"BABES-BOLYAI" UNIVERSITY
Faculty of Chemistry and Chemical Engineering

CONTRIBUTIONS TO THE SYNTHESIS AND COMPLEXATION OF SOME MACROCYCLIC AND HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN

Summary of Phd Thesis

Monica BUCŞA

Scientific Advisor:
Prof. Dr. Mircea VLASSA

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Keywords: perazacrown ethers, metal complexes of functionalized azacrown ethers, organoselenium compounds, acridines derivatives, Raman spectroscopy.

INTRODUCTION

Paper entitled "*Contributions to the synthesis and complexation of macrocyclic and heterocyclic compounds containing nitrogen*" is a part of a widely used field of supramolecular and heterocyclic chemistry, the new synthetic methods and the prepared compounds having numerous applications in chemistry, medicine or industry. Crown ether complexes are used in various fields of human activity: synthetic metallo-enzymes[1], contrast agents in magnetic resonance (MRI)[2], radioimunotherapy[3], cancer or AIDS, treatment [4], hydrolysis catalysts of DNA or RNA [5], electride[6], molecular photonic devices,[7] or crystalline engineering spacer.[8] Acridine derivatives are widely used as bioactive compounds with antimicrobial and antiprotozoal activities.[9]

The research was structured in two chapters. The first chapter describes some of the literature and original contributions made in the studies of crown ethers synthesis and their complexation. The most important property of these ligands is to encapsulate cations in their cavity to form stable complexes. The directions pursued in the individual contributions were the follows: (a) the development of a simple and economically efficient methods for the perazacrown ethers synthesis, (b) obtaining new perazacrown ethers using the new synthetic method, (c) functionalization of perazacrown ethers and their complexation with transitional metals and (d) synthesis of new selenium ligands.

The second chapter presents the synthesis and electrochemical behavior of some acridine derivatives and a new approach of electrochemical impedance spectroscopy when only charge transfer and diffusion limitations are present and the new results, concerning the parametric equations of Nyquist plot corresponding to redox multielectrodes has been obtained.

A. NEW METHODS FOR THE SYNHESIS OF MACROCYCLES AND THEIR DERIVATIVES

I. A NEW METHOD FOR AZACROWN PREPARATION

I. 4. Original contributions

This subchapter presents the original contributions to the studies on the synthesis of peraza crown ethers. Starting from commercially available materials, crown ethers were obtained using known or new synthesis techniques.

Richman-Atkins method was used to prepare a large variety of peraza crown ethers. In the first stage of this method the bis-sulfonamide sodium salt in an inert atmosphere is obtained. The cyclization of this salt with ester sulfonate in an aprotic solvent (DMF), is using sometimes but not required, high-dilution technique of Stetter and Ross procedure. [45]

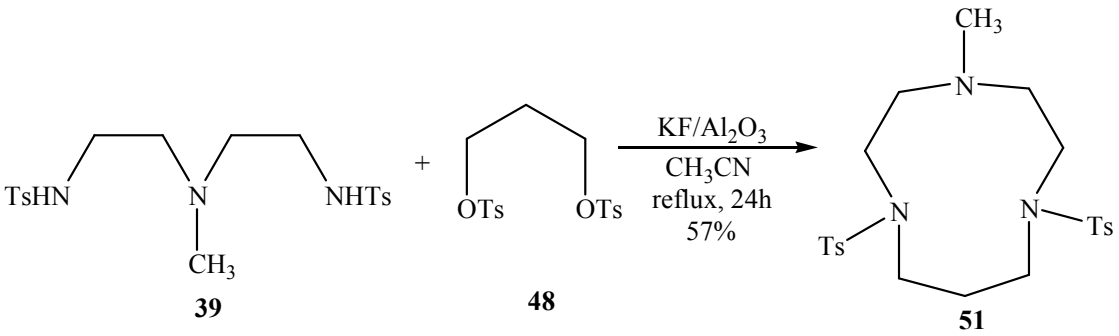
We tried to prepare peraza crown compounds through a new synthetic method, in a single step avoiding work in an inert atmosphere and high-dilution condition. We could synthesis the desired compounds using ditosylates as the reagents in the presence of KF/Al_2O_3 which influences the reaction medium by its strongly basic nature.[47]

I. 4. 3. Synthesis of 1-methyl-4,8-bis(p-toluenesulfonyl)-1,4,8 triazacyclodecane

a) in the presence of KF/Al_2O_3 [70]

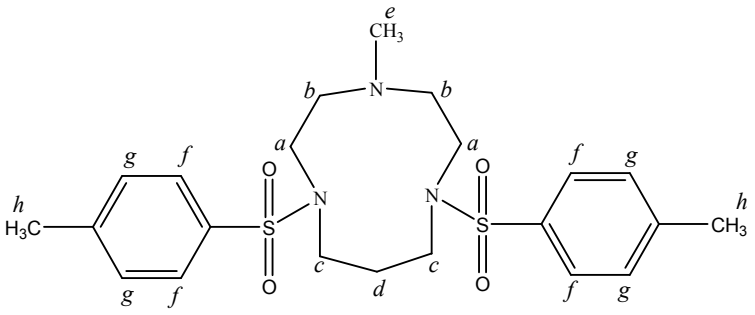
The intermediates were prepared according to the literature.[71-74]

To obtain the 1-methyl-4,8-bis(p-toluenesulfonyl)-1,4,8 triazacyclodecane **51** we mixed 4-methyl-1,7-bis(p-toluenesulfonyl)-1,4,7-triazaheptane **39** with 1,3-bis(p-toluenesulfonyl-oxy)-propane **48** and with KF/Al_2O_3 in acetonitrile, at reflux (scheme 16). The identity of this new aza-crown ether was confirmed by ^{1}H-NMR,^{13}C-NMR and Mass spectrometry analysis.



Scheme 16. Synthesis of 1-methyl-4,8-bis(p-tolylsulphonyl)-1,4,8 triazacyclodecane **38** in the presence of KF/Al_2O_3

^{1}H-NMR spectrum presented in figure 1 shows two doublets of 4H each at 7.68 ppm (*f*) respectively 7.34 ppm (*g*) corresponding to the p-toluenesulfonyl protons located on the aromatic ring. In the aliphatic area three triplets occurs at values 3.27 ppm (*a*), 3.12 ppm (*c*), respectively 2.79 ppm (*b*) corresponding to 12 protons (4H for each signal) and one multiplet at 1.76 ppm (*d*) representing the signal of 2H bonded by $NCH_2CH_2CH_2N$ from triazacyclodecane. The singlet at 2.35 ppm (*e*) corresponds to 3H methyl bonded of C-N and the singlet at 2.45 ppm (*f*) corresponds to 3H methyl bonded of C-Ar.



