"BABES-BOLYAI" UNIVERSITY CLUJ-NAPOCA
FACULTY OF CHEMISTRY AND CHEMICAL ENGINEERING
ORGANIC CHEMISTRY DEPARTMENT

Ph.D. THESIS ABSTRACT

SYNTHESIS, STEREOCHEMISTRY AND PROPERTIES OF SOME NEW SPIRANE-TYPE COMPOUNDS CONTAINING 1,3-DIOXANE UNITS, AND OF SOME NEW MACROCYCLES WITH PHENOTHIAZINE UNITS

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CONTENTS:

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1,3-dioxane; benzo-1,3-dioxane; (poly)spirane; benzo-spirane; 1,2-dithiolane; cyclic disulfide; iodo-phenothiazine; oligophenothiazine; ferrocene; Suzuki cross-coupling; Negishi cross-coupling; Sonogashira cross-coupling; McMurry reductive coupling; cyclophane; coronand; stereochemical analysis; adsorption on gold; adsorption on gold nanoparticles.

INTRODUCTION

The research work presented in this Ph.D. Thesis is conducted in two main fields represented one side by the study on the synthesis, stereochemistry and properties of some new derivatives of saturated and unsaturated heterocycle spiranes, and on the other side by the synthesis and properties of new phenothiazine oligomers and macrocycles containing phenothiazine units.

The first subject of the thesis was developed at "Babes-Bolyai" University Cluj-Napoca in the research group I am belonging, while the investigations concerning the second subject of my thesis were made in the research group of Prof. Thomas Müller (Ruprecht Karls Universität Heidelberg) during a 12 months research stage financed by a DAAD fellowship (iodo-phenothiazines, oligophenothiazenes and ferrocene-phenothiazine macrocycles), and in Cluj-Napoca (phenothiazine coronands).

The research concerning the saturated six-membered ring heterocycles was first oriented to the study of the stereochemistry of benzo-spiranes by means of NMR and X-ray diffraction. Another direction of the research was represented by the synthesis of some new spiranes containing 1,2-dithiolane units as cyclic disulfides, and the adsorption of these on the gold surface in order to obtain 2D and 3D monolayers of (poli)spiranes.

The objectives of the research on phenothiazines were dedicated to the synthesis of oligophenothiazines as well as ferrocene-phenothiazine derivatives, including ferrocene-phenothiazine macrocycles. Also, the obtainment of phenothiazine coronands as possible selective cation receptors was investigated and realized.

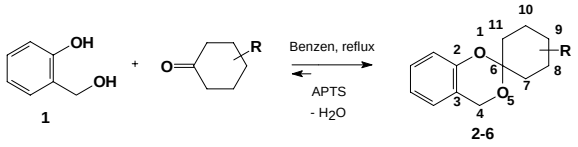
PART A.
SYNTHESIS, STEREOCHEMISTRY AND PROPERTIES OF SOME NEW SPIRANE-TYPE COMPOUNDS CONTAINING 1,3-DIOXANE UNITS

1.1. INTRODUCTION

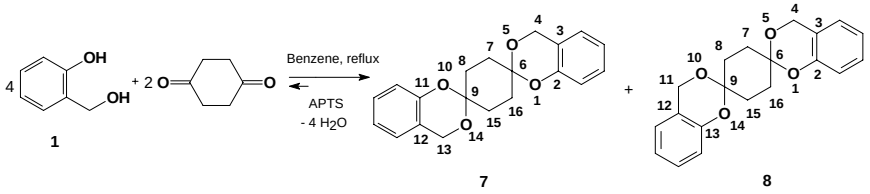
1,3-Benzodioxanes represent an interesting motif in applied chemistry. They were reported as agrochechemical fungicides,[1] biocides,[2] pesticides[3] and herbicides.[4] Some 1,3-benzodioxanes were tested for pharmacological activity and were found to have antiinflammatory activity and low toxicity,[5] or antiinflammatory, analgesic, mucolytic, and antipiretic activity.[6] The unsaturated spiranes occur in the acidic degradation of steroides[7] or are a part of the skeleton of saponine of *Ruscus aculeatus L.*[8] Despite the various and numerous reports, few papers are dealing with the stereochemistry of 1,3-benzodioxanes.[9] This prompted us to investigate in details the stereochemistry of a series of benzocondensed dioxa-monospiranes and of a dibenzocondensed tetraoxa-dispirane.

1.2. SYNTHESIS AND STRUCTURAL ASPECTS IN SOLUTION

The synthesis of one of the target compounds (**2**) was previously described.[10] We have obtained the benzo-spiranes[11] by ketalization of several cyclohexanones with salicylic alcohol in fair to good yields (Scheme 1).



R	Product	Yield
H	**2**	40
8-CH_3	**3**	38
8-R(+)-CH_3	**4**	42
9-CH_3	**5**	40
9-$C(CH_3)_3$	**6**	40



Scheme 1

The reactions equilibra were shifted toward products by using anhydrous sodium sulfate to remove the reaction water. The flash chromatography (silica gel, petroleum ether:ethyl acetate=10:1) was used to purify the crude products.

The ^{1}H-NMR spectra of the products present the signals corresponding to the cyclohexane ring (δ = 1-2.15 ppm), which are slightly shifted to higher fields than the

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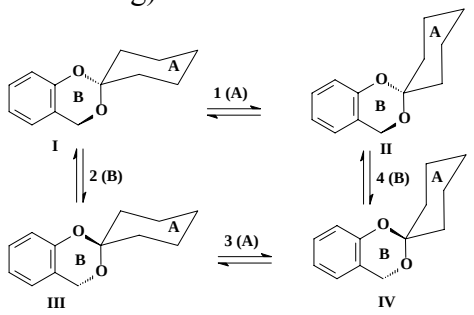
[1] Simon,W.E.J. Can. Pat. Appl. CA 2117503 AA, **1995**.
[2] Simon, W.E.J. Eur. Pat. Appl. EP 645373 A1, **1995**.
[3] a) Anderson, M.; Brinnand, A.G.; Woodall, R.E. Eur. Pat. Appl. EP 525877 A1, **1993**. b) Anderson, M.; Brinnand, A.G.; Woodall, R.E. Eur. Pat. Appl. EP 469686 A1, **1992**.
[4] Enomoto, M.; Nagano, H.; Haga, T.; Morita, K.; Sato, M. Jpn. Kokai Tokkyo Koho JP 63275580 A2, **1988**.
[5] Dauksas, V.; Gaidelis, P.; Brukstus, A.; Ramanauskas, J.; Labanauskas, L.; Gasperaviciene, G.; Jautakiene, I.; Lapinskas, V.; Lauzikiene, N. *Khim-Farm. Zh.* **1989**, *23(8)*, 942.
[6] Torre, A. Eur Pat Appl EP 272223 A1, **1988**.
[7] a) Koga, T.; Nogami, Y. *Tetrahedron Lett.* **1986**, *27*, 4505. b) Izawa, H.; Katada, Y.; Sakamoto, Y.; Sato, Y. *Tetrahedron Lett.* **1969**, *10*, 2947.
[8] Lapin, H.; Sannie, C. *Bull. Soc. Chim. Fr.* **1955**, 1552.
[9] Brink, M. *Monatsh. Chem*. **1973**, *104*, 619.
[10] Chondhury, P.K.; Almene, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 17373.
[11] Gropeanu, R.A.; Grosu, I. "SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW SPIRO BENZO-1,3-DIOXANE DERIVATIVES" *Central European Journal of Chemistry* **2005**, submitted.

corresponding signals of the starting cyclohexanones. Beside of these, the spectra present the aromatic protons (δ = 6.70-7.20 ppm) and the 1,3-dioxine methylene (δ = 4.80-4.90 ppm).

Monospirane **2** has a flexible structure, both 4[H]-1,3-dioxine (B) and cyclohexane (A) rings are flipping (Scheme 2). The 4[H]-1,3-dioxine prefers the chiral half-chair conformations with C6 and O5 out of the plain of the aromatic ring. The flipping of the heterocycle determines an enantiomeric inversion (I and III; II and IV are enantiomers). The flipping of the cyclohexane ring represents diastereomeric equilibrium, structures I and III exhibit the O-C_6H_4- moiety in equatorial orientation while structures II and IV have the O-CH_2-C_6H_4- group in equatorial position (refereed to the cyclohexane ring).



