that the two tris(biphenyl)benzene units of molecule are parallels. In **Table 5** guest molecules used in complexation study are presented.

Table 5. Guest molecules used in molecular modeling studies.

Guest molecules	
	
	

4.3.3. UV-Vis and fluorescence studies

UV-Vis analysis

Electronic transitions have been evidenced by radiations in ultraviolet and visible spectral domain for the macrocycle and their complexes with decacyclene and the starting material. The UV-Vis spectra were performed using 10^{-5}-10^{-6} M concentrations in DMSO.

UV-Vis spectrum of the cryptand **48** in DMSO is illustrated in **Figure 91**. The spectrum is characterized by one single absorption maximum at λ = 299 nm.

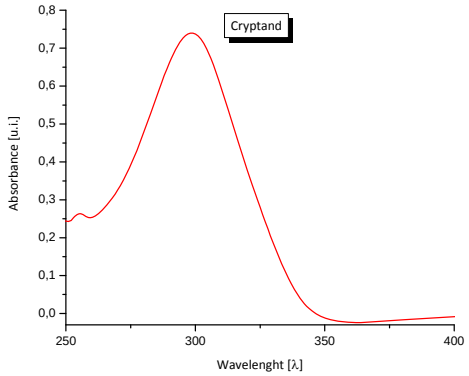


Figure 91. UV-Vis spectrum of cage molecule **48** in DMSO.

Cryptand molecule **48** has been used in some UV-Vis studies as host molecule for the 1,3,5-tris(4-hydroxyphenyl)benzene derivative **11** or decacyclene **31**.

When the ratio between host and guest molecule is changed (1/1), an additive effect of individual absorption maxima can be observed (**Figure 95**).

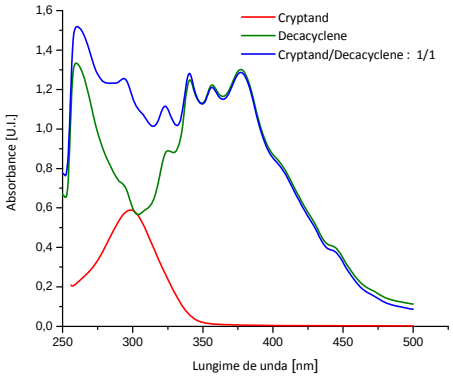


Figure 95. Overlapped UV-Vis spectra of **48**, Decacyclene, **48**/Decacyclene (1/1) in DMSO.

UV-Vis spectroscopy studies showed (major changing of the position of the absorption maximum of the complex with respect to the absorption maxima of the two components involved in complexation reaction) indicated the formation of a stable complex by the association between cryptand **48** and decacyclene.

Fluorescence analysis

The light-emitting properties of cage molecule **48** have been also investigated. Fluorescence spectrum was recorded between 350-450 nm, using different excitation wavelengths (305 nm, 328 nm and 342 nm). The maximum emission band has been found at 382 nm (**Figure 96**).

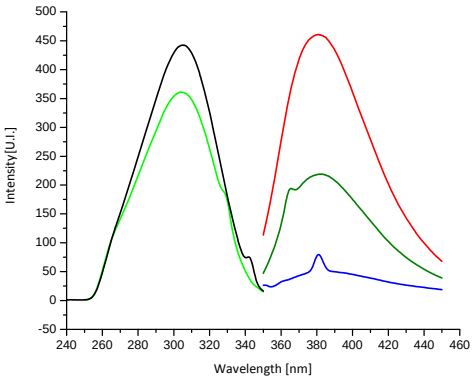


Figure 96. Fluorescence spectrum of **48** in DMSO.

Complexation study by fluorescence investigations (**Figure 98**) confirmed the results highlighted above. The formation of a stable supramolecular complex cryptand **48**/decacyclene conduct to the quenching of the fluorescence emitted by the cage molecule.

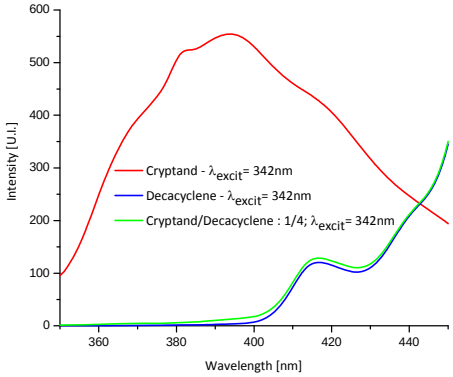


Figure 98. Overlapped fluorescence spectra of **48**, Decacyclene, **48**/Decacyclene (1/4) in DMSO.