51

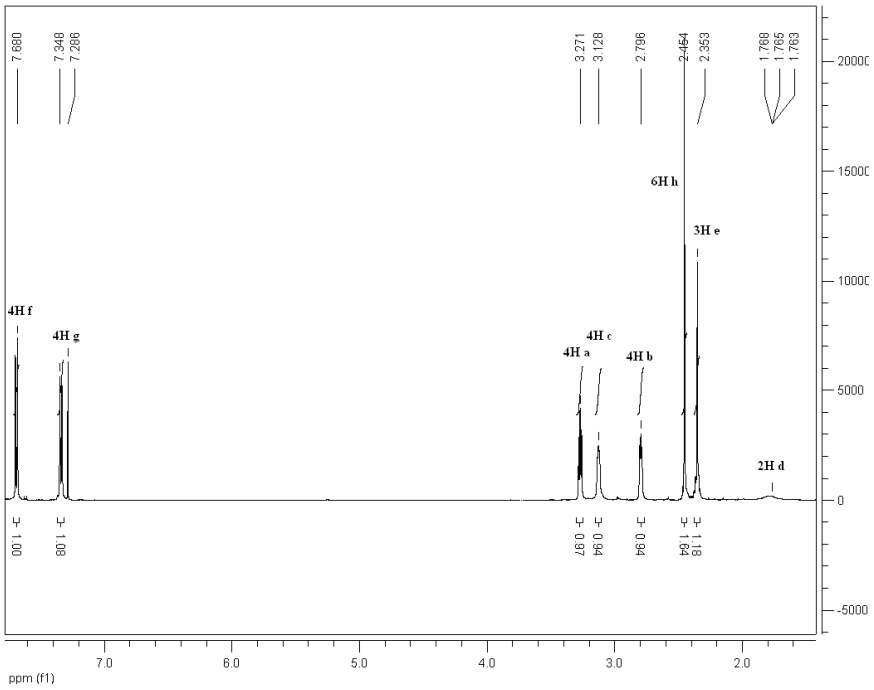
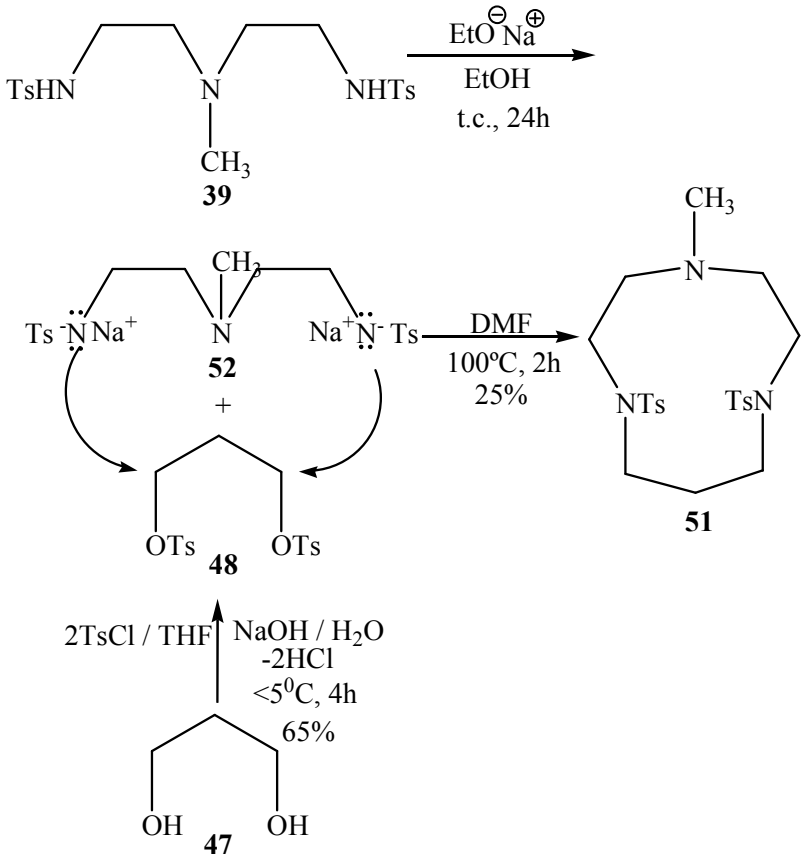


Figure 1. ^{1}H-RMN spectrum of 1-methyl-4,8-bis(p-toluenesulfonyl)-1,4,8 triazacyclodecane **51**

b) Richman-Atkins Methods

We prepared monomethylated bistosylated triazacyclodecane **51**, by Richman-Atkins method, starting from disodium salt of 4-methyl-1,7-bis(p-toluenesulfonyl)-1,4,7-triazaheptane **28** with 1,3-bis(p-toluenesulfonyl-oxy)-propane **48** in dry DMF (scheme 17).



Scheme 17. Synthesis of 1-methyl-4,8-bis(p-toluenesulfonyl)-1,4,8 triazacyclodecane **51**, by Richman-Atkins method

Compound **51** was synthesized by two methods and the yields of reactions are presented in Table 3.

Table 3. Preparation yields of 1-methyl-4,8-bis(p-toluenesulfonyl)-1,4,8-triazacyclodecane **51**.

Synthesis method	**Yield %**
In the presence of KF/Al_2O_3	57
Richman-Atkins method	25

Comparative analysis of the presented data in tabel 3 shows that the new method is greater than Richman-Atkins method in terms of yield and has fewer synthetic steps.

This new synthetic method was also used for preparation of some known crown ethers like: 1-methyl-1,4,7-triazacyclononane **43,** 1,4,7-triazacyclodecane **50**, 1-methyl-1,4,7,10-tetraazacyclododecane **56**, 1,4,7,10,13,16,19-heptatosyl-1,4,7,10,13,16,19-heptaazacycloheneicosane **64** and 1,4-bis(*p*-toluenesulfonyl)-1,4,7-triazacyclononane **68**.

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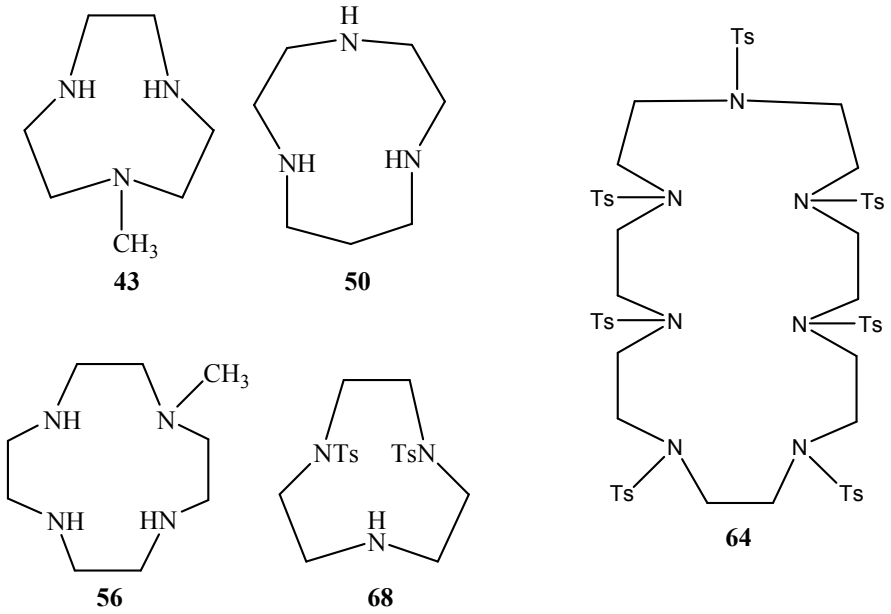


II. AZA CROWN ETHERS FUNCTIONALIZATION. METAL COMPLEXES OF FUNCTIONALIZED AZACROWN ETHERS

II.1. Aza crown ethers complexation

The most important property of these ligands is to encapsulate cations in their cavity in order to obtain their stable complexes.

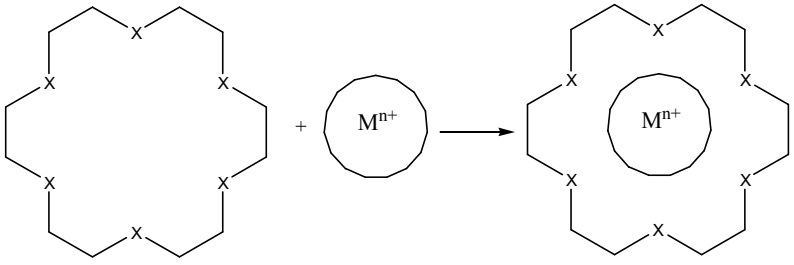


Figure 9. Complexation reaction of some crown ether with a metal ion

The complexation of the ligands depends on:

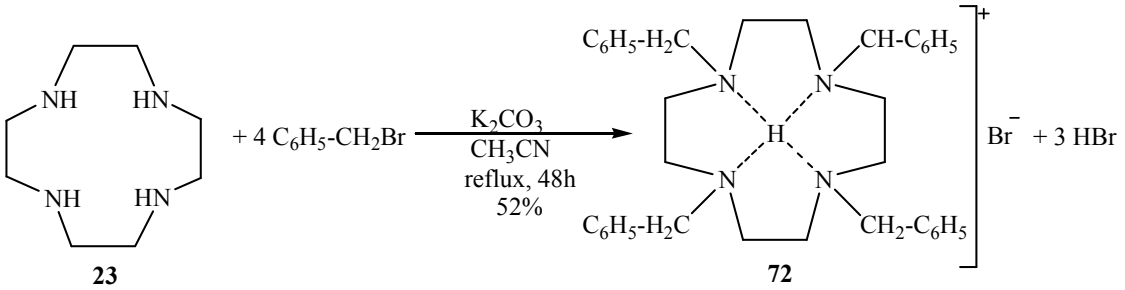
- cavity size,
- ligand rigidity,
- ligand symmetry,
- nature of donor atom. [106]

II. 2. Original contributions

In this part of thesis I present the synthesis of the crown ether **72**, according to literature[125] and its complexation reaction with different metal cations.

II. 2. 1. Synthesis of 1,4,7,10-tetrakisbenzyl-1,4,7,10-tetraazacyclododecane · HBr

1,4,7,10-tetrakisbenzyl-1,4,7,10-tetraazacyclododecane · HBr, **72,** was obtained from benzyl bromide and cyclen in acetonitrile, in the presence of potassium carbonate according to scheme 27.