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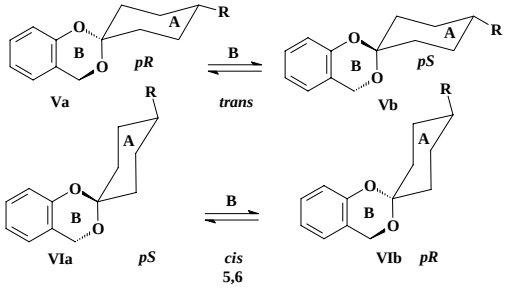
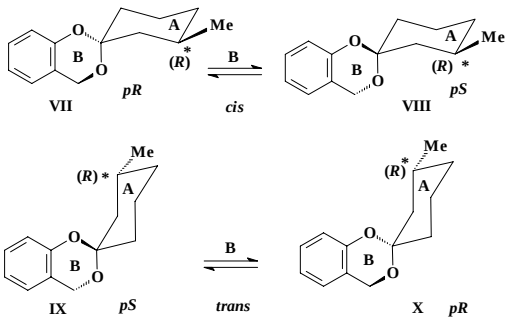
Scheme 2

These possibilities have as result a fast equilibrium between the four conformers at room temperature in solution, which was shown by the ^{1}H-NMR spectrum. The 1,3-dioxine methylene (position 4) gives rise to a singlet at δ 4.81 ppm, and the axial and equatorial cyclohexane protons could not been distinguished, the corresponding signals being mediated.

Compounds **3-6** have semiflexible structures, the substituted cyclohexane ring is anancomeric (the R group is *holding group* and exhibits equatorial orientation) and the 4[H]-1,3-dioxine ring is flipping (Schemes 3). These compounds show *cis* (scheme 16: VIa and VIb; scheme 17: VII and VIII) and *trans* isomers (scheme 3: Va and Vb; scheme 4: IX and X). R and O-C_6H_4- are considered as references. At the same time the chirality (planar) of the 4[H]-1,3-dioxine ring determines the chirality of the compounds and the flipping of the heterocycle determines the enantiomeric inversion for **3-5** (Va ⇆ Vb; VIa ⇆ VIb) and the diastereomeric equilibrium for **6** (VII ⇆ VIII; IX ⇆ X). The *cis* and *trans* structures could not be isolated as single isomers and the compounds were investigated as mixture of isomers.



Scheme 3



Scheme 4

The ^{1}H-NMR spectra of **3-6** show many signals in the part of the spectrum corresponding to the protons of the cyclohexane ring due to frozen flipping of this ring and to the differentiation of axial and equatorial orientations. The singlet corresponding to the CH_2 protons of the heterocycle is more shielded for the *trans* isomer ($\Delta\delta_{\mathbf{3-6}} = \delta_{cis} - \delta_{trans}$ = 0.05-0.10 ppm).

The diastereoisomers have only very small differences of the physico-chemical properties, so it was difficult to separate them and duly characterize. After the column chromatography separation, only samples enriched in one isomer could been obtained. The ratio between isomers was determined comparing the 1,3-dioxine methylene signals and the results are presented in Table 1.

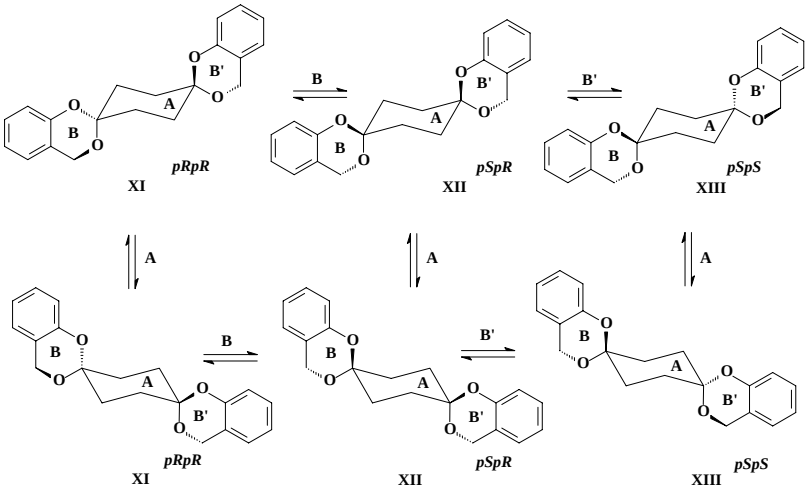
Table 1. Ratio of diastereomers in enriched fractions and the chemical shift of the corresponding 1,3-dioxine methylene ($CDCl_3$, 300 MHz, *rt*)

Entry	Compound	Ratio of diastereomers (DIA 1:DIA 2)*		Chemical shift (δ, ppm)	
		First sample	Last sample	DIA 1	DIA 2
1	**3**	82:18	27:73	4.80	4.89
2	**4**	80:20	34:66	4.80	4.89
3	**5**	100:0	24:76	4.80	4.87
4	**6**	58:42	42:58	4.80	4.89

* The two isomers were formally named DIA 1 and DIA 2 tacking into account the Rf values.

The exception was brought by the dispirane obtained by ketalization of 1,4-cyclohexanedione, which presents two well distinguished and separable isomers: **7 (***trans*) and **8** (*cis*).

Dibenzo-dispiro derivatives **7** and **8** exhibit three stereogene elements, two 4[H]-1,3-dioxine rings with planar chirality[12] and the differently substituted cyclohexane ring which determines *cis* and *trans* isomers. *Cis* and *trans* isomers of **6** were separated by flash chromatography and were investigated as single compounds. The chirality of the heterocycles determines *like* (*pRpR*; *pSpS*) and *unlike* (*pRpS* = *pSpR*) structures (Schemes 5 and 6). *Cis* isomer (XI-XIII) exhibits the reference groups ($-C_6H_4$-O-) in axial-equatorial orientations and the flipping of the cyclohexane ring is an homomeric equilibrium while the flipping of 4[H]-1,3-dioxine rings determines the diastereoisomeric equilibrium. *Trans* isomer (XIV-XIX) exhibits the reference groups either in axial-axial, either in equatorial-equatorial orientations. The flipping of the cyclohexane or of the 4[H]-1,3-dioxine rings represents diastereoisomeric equilibria.

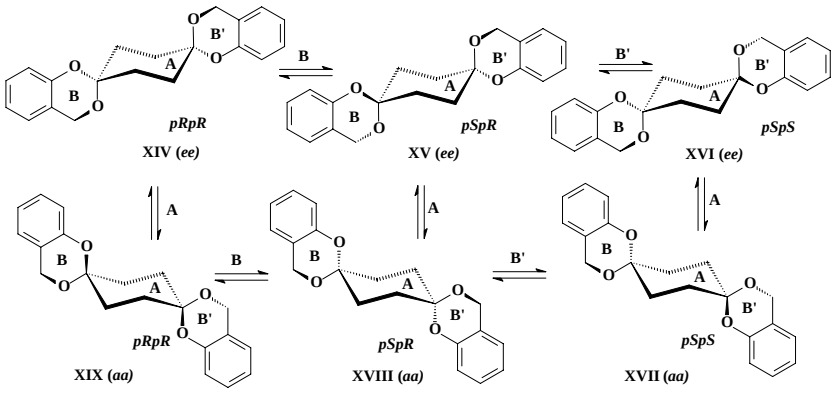


8

Scheme 5

[12] Eliel, E.L.; Wilen, S.H. Configuration and Conformation of Cyclic Molecules. In: Stereochemistry of Organic Compounds (1994), John Wiley and Sons, Inc., New York, p.726.

Cis and *trans* isomers are flexible compounds and the flipping of the central cyclohexane ring and of the heterocycles renders in equilibrium all possible isomers (enantiomers and diastereoisomers; *cis*: XI-XII, *trans*: XIV-XIX). The *rt* ^{1}H NMR spectra of *trans* and *cis* exhibit only singlets for the protons of 4[H]-1,3-dioxine rings (**7**-*trans*: $\delta_{4,13}$ = 4.85 ppm; **7**-*cis*: $\delta_{4,11}$ = 4.86 ppm). The spectra display a singlet for the protons of the cyclohexane ring of the *trans* isomer and overlapped multiplets for those of *cis* one (**7**: $\delta_{7,8,15,16}$ = 2.03 ppm; **8**: $\delta_{7,8,15,16}$ = 1.93-2.09 ppm; Schemes 5, 6).