4.3.4. Cyclic voltammetry studies

Cyclic voltammetry studies have been made to observe changes of oxidation and reduction potentials in the case of cryptand **48**/guest molecules complex systems by comparison with those of the molecules involved in complexation reaction.

The CV of compound **48** deposed in potentiodinamic conditions (**Figure 100**) shows a large redox system.

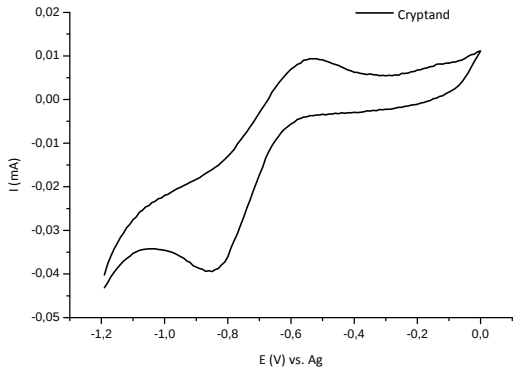


Figure 100. CV of compound **48** in 0.1 M ammonium tetrabutylperchlorate/DMSO (v = 100 mV/sec).

The study of complexation properties of cage molecule **48** with decacyclene has been performed by cyclic voltammetry in ammonium tetrabutylperchlorate solution. In **Figure 101** a negative shift of oxidation peak with about 200 mV with respect to cage molecule and with 100 mV with respect to decacyclene. This behavior was explained by the caption of decacyclene inside de cavity formed in macrocycle.

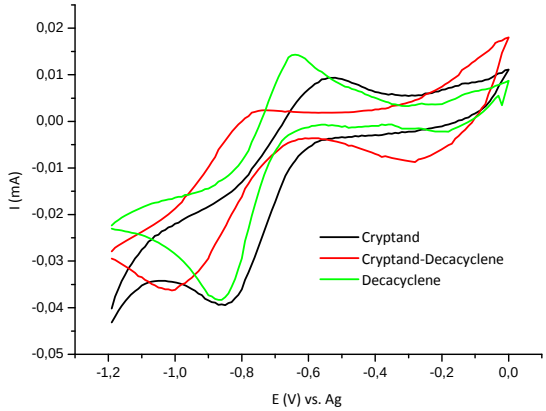
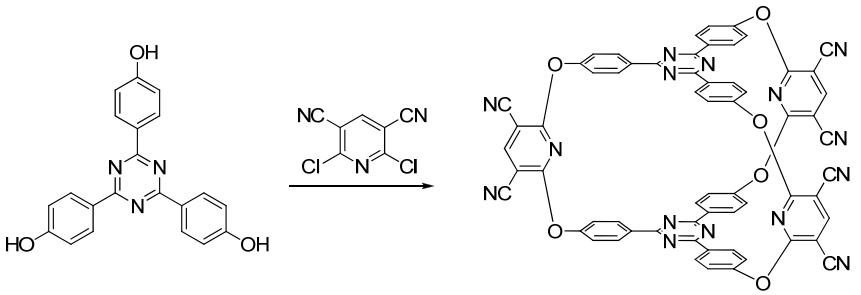


Figure 101. Overlapped CV of compound **48**, decacyclene and **48**/decacyclene in 0.1 M ammonium tetrabutylperchlorate/DMSO (v = 100 mV/sec).

4.4. CAGE MOLECULES CONTAINING 1,3,5-TRIS(PHENYL)-2,4,6-TRIAZINE UNITS

4.4.1. Synthesis and structural analysis

The three-dimensional cage molecule **49** was obtained in 42% yield by the reaction between trisphenol **26** and 2,6-dichloropyridine-3,5-carbonitrile **41** in DMSO (**Scheme 40**).



26 **49**

Scheme 40.

The structure of compound **49** was proved by NMR spectroscopy (^{1}H NMR, ^{13}C NMR, COSY and HSQC) and mass spectrometry.

A freshly prepared solution of **49** could be analyzed by ^{1}H NMR spectroscopy (**Figure 103**) showing signals for protons $H_{2'}$ at 8.50 ppm (^{3}J = 8.75 Hz) and for $H_{3'}$ at 7.23 ppm (^{3}J = 8.75 Hz). One singlet signal also appears at 9.16 ppm and is assigned for protons $H_{4''}$.