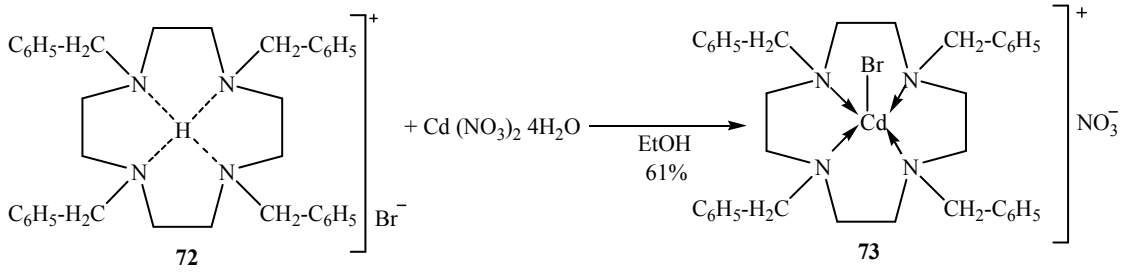


23 **72**

Scheme 27. Synthesis of 1,4,7,10-tetrakisbenzyl-1,4,7,10-tetraazacyclododecane · HBr, **72**

II. 2. 2. Synthesis of 1,4,7,10- tetrakisbenzyl-1,4,7,10-tetraazacyclododecane · HBr complex with Cd(II)

The reaction of the crown ether **72** with $Cd(NO_3)_2 \times 4H_2O$ in dry ethanol according to scheme 28, afford the complex **73**.



Scheme 28. Synthesis of complex **73**

ESI-MS spectrum of compound **73** is presented in Figure 13. The signal from 725.2 (M^+) represent the molecular peak of the complex (M = 725,09 g/mol).

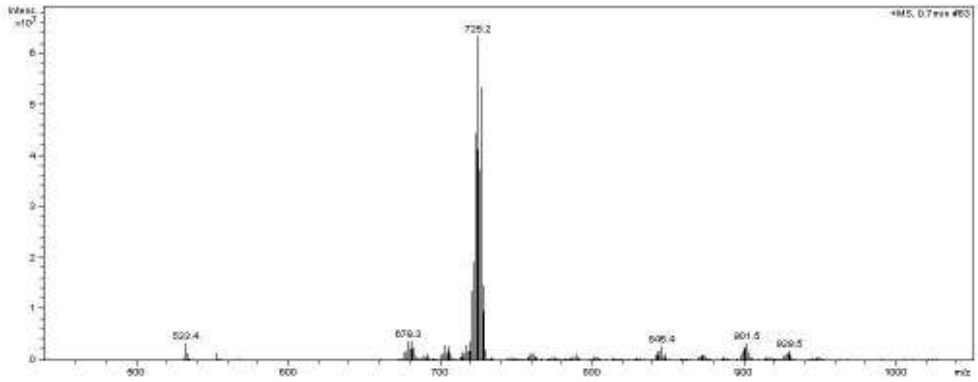
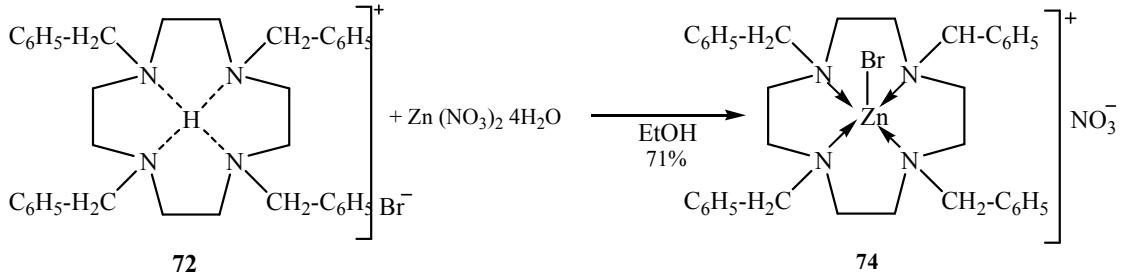


Figure 13. ESI-MS spectrum of complex **73**

XRF analysis was performed using a source of ^{241}Am (acquisition time ~ 200 s), calibration curves were recorded using standard tablet of $CdCl_2$. The reference was recorded using tablets containing $Cd(NO_3)_2 \times 4H_2O$. Exp.: Cd-15,7%, Br-15.1%. Calc.: $C_{36}H_{44}N_4BrCd$ C-59,64%; H-6,11%; N-7,73; Br-11,02%, Cd-15,50%.

II. 2. 3. Synthesis of 1,4,7,10- tetrakisbenzyl-1,4,7,10-tetraazacyclododecane ·HBr complex with Zn(II)

The reaction of ligand **72** with $Zn(NO_3)_2$ x $4H_2O$ in absolute ethanol allowed us to obtain the complex **74** (scheme 29).



72 **74**

Scheme 29. Synthesis of complex **74**

ESI-MS spectrum of compound **74** is presented in Figure 15. The signal from 677,3 (M^+) represents the molecular peak of the complex (M = 678,01g/mol).

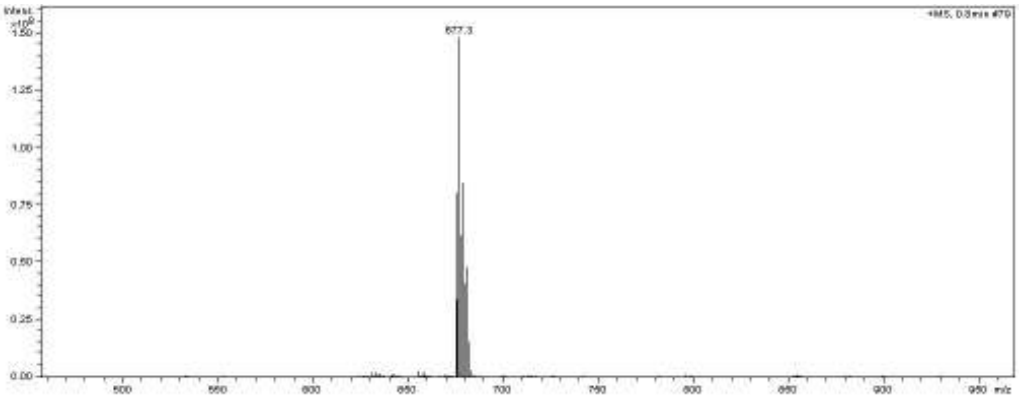


Figure 15. ESI-MS spectrum of the compound **74**

The crystals of the compound **74** were obtained from chloroform and the molecular structure was determined by single-crystal X-ray diffraction. Figure 16 shows the ORTEP diagram of the compound **74**.

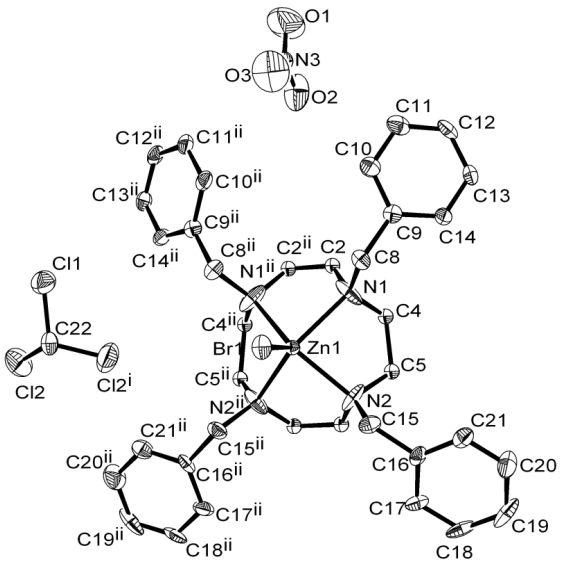


Figure 16. Ortep-like representation and atom numbering scheme for compound **74**

Molecules are associated in polymer chains (figure 17) connected by intermolecular Van der Waals bonds.