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Scheme 6

The variable temperature ^{1}H NMR experiments run with **7** and **8** (Figure 1 and 2) show the freezing of the flipping of the rings at low temperatures (that determines a higher number of signals in the NMR spectra). Two net coalescence points for 7 isomer (T_c = 224 K for the signals belonging to the protons of the cyclohexane ring, T_c' = 220 K for the protons of the heterocycles) and one coalescence point for *cis* isomer [the signals corresponding to the 4[H]-1,3-dioxine ring (T_c = 217 K)] could be measured.

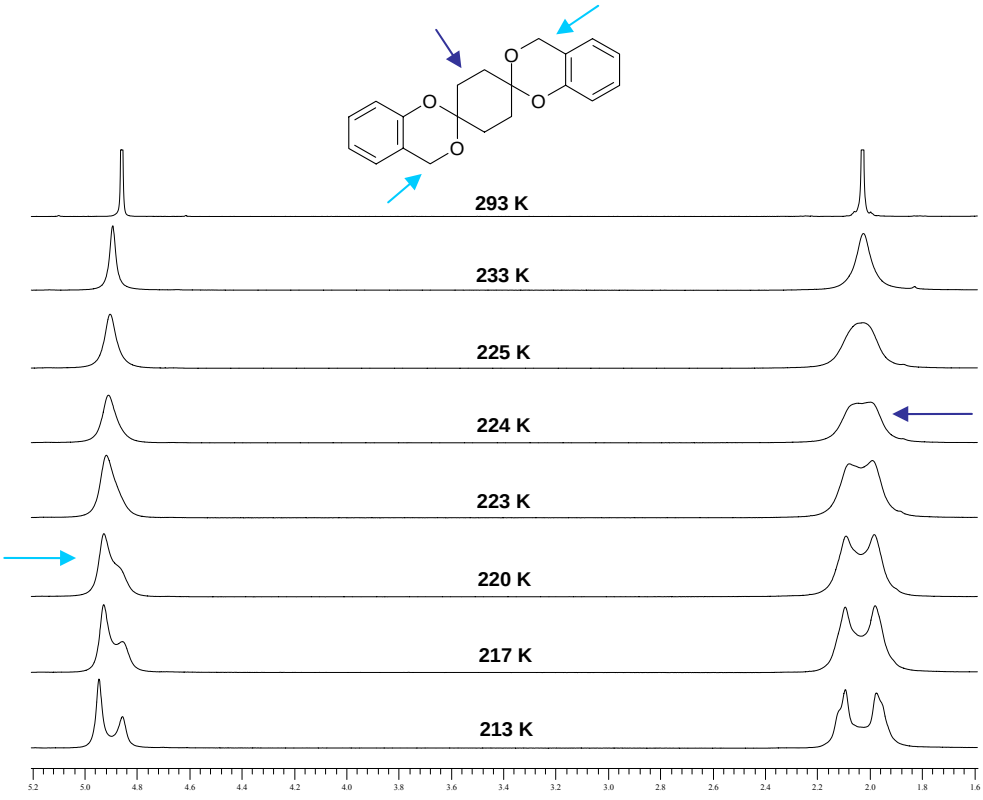


Figure 1. ^{1}H-NMR spectra of 7 recorded at different temperatures ($CDCl_3$, 300 MHz)

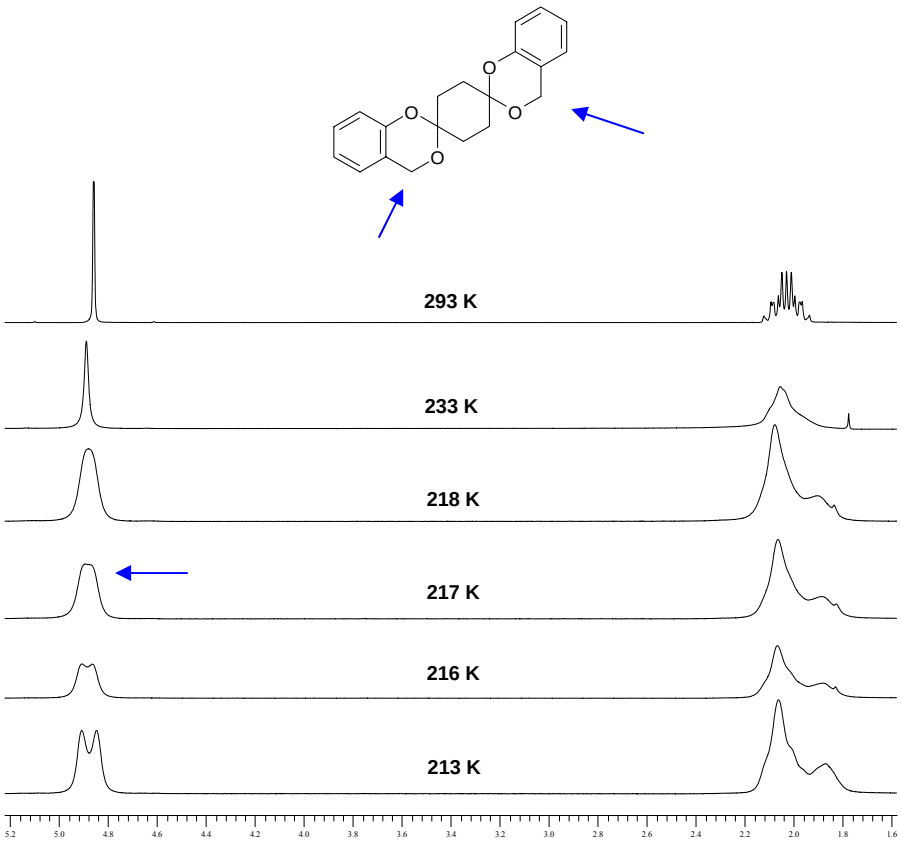


Figure 7. ^{1}H-NMR spectra of 8 recorded at different temperatures ($CDCl_3$, 300 MHz)

1.3. STEREOCHEMICAL ASPECTS OF BENZO-SPIRANES IN SOLID STATE

The solid-state molecular structure was determined for **7** (Figure 8) using X-ray diffractometry on a monocrystal. The cyclohexane ring exhibits chair conformation having the O-Ph formal substituents in equatorial orientation, while the O-CH_2 substituents are disposed in axial positions. The 1,3-dioxine rings have a twisted chair conformation, with the O2 and O14, respectively, outside the plane of the benzene (Figure 9). The initial assumption that the oxygen and spirane carbon atoms are in the same plane was close to reality, taking into account that the dihedral angle between O1-C10-O9 plane and O13-C14-O22 plane is 3.35°. The two benzene rings are oriented in *anti* conformation and are parallel (dihedral angle 1.471°).

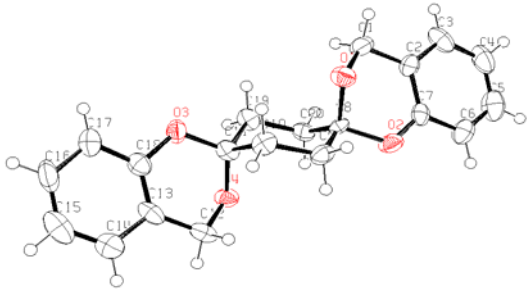


Figure 3. ORTEP[13] drawing of 7

The package of molecules in the monocrystal caused an interesting stacking pattern by the interaction between one benzene ring and one hydrogen atom belonging to the methylene group of the 1,3-dioxine moiety of a neighboring molecule (Figure 4). The distance between this hydrogen and the centre of the neighboring phenylene is 2.66 Å.

[13] Farrugia, L.J. *J Appl Cryst* **1997**, *30*, 565.