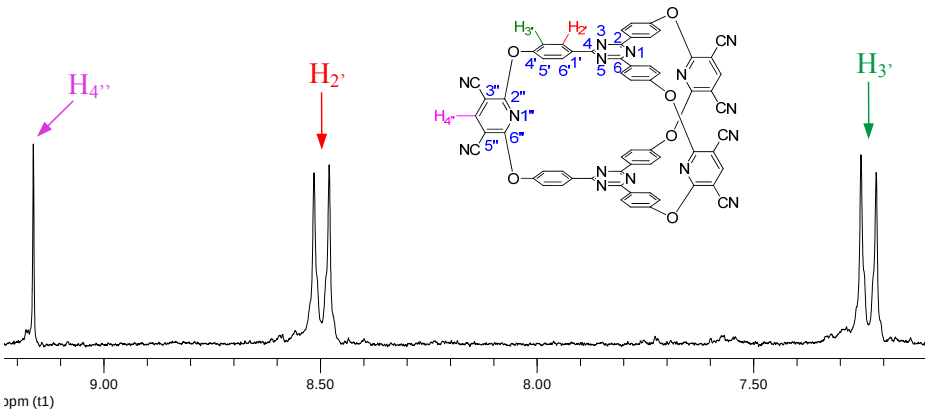


Figure 103. Fragment of ^{1}H NMR spectrum (250 MHz, DMSO-d_6) of compound **49**.

ESI– spectroscopy was employed to characterize cage molecule **49**. In this case cleavage fragment at *m/z* 1106.7 is detected, which correspond to the molecular peak. This product ion may then undergo a pyridine derivative loss to yield the fragment ion at *m/z* 981.5 [M-Py+HO$^-$] (**Figure 107**).

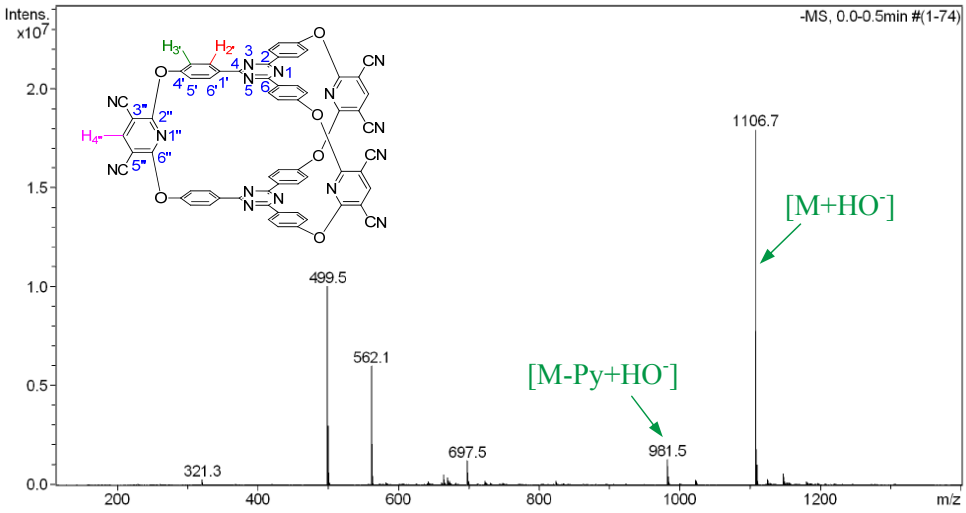
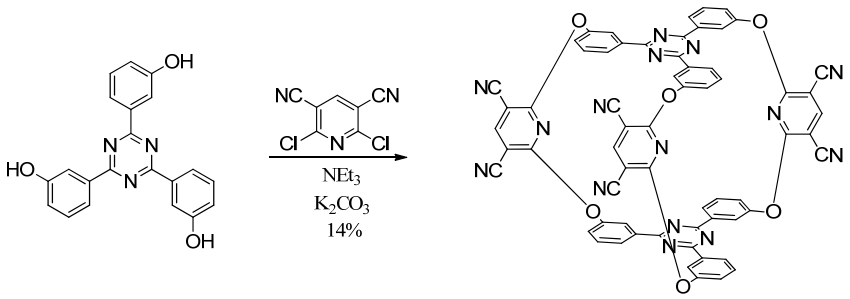


Figure 107. ESI– spectrum of macrocycle **49**.