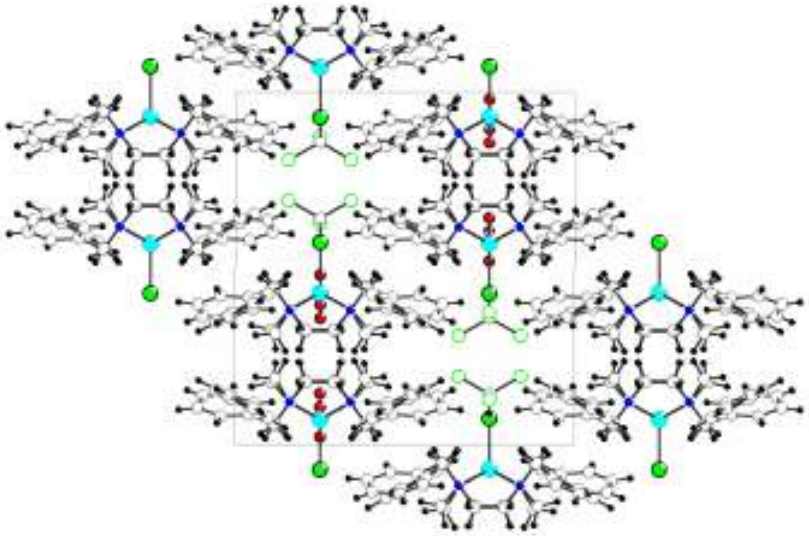
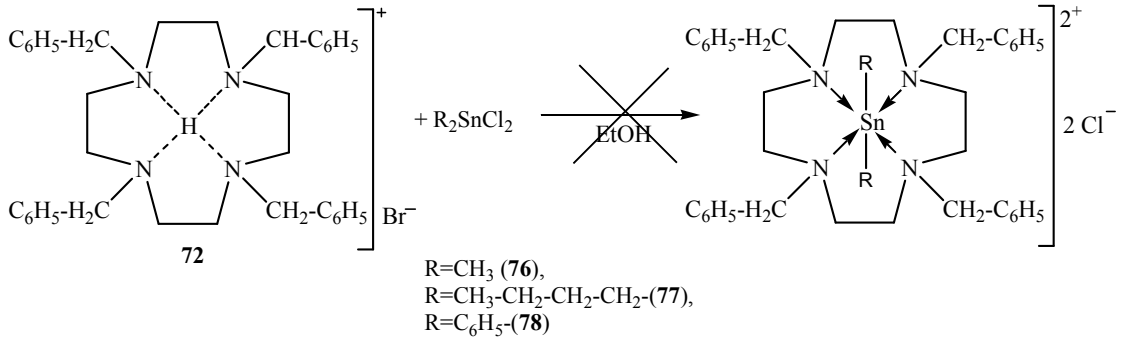


Figure 17. View along the c axis of the association between crystal polymers chain from compound **74**

II. 2. 4. Synthesis of 1,4,7,10- tetrakisbenzyl-1,4,7,10-tetraazacyclododecane ·HBr complex with Sn(IV)

I have tried to obtain ligands **76-78** by reactions of the ligand **72** with $(CH_3)_2SnCl_2$, $(C_4H_9)_2SnCl_2$, Ph_2SnCl_2 in absolute ethanol.



R=CH_3 (**76**),
R=CH_3-CH_2-CH_2-CH_2-(**77**),
R=C_6H_5-(**78**)

Scheme 31. Synthesis of ligands **76-78**

Complexation reaction of macrocycles **72** with Sn (IV) did not occur because Sn atom is probably too bulky for the cavity of the ligand.

III. SYNTHESIS OF SELENIUM CROWN ETHERS

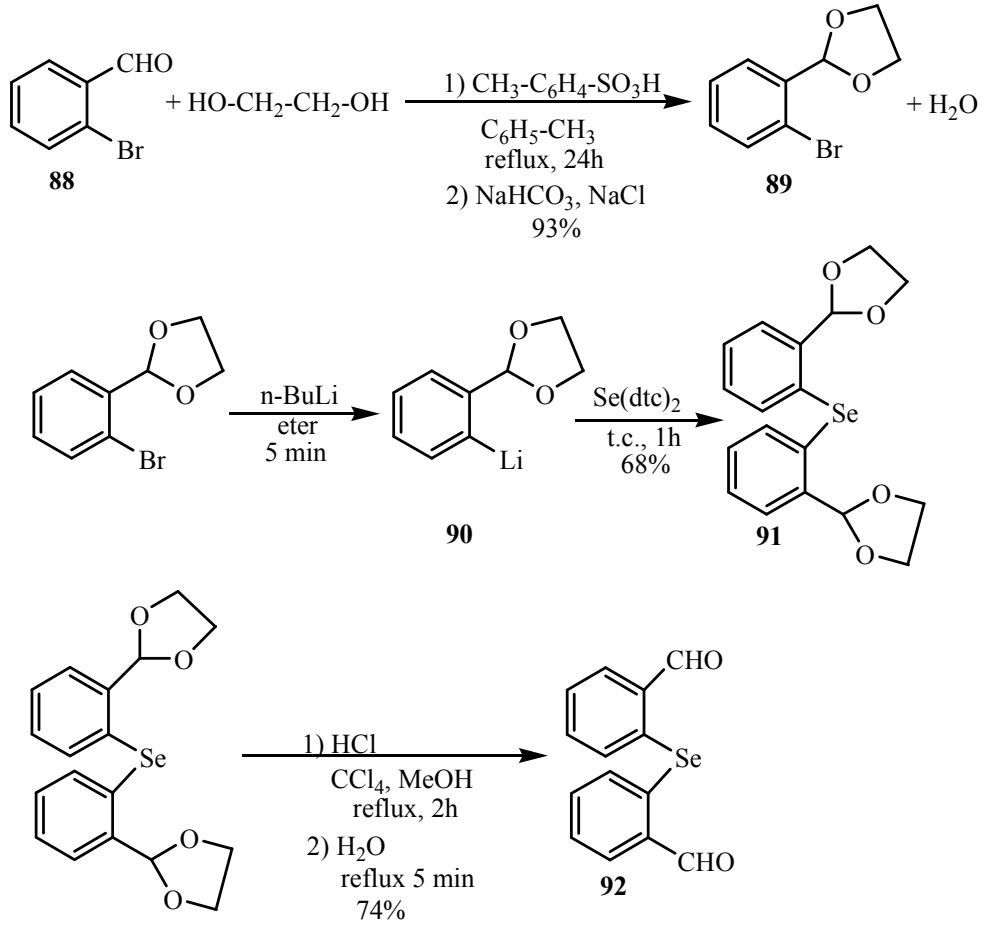
III. 2. Original contributions

The design and synthesis of some macrocyclic Schiff bases in order to coordinate metals presents a special interest.[166] Incorporation of some large metalic atoms such Se and Te in these kind of macrocycles will change the size of the cavity and will allow special complexation behaviors. The good σ donor capacity of Se and Te will facilitate the complexation of a large variety of metalic ions.[167]

I tried to synthesized these kind of compounds, new or known one, which can participate to the complexation phenomenon of metalic ions. So, a known compound, bis (diphenyl)selenide **92** and four new macrocycles **94**, **95**, **97** and **98** were prepared.

III. 2. 1. Synthesis of organoselenium crown ethers precursors

The selenide synthesis starts with the preparation of intermediaries from *o*-bromine-benzoic aldehyde according to the literatura data (scheme 36).[167] After the protection of aldehyde with ethyleneglicol, at the obtained product, **89,** was added n-butyl lithium in ether at room temperature after Piette and Rensen method.[169] Treatment of *o*-lithiobenzaldehyde acetal with selenium dithiocarbamate for an hour at room temperature followed by extraction with ether led to compound **91**. Bis(aldehyde) **92** was obtained by refluxing **91** compound in concentrated hydrochloric acid for removing protective group.

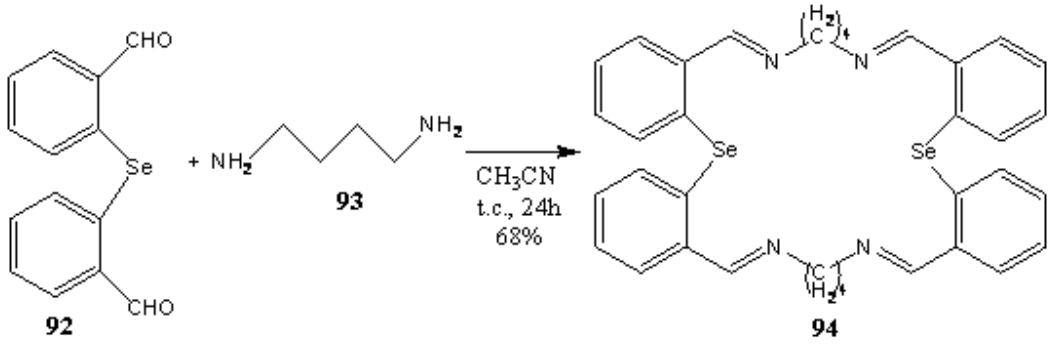


Scheme 41. Synthesis of bis(*o*-formylphenyl)-selenide **92**

Compounds were characterized by IR spectroscopy, NMR (^{1}H, ^{13}C, ^{77}Se) and mass spectrometry.

III. 2. 2. Synthesis of macrocyclic bis(selenide) 94

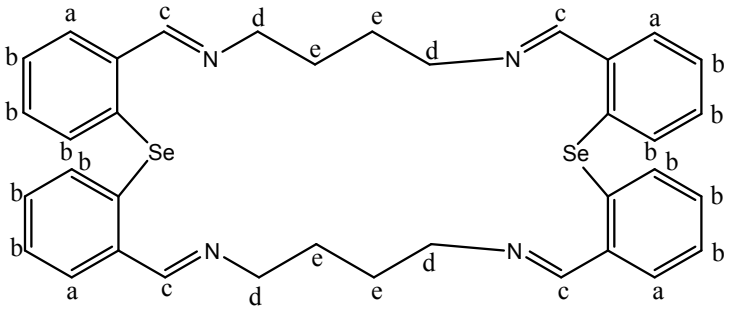
[2+2] condensation of bis(*o*-formylphenyl)-selenide **92** with 1,4-diaminobutane in acetonitril without a template cation led to compound **94** (scheme 37).