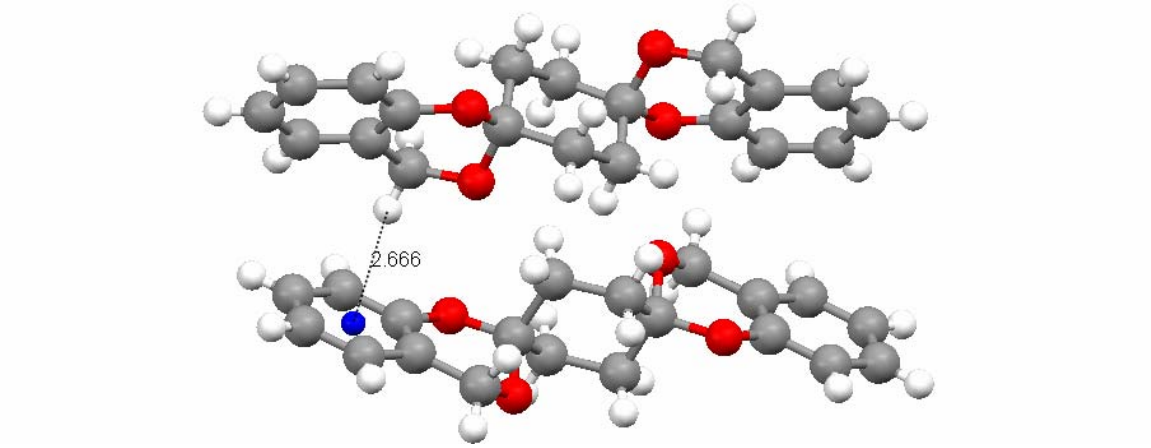
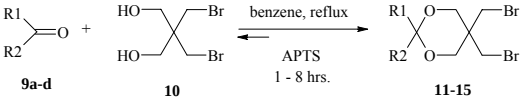


Figure 4. Mercury drawing of two neighboring molecules in the monocrystal of 7

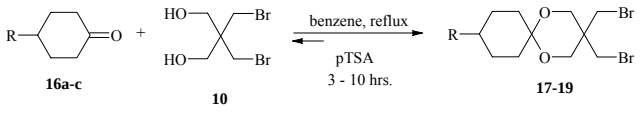
2. SYNTHESIS, STEREOCHEMISTRY AND ADSORPTION STUDIES OF SOME NEW (POLY)SPIRANES CONTAINING 1,2-DITHIOLANE UNITS

2.1. The Synthesis

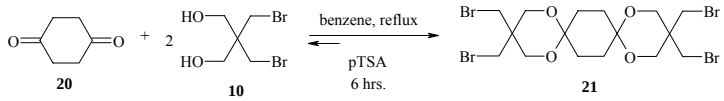
The synthesis[14,15] of the target (poly)spiranes involves as the first step the (a)cetalization reaction of various carbonyl compounds with 2,2-bis(bromomethyl)-1,3-propanediol (Scheme 7). The equilibrium of the reaction was shifted toward products by removing the water by azeotropic distillation of the reaction water with the solvent (benzene or toluene).

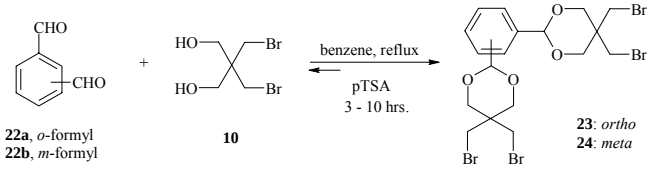


R1	R2	Carbonyl Compound	Product
CH_3	CH_3	**9a**	**11**
H	C_6H_5	**9b**	**12**
H	1-$C_{10}H_7$	**9c**	**13**
CH_3	C_6H_5	**9d**	**14**
CH_3	1-$C_{10}H_7$	**9e**	**15**



R	Ketone	Product
H	**16a**	**17**
C_6H_5	**16b**	**18**
CH_3	**16c**	**19**





Scheme 7

The assigned structures were confirmed by NMR spectra.

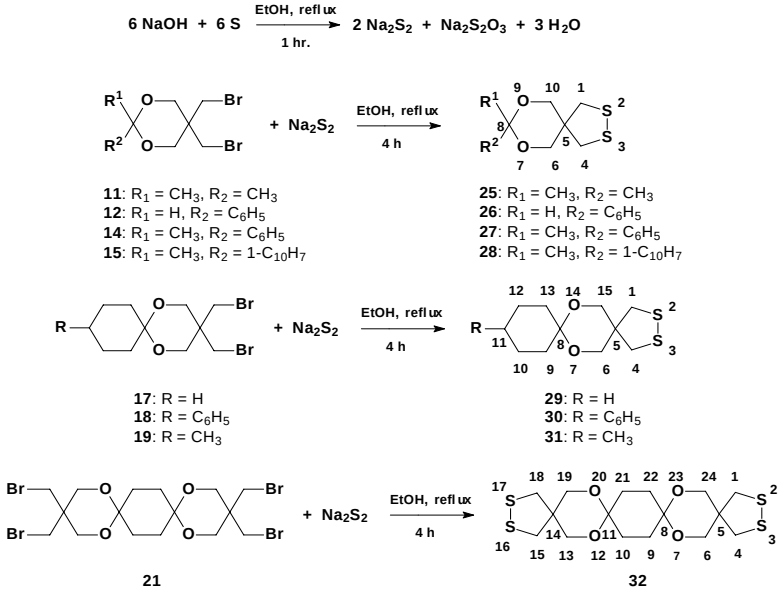
For the obtainment of the target cyclic disulfides **25-32** we have modified a procedure previously reported by *Chorbadijev et al*[16] for the synthesis of dome acyclic disulfide derivatives (Scheme 8) *via* substitution of a halide atom with disodium disulfide (previously generated from

[14] Gropeanu, R.A.; Woiczechowski-Pop, A.; Tintas, M.; Turdean, R.; Grosu, I. *Studia Univ. Babes-Bolyai, Ser. Chim.* **2005**, *50*, 247.

[15] Gropeanu, R.A.; Tintas, M.; Pilon, C. ; Morin, M.; Breau, L.; Turdean, R.; Grosu, I. "SYNTHESIS, STEREOCHEMISTRY AND ADSORPTION STUDIES OF NEW (POLY)SPIRANES CONTAINING 1,2-DITIOLANE UNITS "*Monatshefte für Chemie* **2005**, submitted.

[16] Chorbadjiev, S.; Roumian, C.; Markov, P. *J. Prakt. Chem.* **1977**, *319*, 1036

sulphur and sodium hydroxide). In order to increase the yield of the cyclic disulfide *via* suppression of polymer generation we greatly reduced the reagent concentrations (from 0.5 M to 0.03M).



Scheme 8

The target (poly)spiranes afforded after the flash chromatography in fair to good yields (35-74% for **25-31** and 27% for **32**). The mass spectra and NMR spectra of the products confirmed the assigned structures.

2.2. The Stereochemistry of (Poly)spiranes Containing 1,2-Dithiolane Units

Monospirane **25**, dispirane **29** and tetraspirane **32**, that are showing symmetrical substituted six-membered rings, exhibit flexible structures. The six-membered rings prefer the chair conformation. Taking into account the literature data concerning the conformation of 1,2-dithiolane ring we propose for this heterocycle, in our compounds, the envelope conformer with the spirane atom out of the plane. The flipping of the 1,3-dioxane (A) and 1,2-dithiolane (B) rings in **25** (Scheme 9) renders equivalent in NMR positions 1 with 4 and 6 with 10. The ^{1}H-NMR spectrum at *rt* do not discriminate the axial and equatorial orientations of the protons or of the similar group and exhibits only three singlets ($\delta_{1,4}$ = 2.94, $\delta_{6,10}$ = 3.71, $\delta_{8\text{-Me}}$ = 1.37 ppm). Compound **29** shows four isomers of configuration, due to the chirality of the spiranes units with six-membered rings[17,18] and to the *syn* or *anti* arrangement of the peripheral rings for di or polyspirane skeleta.[19,20,21] The flipping of 1,3-dioxane, cyclohexane and 1,2-dithiolane rings (Scheme 10) determines the conformational equilibrium of all the possible isomers. The ^{1}H-NMR spectrum of **29** presents only two singlets for the protons of 1,3-dioxane and 1,2-dithiolane rings ($\delta_{1,4}$ = 2.96, $\delta_{6,15}$ = 3.74 ppm). The flipping of the peripheral 1,2-dithiolane rings and of the middle six-membered cycles of tetraspirane **32** determines the equilibrium of all possible isomers. The ^{1}H-NMR spectrum of **32** is very simple and shows only three singlets ($\delta_{1,4,15,18}$ = 3.00, $\delta_{6,13,19,24}$ = 3.76, $\delta_{9,10,21,22}$ = 1.87 ppm).