Compound **51** was further involved in a macrocyclization reaction in DMSO (triethylamine and potassium carbonate), to obtain cage compound **52** in 14% yield (**Scheme 42**).



51 **52**

Scheme 42.

NMR spectroscopy analyses are not concluding in the characterization of the new cage molecule obtained. Further studies will be employed to confirm the structure of the compound (variable temperature NMR, change of the deuterated solvent). APCI+

spectrum (**Figure 108**) of **52** shows a peak at *m/z* 1090.2, corresponding to the protonated ionic form [M+H$^+$].

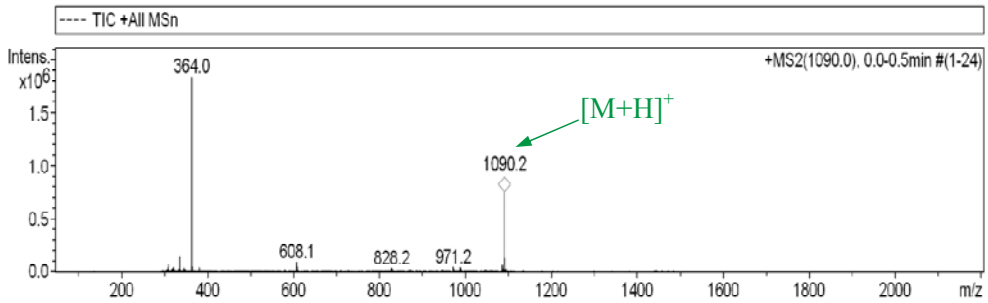
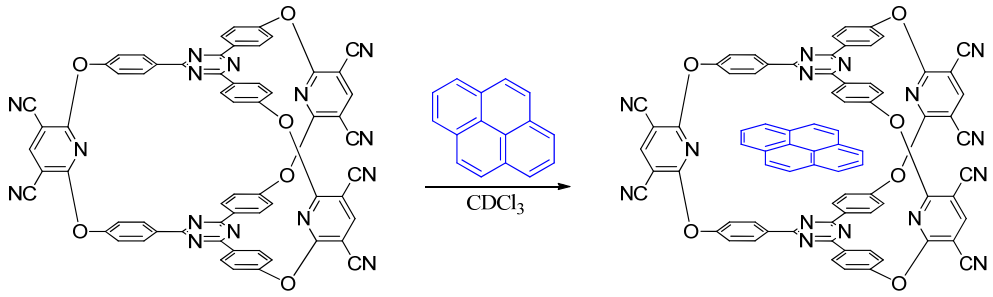


Figure 108. APCI+ spectrum of macrocycle **52**.

4.4.1. Complexation properties by ^{1}H NMR studies

In order to study the supramolecular properties of cage molecule **49**, some organic molecules were used as guests (anthracene and pyrene). ^{1}H NMR analyses were carried out to determine the complexation properties of the macrocycle **49**.

Cage molecule **49** was reacted with pyrene in deuterated chloroform at room temperature to obtain target complex **54** (**Scheme 44**).



49 **54**

Scheme 44.

When the spectra of macrocycle **49**, pyrene and complex **54** are compared (**Figure 110**), no changes are observed with respect to the signals for the cage molecule. A new set of signals are observed between 7.17 ppm and 7.28 ppm.