Scheme 37. Synthesis of macrocycle **94**

This new compound was analyzed by (^{1}H-, ^{13}C-, ^{77}Se-) NMR, IR spectroscopy and mass spectrometry.

^{1}H-NMR spectrum of compound **94** in $CDCl_3$ (figure 22) confirms obtaining the macrocycle, the values of resonance signals are following: δ (ppm) 8.58 (s, 4H, Ar-C*H*=N); 7.78 (d, 4H, Ar(*H*)); 7.23 (m, 12H, Ar(*H*)); 3.54 (t, 8H, N-CH_2-CH_2-CH_2-CH_2-N); 1.78 (m, 8H, N-CH_2-CH_2-CH_2-CH_2-N). To the value of 8.58 ppm appears the imine corresponding proton signal.



94

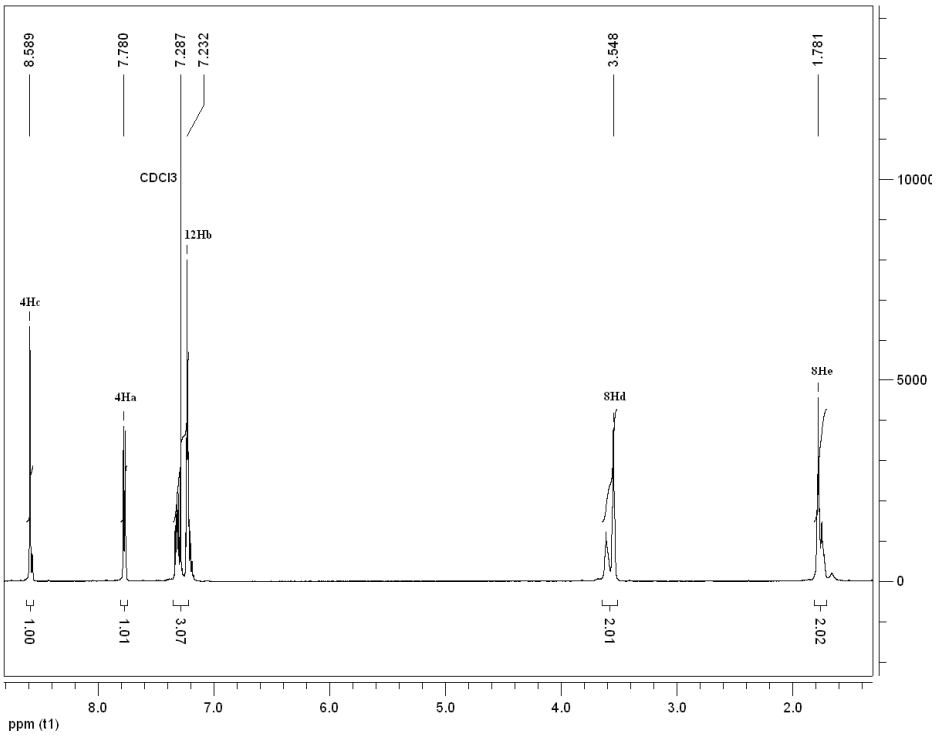
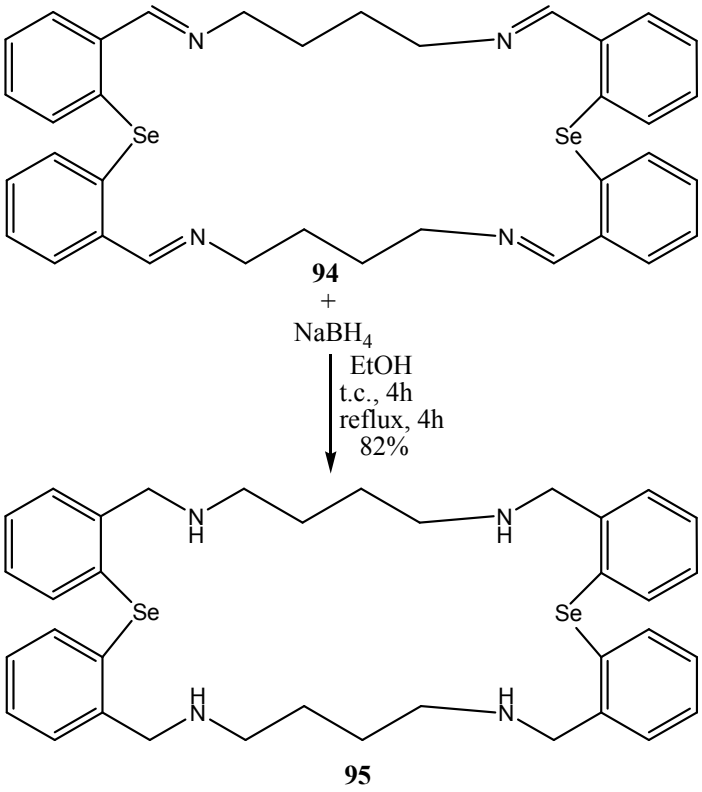


Figure 22. ^{1}H-NMR spectrum of macrocycle **94** in $CDCl_3$

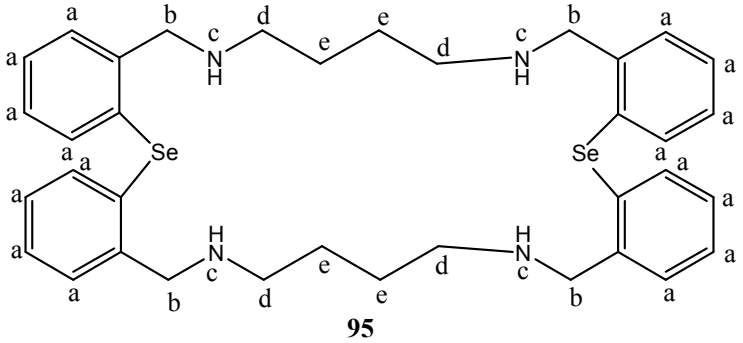
III. 2. 3. Synthesis of macrocycle 87

The Schiff base **94** was reduced to amine **95** with sodium borohydride in ethanol (scheme 39).



Scheme 39. Synthesis of macrocycle **95**

This new compound was analysed by NMR, its ^{1}H-NMR spectrum (figure 26) shows the following resonance signals δ (ppm): 7.74-7.21 (16H, Ar(*H)*), 5.30 (s, 8H, Ar-*CH*$_2$-NH), 3.52 (t, 8H, NH-*CH*$_2$-CH$_2$-CH$_2$-C*H*$_2$-NH), 2.16 (s, 4H, N*H*), 1.75 (m, 8H, NH-CH$_2$-*CH*$_2$-C*H*$_2$-CH$_2$-NH).