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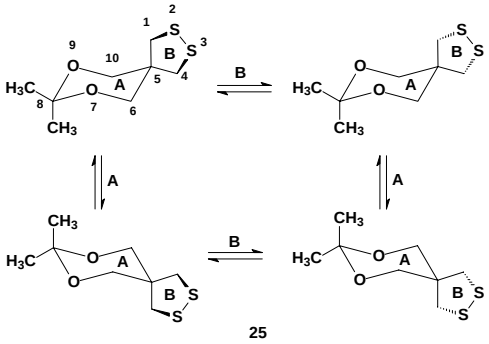
[17] Grosu, I.; Mager, S.; Ple, G.; Horn, M. *J. Chem. Soc., Chem. Commun.* **1995**, 167.
[18] Grosu, I.; Mager, S.; Ple, G. *J. Chem. Soc. Perkin. Trans. 2* **1995**, 1351.
[19] Grosu, I.; Mager, S.; Ple, G.; Mesaros, E. *Tetrahedron* **1996,** *52,* 12783.
[20] Opris, D.; Grosu, I.; Toupet, L.; Ple, G.; Terec, A.; Mager, S.; Muntean, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2413.
[21] Terec, A.; Grosu, I.; Condamine, E.; Breau, L.; Ple, G.; Ramondenc, Y.; Rochon, F.D.; Peulon-Agasse, V.; Opris, D. *Tetrahedron* **2004**, *60*, 3173.



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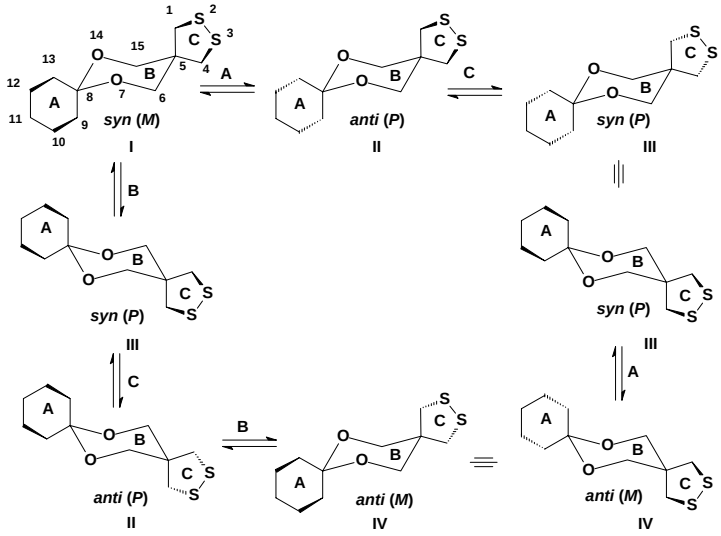
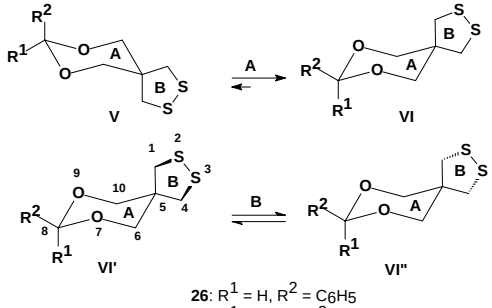
Scheme 9



29

Scheme 10

Spiranes **26**-**28**, with differently substituted 1,3-dioxane units exhibit anancomeric 1,3-dioxane rings. The flipping of the heterocycle is shifted towards the conformation in which the most bulky substituent is placed in equatorial position (Scheme 11; Ph for **26** and Me for **27** and **28**; for similar cases see references[22,23,24]). The flipping of the 1,2-dithiolane ring renders equivalent in NMR positions 6 and 10. However the ^{1}H-NMR spectra of **26**-**27** are more complex and exhibit different signals for the equatorial and axial protons at positions 6 and 10 and for the axial and equatorial methylene groups of the 1,2-dithiolane ring (*e.g.* compound **26**: $\delta_{6a,10a}$ = 3.90, δ_{6e10e} = 4.13, δ_{CH2a} = 3.49, δ_{CH2e} = 2.71 ppm).

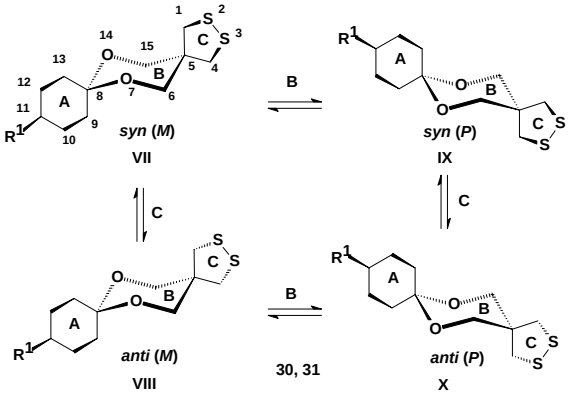


26: R^1 = H, R^2 = C_6H_5
27: R^1 = C_6H_5, R^2 = CH_3
28: R^1 = 1-$C_{10}H_7$, R^2 = CH_3

Scheme 11

[22] Anteunis, M.J.O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4***,** 293.
[23] Mager, S.; Grosu, I. *Stud. Univ. "Babes-Bolyai", Ser. Chemia* **1988**, *33*, 47.
[24] Grosu, I.; Plé, G.; Mager, S.; Mesaros, E.; Dulau, A.; Gego, C. *Tetrahedron* **1998**, *54*, 2905.

Dispiranes **30** and **31** display semiflexible structures (Scheme 12), the cyclohexane ring is rigid, the substituent of this cycle being an efficient "holding group" and the 1,3-dioxane and 1,2-dithiolane parts are flipping and render in equilibrium the possible stereoisomers (VII-X). The ^{1}H-NMR spectra do not differentiate the axial or equatorial orientation of the protons of the heterocycles but exhibit different signals (singlets) for the diastereotopic positions 6 and 15 (**30**: δ_6 = 3.81, δ_{15} = 3.85, $\delta_{1,4}$ = 3.04 ppm and **31**: δ_6 = 3.71, δ_{15} = 3.76, $\delta_{1,4}$ = 2.98 ppm). The diastereotopicity of positions 6 and 15 is observed in ^{13}C-NMR spectra, too (**30**: δ_6 = 66.32, δ_{15} = 66.50 ppm and **31**: δ_6 = 66.34, δ_{15} = 66.61 ppm). Position 6 is *procis* and position 15 is *protrans* referred to the substituent at position 11.



Scheme 12

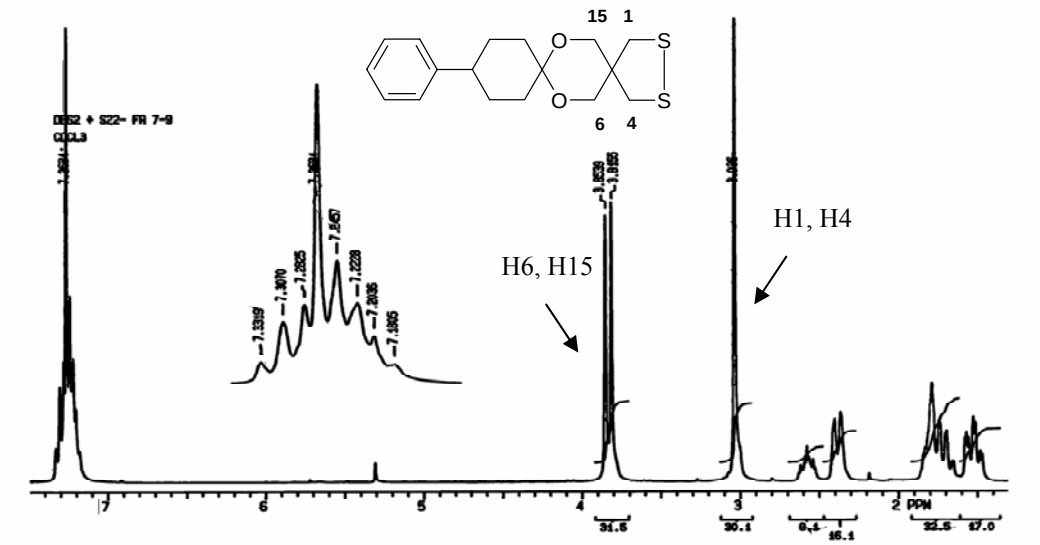


Figure 5. ^{1}H-NMR spectrum of 30 ($CDCl_3$, 300 MHz, *r.t.*)

2.3. ADSORPTION STUDIES

A. Adsorption on planar gold surfaces

Individual gold (111) surfaces were immersed in 1 mM ethanolic solutions of the cyclic disulfides, **29** to **32,** for at least 24 hours in order to form monolayers. The monolayers were then analyzed by reflective IR spectroscopy. The relevant fragments of the spectra of two compounds are depicted in Figures 6 and 7. The wave numbers of the vibrational bands of their IR spectra are presented in Table 2. The assignment of the vibrational bands and the direction and magnitudes of the vibrational dipole moments were obtained from Hartree-Fock calculations done with Gaussian 98® software.