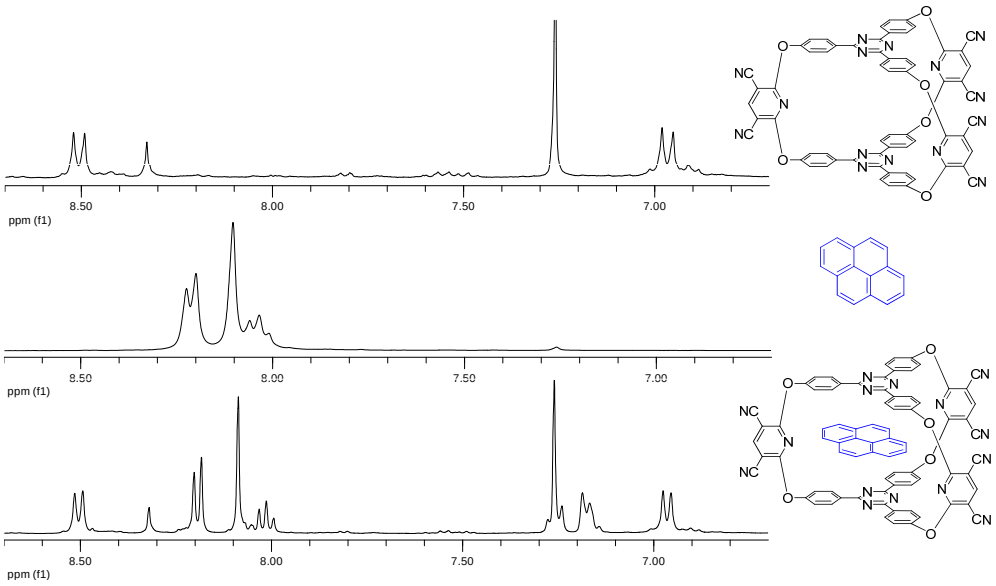


Figure 110. ^{1}H NMR fragments (300 MHz, $CHCl_3$) of cage molecule **49**, pyrene and complex **54**.

The results obtained by NMR studies are interesting, but not concludent. Further analyses will be performed to confirm the exact structure of the complexes.

5. CONCLUSIONS

◊ Starting from commercially available acetophenone, benzonitrile and 2-acetylnaphthalene derivatives, 7 trisubstituted aromatic building blocks with C_3 symmetry (**2**, **5**, **10**, **20**, **23**, **26** and **29**) were synthesized by a trimerization reaction in acid conditions (triflic acid) in different solvents. Compound **29** was first described in this thesis.

◊ An improved and less toxic synthetic methodology (tetrahydrofurane and dimethylformamide instead of benzene and N,N-formylpiperidine) was employed for the synthesis of 2 triformyl derivatives (**3** and **6**); among them, no data for compound **6** are known to date.

◊ Suzuki coupling reaction was used to synthesize 1 biphenylketone and 2 tris(biphenyl)benzene derivatives (**13**, **14** and **16**), according to literature data.

◊ 4 trihydroxy derivatives (**7**, **11**, **15** and **17**) were obtained by the reduction of the carbonyl groups or by demethylation reaction with pyridinium hydrochloride. Among them, 3 compounds are not known in literature.

◊ Derivatization of the trihydroxy derivatives by reactions with propargylbromide, adapting a procedure reported in literature for similar compounds, led to 3 new tripodands with terminal triple bonds (**8**, **18** and **27**). The yield for the synthesis of compound **27** was raised up from 8% to 42% by changing the reaction conditions.

◊ Following a typical procedure, 1 new triazide (**24**) was synthesized.

◊ The intermediates were characterize by monodimensional and bidimensional NMR spectroscopy, mass spectrometry, UV-Vis and fluorescence analyses.

◊ 2,6-dichloropyridine-3,5-dicarbonitrile was for the first time analyzed by X-ray diffraction analysis.

◊ 2 new isomer cage molecules (**40a** and **40b**) with trisphenylbenzene units as spacers and 3-nitropyridine units as linkers were obtained, but they are not separated yet.

◊ 1 new macrocycle (**42**) based on trisphenylbenzene as central units and pyridine-3,5-dicarbonitrile as linkers was synthesized and completely characterized. NMR spectroscopy, APCI- mass spectrometry, UV-Vis, fluorescence and X-ray crystallography were employed to describe the cage molecule. Complexation properties of cage molecule **42** with different neutral organic compounds were investigated using molecular modeling, NMR, UV-Vis and fluorescence.

◊ 1 new cage molecule with tris(biphenyl)benzene units **48** was synthesized, characterized by NMR spectra and the complexation properties were investigated by molecular modeling, UV-Vis, fluorescenece and cyclic voltammetry analyses.

◊ Starting from triazine derivatives 2 new cage molecules were obtained (**49** and **52**). Compound **49** was characterized by NMR spectroscopy and mass spectrometry. NMR spectrometry studies were carried out to investigate the complexation of cage molecule **49**. The formation macrocycle **52** was proved by ESI-MS spectrometry.

◊ The complexation studies proved that the formed cavity of the cage molecules are suitable for binding different guest molecules, but the supramolecular complexes could not be isolated and no association constant could be measured.

Keywords: cage molecule, complexation, host-guest, cryptand, UV-Vis, fluorescence, cyclic voltammetry, tris(phenyl)benzene, tris(biphenyl)benzene, 1,3,5-tris(phenyl)-1,3,5-triazine, supramolecular complexes.