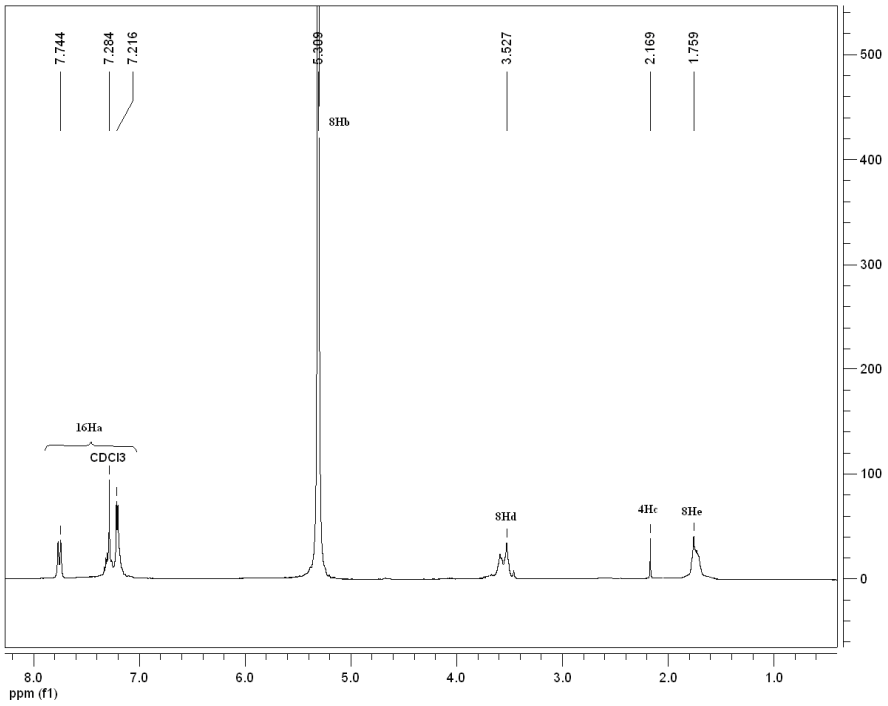
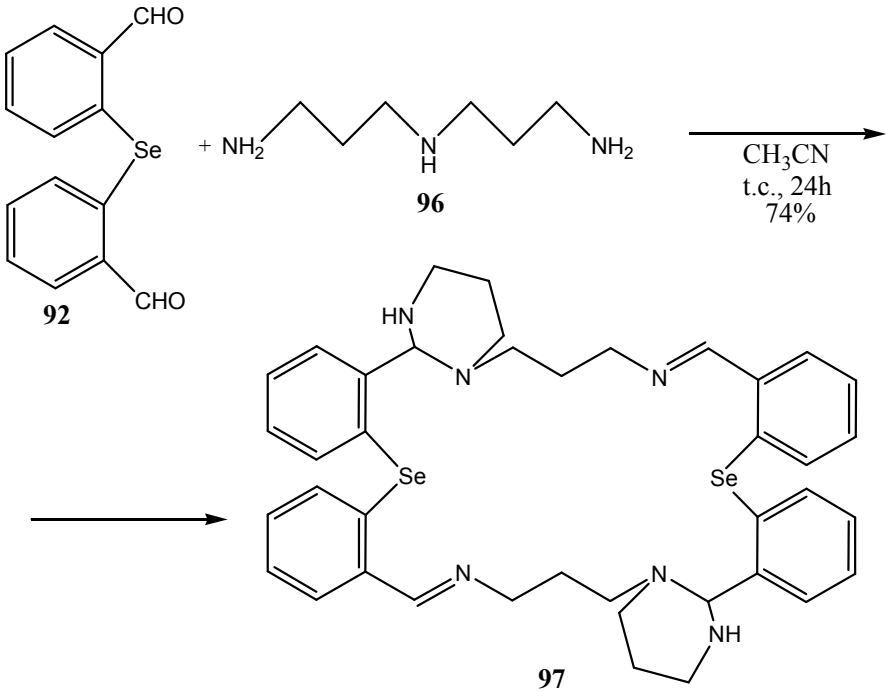


Figure 26. ^{1}H-NMR spectrum of macrocycle **95**

III. 2. 4. Synthesis of macrocyclic bis(selenide) 97

Condensation of bis(*o*-formylphenyl)-selenide **92** with bis(3-aminopropyl)-amine **96** in acetonitril without a template cation led to compound **97** (scheme 40).



Scheme 40. Synthesis of macrocycle **97**

Molecular structure of the compound was established by X-ray diffraction, single crystals of compound **97** were grown from dichloromethane/n-hexane. Figure 28 shows the ORTEP plot of compound **97**.

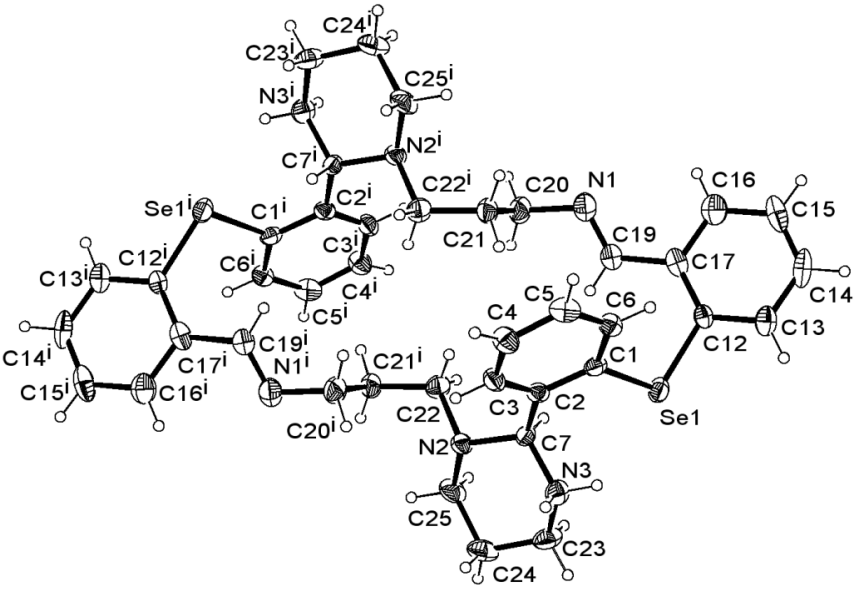
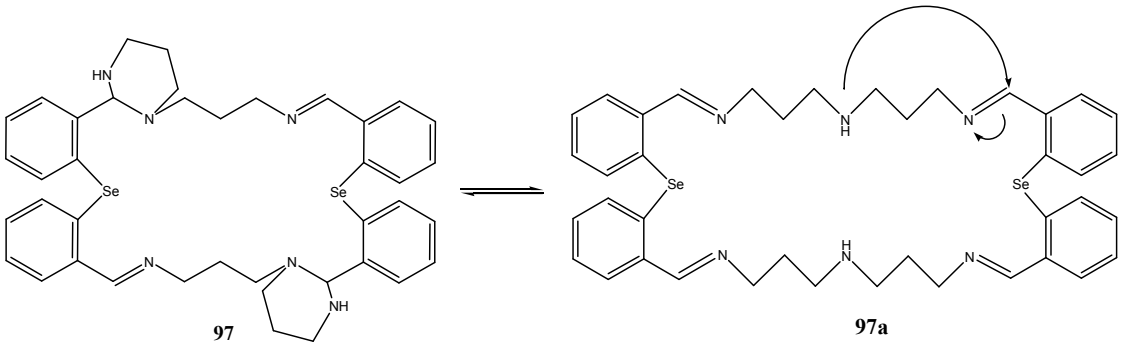


Figure 28. Ortep-like representation and atom numbering scheme for compound **97**

From the ORTEP difractogram and literature data we supposed that this macrocycle could have many isomers, showed in schemes 41. The single crystal X-ray diffraction shows the appearance of a ring-chain tautomerism, compound **98** being in its cyclic form. This type of tautomerism is an intramolecular reversible addition of the NH group at the imine bond which led to a cyclic structure.[170] This process influences reactivity and synthetic properties of these compounds. In literature are very few cases of this behavior and in the case of selenium crown ethers field is for the first time when is observed this tautomerism. According to Baldwin rule[171-173] this ring closure is favored by the formation of heterocycle rings with 6 atoms and disadvantageous for 5 atoms heterocycles shaping. A. Panda and colab.[167] supposed that this behavior appears at some studied selenium ethers but they couldn't confirm it. This process was intensively studied because of its practical and theoretical importance, the isomers equilibrium being studied in all phases.[170]

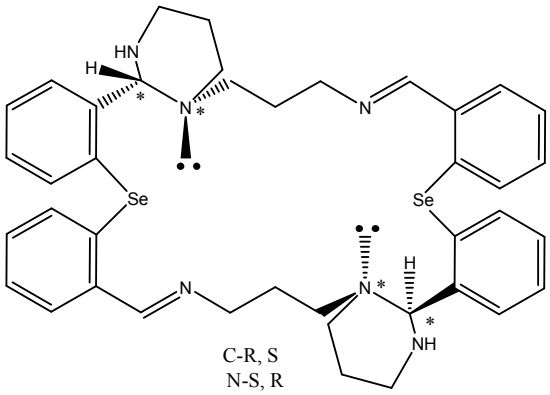
The isomers of **97** are in tautomeric mixture, their equilibrium being described by the following equation: log Kx = $\rho\sigma^+$ + log X=H, where: Kx-the equilibrium value, σ^+-

Hammett-Brown parameter of X substituent and ρ-parameter depending of temperature and the solvent nature. The tautomers report and the parameters of above equation are strongly influenced by the steric effect of R group on N atom.



Scheme 41. Ring-chain tautomerism of compound **97**

Compound **97** presents two chiral C atoms, so it will be 2 enantiomers: (R, R), (S, S); and a *mezzo* form (R, S). The two chiral N atoms also exhibit the same number of optical isomers. The single-crystal X-ray diffraction of compound **97** reveals presence of two chiral C atoms with (R, S) configuration and two chiral N atoms with (S, R) configuration (scheme 42).