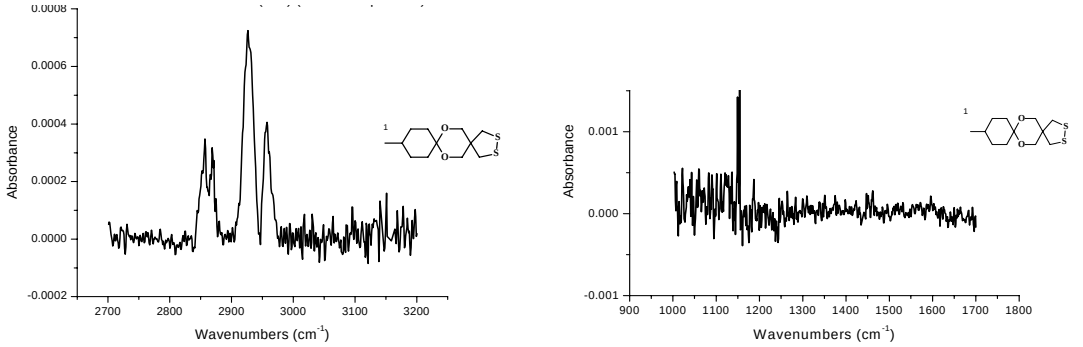


Figure 6. IR reflexion-absorption spectrum of a monolayer of 31 adsorbed on a gold (111) surface (relevant fragments)

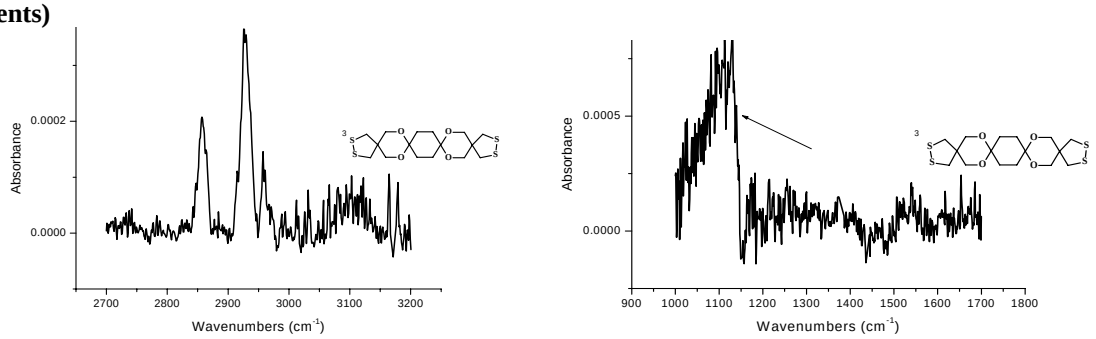


Figure 7. IR reflexion-absorption spectrum of a monolayer of 32 adsorbed on a gold (111) surface (relevant fragments)

The widths of the bands at half-height in the IR spectra are in the range of 20-40 cm^{-1} which suggests that the molecules are disordered on the gold surface. Also, the methylene $\nu_a(CH_2)$ band at 2926-2930 cm^{-1} (that is present in all samples) is indicative of a liquid like monolayer. This disorder is probably due to the complex and relatively rigid structure of the molecules which results in a large distance between the adsorbed molecules and thus few stabilizing inter-adsorbate interactions that usually results in self-assembly. Although the monolayer is not very organized, some information on the orientation of the adsorbed molecules could be drawn from the IR investigations. Our analysis of the IR spectra are based on the direction of the vibrational dipole moments obtained from a computational chemistry calculation and the infrared surface selection rule for adsorbates on metallic substrates[25] which states that a vibrational mode is IR active if there is a component of its dipole moment perpendicular to the surface.

Table 2. IR wave numbers (ν/cm^{-1}) of the *SAMs* for each cyclic disulfide **29-32** on a gold (111) surface

Assignment	**29**	**30**	**31**	**32**
ν_a(=C-H, Ar)	-	3065 (weak)	-	-
ν_a(=C-H, Ar)	-	3031 (weak)	-	-
ν_a(=C-H, Ar)	-	3017 (weak)	-	-
$\nu_a(CH_3)$	2961[a] (weak)	2959[a]	2958	2958[a] (weak)
$\nu_a(CH_2)$	2928	2930	2926	2926
$\nu_s(CH_3)$	-	2874[a]	2869	-
$\nu_s(CH_2)$	2857	2856	2857	2857
ν_a(C-O-C)	1096	1131	1154	1130

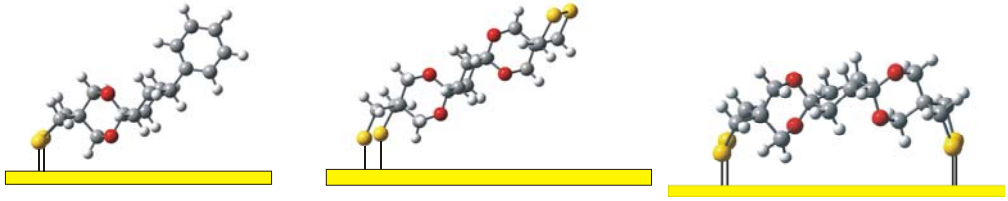
[a] due to a small amount contaminant containing a methyl group

The analysis of the wave numbers and intensity of the vibrational bands of compounds **30** and **32** adsorbed on gold suggest that they adopt the orientations shown in Figures 19 and 20.

[25] Greenler, R.G. J. *Chem. Phys*. **1966**, *44*, 310.

Also, it is likely that both compounds bind to the surface via at least two of their sulphurs, as disulfides are known to dissociate upon adsorption on gold.[26]

The absence of CH deformation bands between 1300 and 1400 cm^{-1} suggests that **32** is not oriented perpendicular to the surface but is rather parallel to the surface. In this orientation the C-H deformation modes of methylenes will have a low intensity. It is thus possible that compound **32** is anchored to the surface by both 1,2-dithiolane rings. However, this would require an important reorganization of the optimized structure shown in Figure 8.

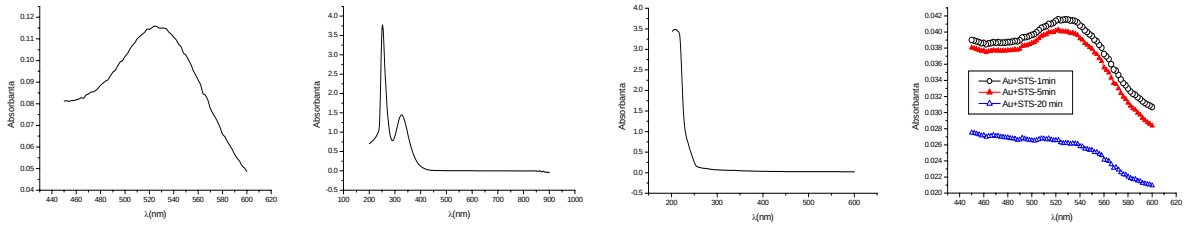


a **b** **c**

Figura 8. Possible orientations of compounds 30 (a) and 32 (b) and (c) adsorbed on Au(111) suggested by the analysis of its IR spectra.

B. Adsorption on gold electrodes and interaction with gold nanoparticles

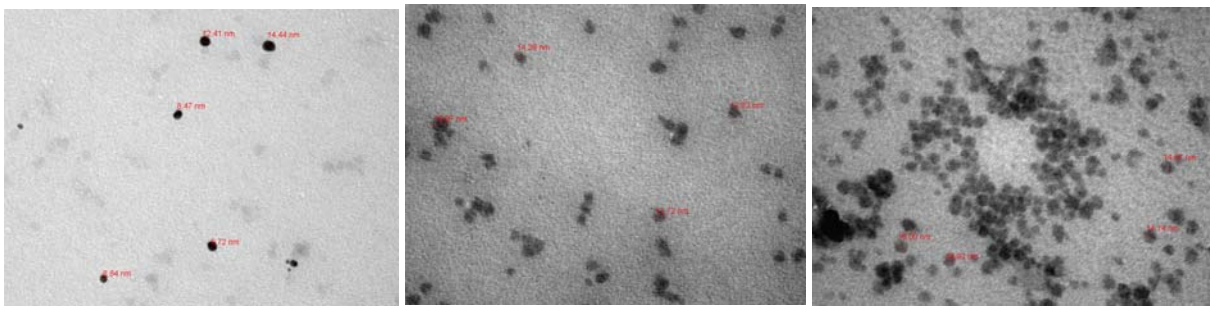
The interaction between some (poly)spiranes having 1,2-dithiolane units and gold nanoparticles (GNP) was studied for the beginning using UV-Vis spectroscopy. Thus, the UV-Vis spectra of the organic ligands in chloroform and of the GNP (water solution) were recorded, as well as the spectra of the samples obtained by mixing cyclic disulfides with GNP solution (Figure 9). The main feature of the samples spectra is the decay of the plasmodic resonance peak. For example, in short time (20 minutes) the absorbance in the 500-550 nm region of the spectra was five times reduced in the case of interaction between **32** and GNP (Figure 9d). Also, the electronic absorption peak of the organic ligand (330 mn) has disappeared (Figure 9c).



a **b** **c** **d**

Figure 9. UV-Vis spectra of the a) water dispersion of GNPs, b) chloroform solution of 32, c) GNPs functionalized with 32, and d) GNPs functionalized with 32, recorded at three different times

These facts suggest an aggregation process of the nanoparticles, which is sustained by the transmission electronic microscope (80 kV) measurements (Figures 10).

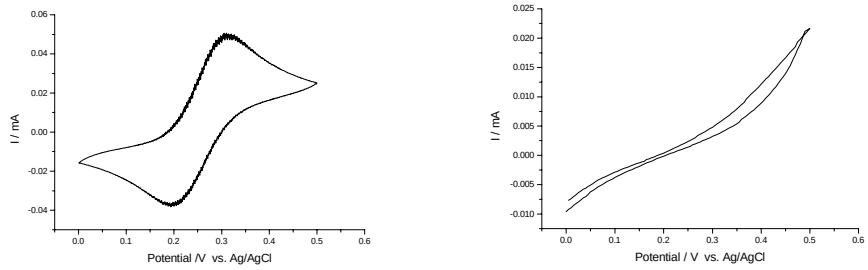


a **b** **c**

Figure 10. Transmission electronic microscope image of the a) GNPs suspension, b) GNPs functionalized with 30, and c) GNPs functionalized with 32

[26] Fenter, P.; Eberhardt, A.; Eisenberg, P. *Science* **1994**, *266*, 1216

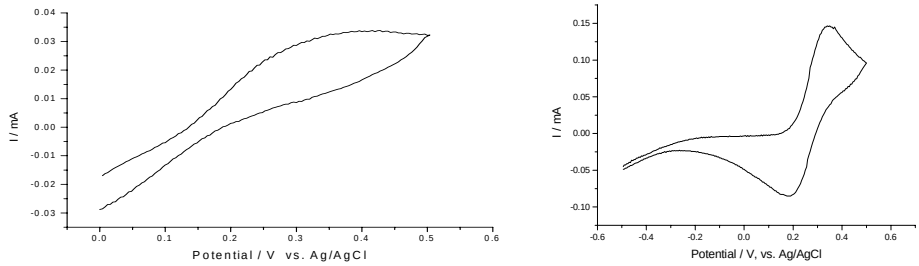
A method which is suitable for the study of the adsorption of the cyclic disulfides on the gold surface is the cyclic voltammetry using a gold electrode as working electrode. After the cleaning operations, the cyclic voltammetry of the standard system [$K_4Fe(CN)_6$ in 0.1 M KCl, Figure 11a] was performed and compared with the cyclic voltammograms run with the gold electrodes functionalized with each of cyclic disulfide **25-27**, **30**, **32**. The absence of a redox process has shown that the spirane monolayer adsorbed on the surface of the gold electrode acts as a dielectric isolator (Figure 11b).



a **b**

Figure 11. Cyclic voltammogram of a solution of 3 mM $K_4Fe(CN)_6$ in 0.1 M KCl using a) bare gold electrode (10 mV/sec) and b) urface functionalized gold electrode with 32 (50 mV/sec)

31 has two cyclic disulfide units per molecule and, therefore, was tested for the functionalization of the gold electrode surface with GNP. Two methods of the preparation were tried: *Method A*: the electrode treated with the organic ligand was immersed in the GNP solution, and *Method B*: the electrode was immersed into the solution obtained by mixing of GNP with organic ligand at different pH values (5.5, 7 and 11).



a **b**

Figure 12. Cyclic voltammograms of a) a solution of 3 mM $K_4Fe(CN)_6$ in 0.1 M KCl (buffered at pH 5.5) using surface functionalized gold electrode with 32 and GNP (10 minutes immersion, pH 7, by *Method A* (50 mV/sec)), and b) a solution of 3 mM $K_4Fe(CN)_6$ in 0.1 M KCl (buffered at pH 7) using surface functionalized gold electrode with 32 and GNP (pH 7) by *Method B* (50 mV/sec)

These functionalized electrodes were subjected to cyclic voltammetry of the standard solution. The results showed us that only the *Method B* run at pH 7 was successful (Figure 12), the voltammograms presenting a reversible redox process. Comparing the voltammograms, we can remark that for the GNP-**32**-modified gold electrode the current maxima are more than two times higher that the corresponding peaks for the non-functionalized gold electrode, meaning that the modification of the surface is increasing the electron transfer between solution and electrode.

PART B.
SYNTHESIS AND PHYSICO-CHEMICAL PROPERTIES OF SOME NEW MACROCYCLES CONTAINING 10H-PHENOTHIAZINE UNITS

1. INTRODUCTION

Phenothiazines belong to a pharmaceutically important class of heterocycles,[27] and due to their pharmacological efficacy they are applied in a broad range as sedatives, tranquilizers, antituberculotics, antipyretics, antitumor agents, bactericides and parasiticides.[28] They are also able to cleave DNA upon photochemical induction.[29] As a consequence of a low oxidation potential, these tricyclic nitrogen-sulfur heterocycles readily form stable radical cations and a key role of their physiological activities can be attributed to this circumstance.[30] An interesting feature of phenothiazines is the fact that the first oxidation step is reversible.[31] Thus, phenothiazine derivatives have become spectroscopic probes in molecular and supramolecular arrangements for photoinduced electron transfer (PET) studies.[32]

Our work in this field had the following goals:

- the synthesis of some new building blocks useful in the preparation of oligophenothiazines of determined number of phenothiazine units
- the synthesis of phenothiazine-ferrocene dyads and triads and to study the electronic communication between the redox-active units of the oligomers, and of ferrocene-phenothiazine cyclophane
- the synthesis of phenothiazine-containing macrocycles (shape-persisted macrocycles, as well as phenothiazine coronands).

2. ORIGINAL RESULTS

2.1. SYNTHESIS OF IODO-PHENOTHIAZINE DERIVATIVES

The corner stone of our strategies was 10-alkyl-3,7-dibromo-10H-phenothiazine (**1**), which is readily available from commercially 10H-phenothiazine (**1**) in two steps: the first step is represented by an alkylation in the position 10 (at the secondary nitrogen of the phenothiazine

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[27] Sainsbury, M. In *Comprehensive Heterocyclic Chemistry*, Vol. 3; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1984**, 995

[28] (a) Mietzsch, F. *Angew. Chem.* **1954**, *66*, 363. (b) Ionescu, M.; Mantsch, H. *Adv. Heterocycl. Chem.* **1967**, *8*, 83. (c) Bodea, C.; Silberg, I. *Adv. Heterocycl. Chem.* **1968**, *9*, 321. (d) Valzelli, L.; Garattini, S. In *Principles of Psychopharmacology*; Clark, W. G., Ed.; Academic Press: 1970, **255**. (e) Okafor, C. O. *Heterocycles* **1977**, *7*, 391. (f) Eckstein, Z.; Urbanski, T. *Adv. Heterocycl. Chem.* **1978**, *23*, 1. (g) Szabo, J. *Chem. Heterocycl. Compd. USSR (Engl. Trans.)* **1979**, *15*, 291. (h) Albery, W. J.; Foulds, A. W.; Hall, K. J.; Hillman, A. R.; Edgell, R. G.; Orchard, A. F. *Nature* **1979**, *282*, 793.