Scheme 42. Optical isomer of macrocycle **97**

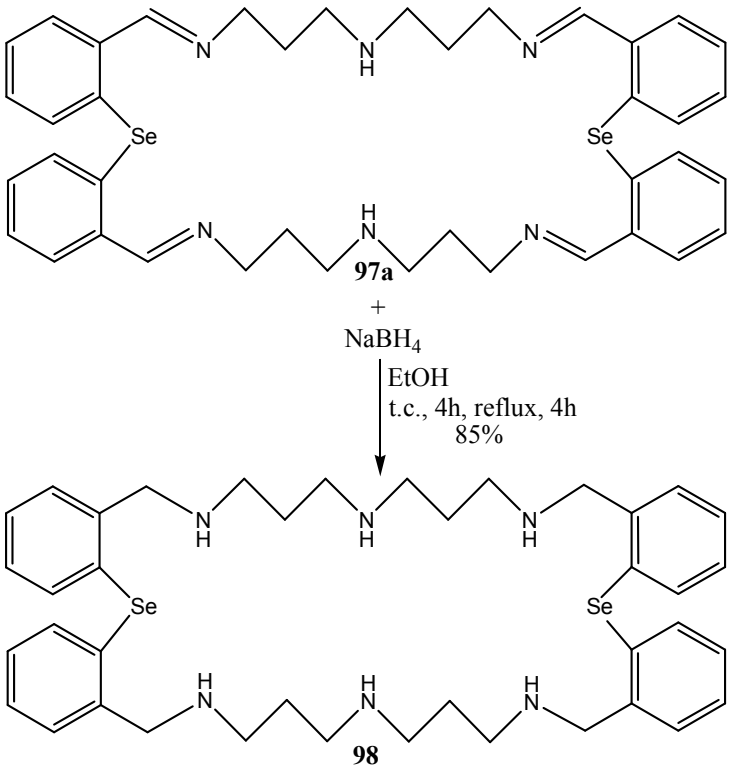
In order to find the most stable conformation from theoretical point of view we appealed to density functional theory (DFT), using the hybrid functional with three

parameters of Becke (B3) and Lee, Yang, Parr (LYP). It was also used BH and HLYP function.

In structures optimization using B3LYP functional and basis set 6-311G (d) we obtained the following values: 6683.92455221 hartree for minimum energy structure **97** and 6683.92455221 hartree for minimum energy structure **97a**. Comparing the data it can be observed that the energy of structure **97** is smaller with 0.00885307 hartree = 5.555 kcal/mol (1 Hartree = 627.509 kcal mol^{-1}) than the energy of structure **97a**.

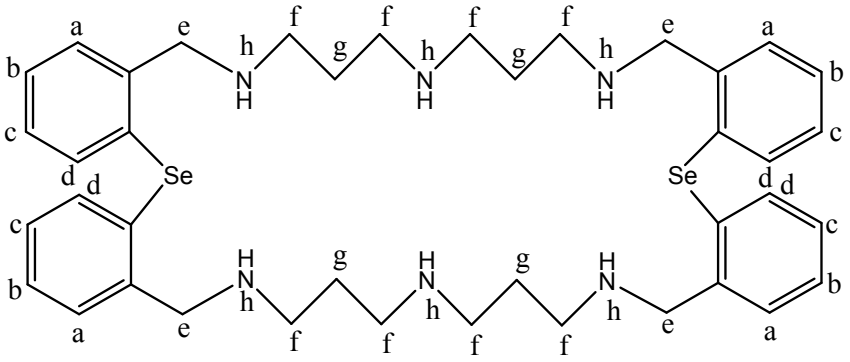
III. 2. 5. Synthesis of macrocycle 98

The Schiff base **97** was reduced with $NaBH_4$ in ethanol with aim to obtained macrocycle **98** (scheme 43).



Scheme 43. Synthesis of macrocycle **98**

^{1}H-NMR ($CDCl_3$) spectrum confirmed the structure of the new compound **98** and following resonance signals are depicted: δ (ppm) 7.34-7.10 (16H, Ar(*H*)), 5.31 (s, 8H, Ar-*CH*$_2$-NH), 3.85 (t, 16H, NH-*CH*$_2$-CH$_2$-C*H*$_2$-NH), 2.68 (s, 6H, N*H*), 1.75 (t, 8H, NH-CH$_2$-*CH*$_2$-CH$_2$-NH). The amino proton signal appears at 5.31 ppm (figure 36).



98

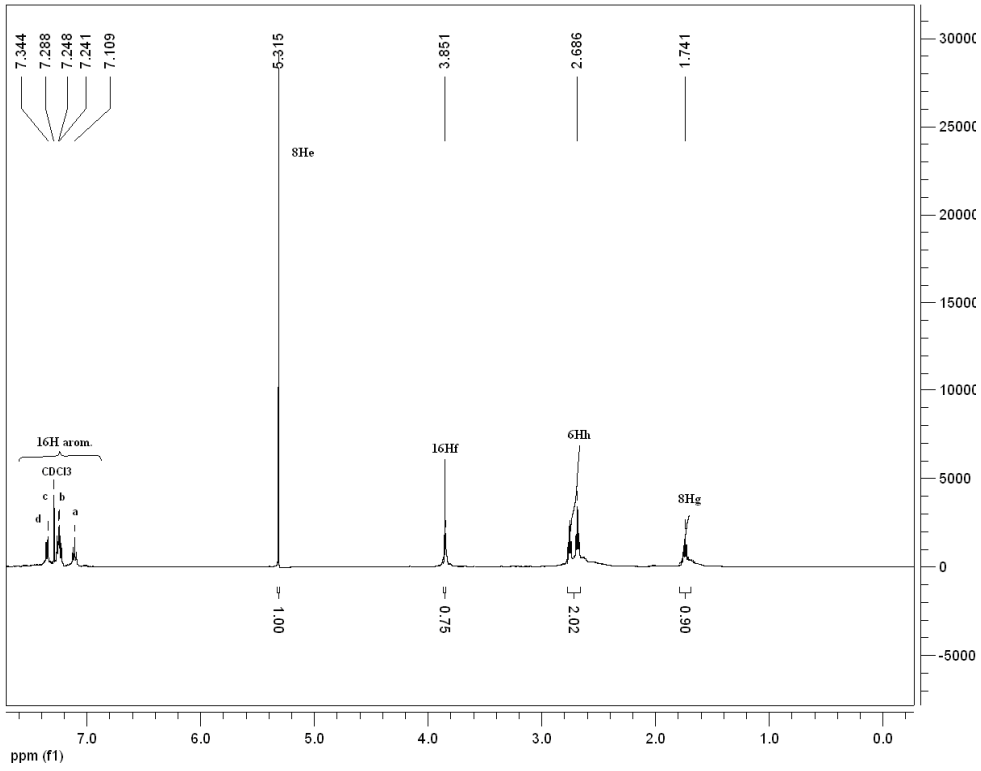


Figure 36. ^{1}H-NMR spectrum of macrocycle **98**

IV. CONCLUSIONS

1. A new method of synthesis of peraza crown ethers was developed using KF/Al_2O_3. The final compounds were obtained in one step reaction avoiding work up in inert atmosphere and high-dilution conditions. 6 Compounds, 5 known and 1 new, were synthesized by this synthetic method: 1-methyl-1,4,7-triazacyclononane **43,** 1,4,7-triazacyclodecane **50**, 1-methyl-1,4,7,10-tetraazacyclododecane **56**, 1,4,7,10,13,16,19-heptatosyl-1,4,7,10,13,16,19-heptaazacycloheneicosane **64** and 1,4-bis(*p*-toluenesulfonyl)-1,4,7-triazacyclononane **68** and 1-methyl-4,8-bis(*p*-toluenesulfonyl)-1,4,8 triazacyclodecane, respectively **51**. The new synthetic method is more economically efficient and less damaging to the environment. A new precursor **59**, was obtained during the synthesis of 1-methyl-1,4,7,10-tetraazacyclododecane **56**. The compounds were characterized by NMR spectroscopy (^1H and ^{13}C) and mass spectrometry.

2. A new method of tosylation of amines using p-toluene-sulfonic acid and $CoCl_2$ as catalyst was developed. The tosylated intermediaries 1,4,7-tris(*p*-toluene-sulfonyl)-1,4,7-triazaheptane **46** and 1,2-bis(p-toluene-sulfonyl)-1,2-diaminoetane **66** were obtained.

3. Cyclen **23,** has been functionalized with benzyl bromide resulting 1,4,7,10-tetrakisbenzil-1,4,7,10-tetraazacyclododecane monobromide **72**. Compounds **73, 74** and **75** were obtained by complexation of **72** with Cd (II) and Zn (II). The complexation of ligand **72** with Sn (IV) was tried but the desired product was not formed because the Sn atom is probably too big for the ligand cavity. The compounds were characterized by NMR spectroscopy RMN (^1H and ^{13}C), ESI-MS spectrometry, MS, XRF analysis, IR spectroscopy and X ray diffraction.

4. New organoselenium crown ethers were synthesized in order to obtain their complexes with metalic ions. A known compound was prepared, namely bis(*o*-formylphenyl)-selenide **92** and four new macrocycles **94**, **95**, **97** and **98.** The compounds were characterized by

NMR spectroscopy RMN (^{1}H-, ^{13}C- , and ^{77}Se-), ESI-MS spectrometry, MS, XRF analysis, IR spectroscopy and X ray diffraction.

5. Compound **97** presents more isomers. In order to highlight the most stable conformation between isomers **97** and **97a** the DFT calculations were used, with the hybrid functional parameters. From the comparison of the theoretic results it was observed that the energy of structure **97** is lower with 5.555 kcal/mol than of **97a**.

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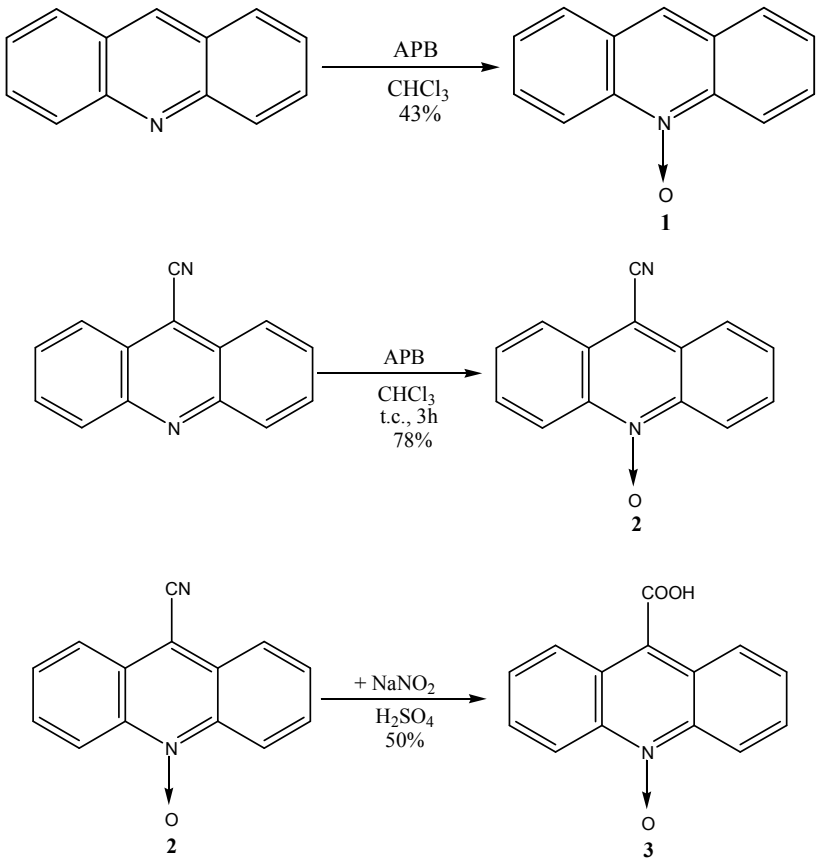
B. SPECTROELECTROCHEMICAL STUDY OF 9-SUBSTITUTED ACRIDINES WITH POTENTIAL ANTITUMOR ACTIVITY

I. ORIGINAL CONTRIBUTION

I synthesized three known compounds acridine-N-oxide **1**, 9-cyan- acridine-N-oxide **2**, 9-carboxy- acridine-N-oxide **3** (scheme 1) with similar yields to those given in literature.[3] These compounds are yellow, they have high melting points, are less soluble in polar solvents, submitting an irritating action to skin and mucous than the adequate acridines. Physical measurements use pure compounds which were recrystallised or purified by chromatography.[18]



Scheme 1. Synthesis of acridine-N-oxide **1**, 9-cyan- acridine-N-oxide **2**, 9-carboxy-acridine-N-oxide **3**

Previously synthesized compounds were investigated using Raman and SER spectroscopy. To improve the signal intensities of compounds they have been deposited on the silver ground[19] to record SER.

In the SER spectra of the compounds (Figure 2), the ring stretching vibration at 1403 cm^{-1}, 1563 cm^{-1} for acridine N-oxide and 1568 cm^{-1} for 9-cyan-substituted compound respectively 1639 cm^{-1} for 9-carboxy-substituted compound are hardly affected by adsorption. [23]

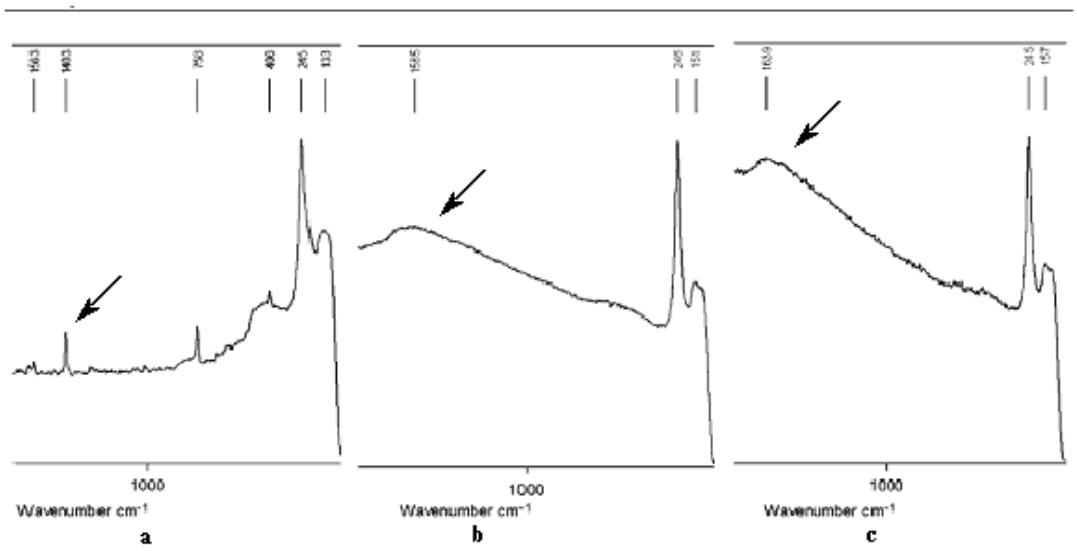


Figure 2. SER spectra of 9-substituted acridines: a) acridine N-oxide; b) 9-CN- acridine N-oxide; c) 9-COOH- acridine N-oxide.

Inspection of ordinary Raman spectra in comparison with SER spectra shows the same values at lower wave number 246 cm^{-1} for out of plane ring bending mode in all the cases and the bandwidths are hardly affected. All other bands which appear in ordinary SER spectra are affected by the strong fluorescence of substituted compounds.

Cyclic voltammograms indicates that only the N→O bond is reduced while the substituents remain unchanged.

To find the classification criteria for the solutions which contain biologically active species I adopted electrochemical impedance method. Parametric equations are discussed in case we have a reference dielectrod and when we have a multielectrod containing 9-carboxy-acridine-N-oxide.[29] Using an impedance analyzer Nyquist diagrams are recorded then I calculate the parametric equations for frequency corresponding to the lowest point on the graph (0,1 Hz). Considering two situations previously specified, in the original circuit it substitute Warburg pseudoimpedance with a coonection a) series respectively b) parallel.

Impedance study proposed is a way to classify solutions containing biologically active species. Electrochemical impedance method in combination with other methods of biologically active compounds investigation could be a way to validate the chemical compounds with biological activity.

III.CONCLUSIONS

1.The electrochemical and spectroelectrochemical behavior of 9-substituted with -CN and -COOH acridine N-oxides with potential antitumor activity was investigated. The Raman and SER spectra of the acridine N-oxides were recorded and compared. SER spectra are strongly affected the fluorescence of the studied compounds and show that the ring stretching vibration at 1568 cm^{-1} for 9-CN-substituted compound respectively 1639 cm^{-1} for 9-COOH-substituted compound are hardly affected by the adsorption on silver surface.

2. Cyclic voltammograms indicates that the reduction potential -0.766 V for -CN substituted compound increase towards -0.745 V for -COOH substituted compound. The reductions of N-oxide acridines take place through N-O bond which is the reactive site. The increased facility to reduction, understood as an increase of electrophilic nature of N-O group showed that only this group is reduced while the substituents remain unchanged.

3. A new approach to the EIS, when only charge transfer and diffusion limitations are present is developed and the new results, concerning the parametric equations of Nyquist plot corresponding to redox multielectrodes has been obtained. The proposed theoretical method in the EIS uses a reference redox dielectrode and a multielectrode containing the N-oxide acridine derivatives. 9-carboxy-NO-acridine introduces inductive properties that may be modeled by considering a pseudoinductance in series with a pseudocapacitance, instead of the Warburg pseudocapacitance. he drug that exert an inductive action, belong to one of the two possible arrangement: CW*(w) and LW*(w) in series or CW**(w) and LW**(w) in parallel. This two possible arrangements of them: in series, respective in parallel can be used like criteria of drug classification.

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