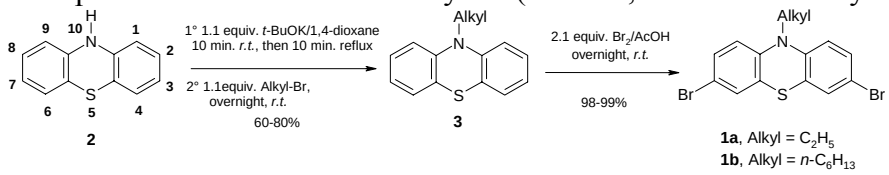
[29] (a) Nishiwaki, E.; Nakagawa, H.; Takasaki, M.; Matsumoto, T.; Sakurai, H.; Shibuya, M. *Heterocycles* **1990**, *31*, 1763.
(b) Decuyper, J.; Piette, J.; Lopez, M.; Merville, M. P.; Vorst, A. *Biochem. Pharmacol.* **1984**, *33*, 4025. (c) Motten, A. G.; Buettner, G. R.; Chignell, C. F. *Photochem. Photobiol.* **1985**, *42*, 9. (d) Fujita, H.; Matsuo, I. *Chem. Biol. Interac.* **1988**, *66*, 27.

[30] (a) Forrest, I.; Forrest, F. *Biochim. Biophys. Acta* **1958**, *29*, 441. (b) Iida, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 663. (c) Moutet, J.-C.; Reverdy, G. *Nouv. J. Chim.* **1983**, *7*, 105.

[31] For cyclovoltammetric and spectroscopic data of phenothiazine, see for example: Tinker, L. A.; Bard, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 2316. (d) Padusek, B.; Kalinowski, M. K. *Electrochim. Acta* **1983**, *28*, 639. (e) McIntyre, R.; Gerischer, H. *Ber. Bunsen Ges. Phys. Chem.* **1984**, *88*, 963.

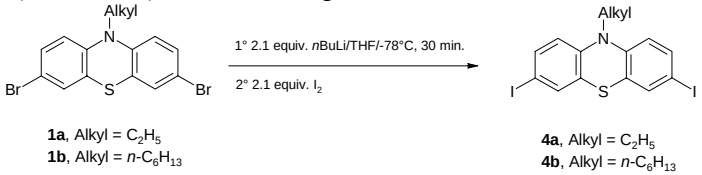
[32] (a) Duesing, R.; Tapolsky, G.; Meyer, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 5378. (b) Jones, W. E. Jr.; Chen, P.; Meyer, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 387. (c) Brun, A. M.; Harriman, A.; Heitz, V.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8657. (d) Burrows, H. D.; Kemp, T. J.; Welburn, M. J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 969. (e) Collin, J.-P.; Guillerez, S.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* **1989**, 776. (f) Daub, J.; Engl, R.; Kurzawa, J.; Miller, S. E.; Schneider, S.; Stockmann, A.; Wasielewski, M. R. *J. Phys. Chem. A* **2001**, *105*, 5655.

nucleus, Scheme 1). After the purification, the intermediate **3** is subjected to a bromination[33] to afford the dibromo-phenothiazine **1** in excellent yield (98-99%, 69-79% overall yield).



Scheme 1

The synthesis of the iodine-phenothiazines was realized[34] by a mono or a double Li-Br exchange with *n*BuLi (Scheme 2) and a subsequent addition of iodine as electrophile.



Scheme 2

The iodine-phenothiazine structures of **4a**, **4b** were revealed by MS (each of the FAB-MS spectra present the molecular peak, *i.e.* for **4b** M = 535, and M/z = 534.9) and by NMR measurements. The ^{1}H-NMR spectra have shown that the products are symmetrical substituted phenothiazine derivatives, because of the occurrence in the aromatic region of three distinct signals corresponding to the three pairs of phenothiazine aromatic protons.

One interesting feature of the iodo-derivatives is the upfield shifting of the signal of the direct bounded carbon atom, compared to the bromine-substituted one. This shift is called "heavy-atom effect". For our compounds, the assigned chemical shift for this type of carbon atom is 84.8 ppm (Figure 1).

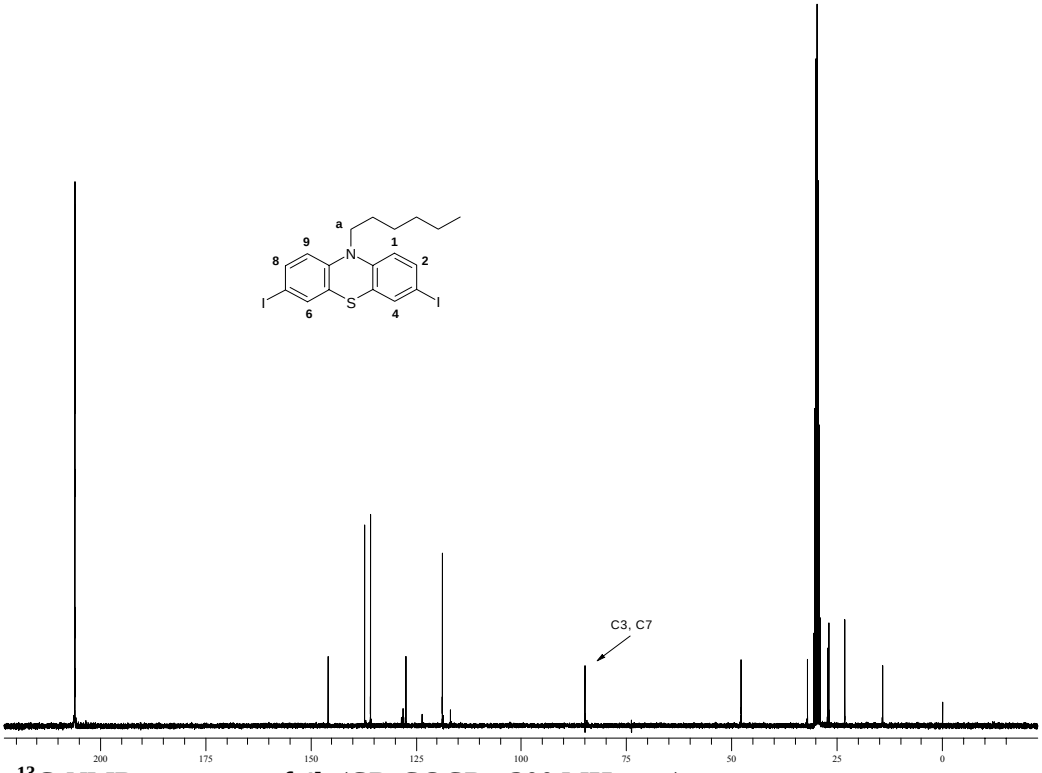
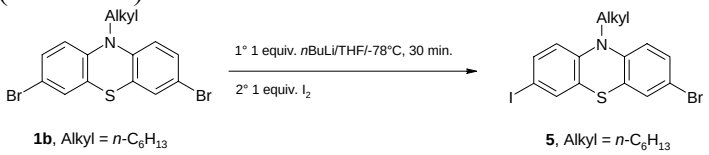


Figure 1. ^{13}C-NMR spectrum of 4b (CD_3COCD_3, 300 MHz, *r.t.*)

[33] Bodea, C; Terdic, M. *Studii si Cercet. Chimie, Acad. RPR Fil. Cluj* **1962**, *13*, 81-87.

[34] Sailer, M.; Gropeanu, R.A.;. Müller, T.J.J. "PRACTICAL SYNTHESIS OF IODO PHENOTHIAZINES. A FACILE ACCESS TO ELECTROPHORE BUILDING BLOCKS" *Journal Of Organic Chemistry* **2003**, *68*, 7509.

The success of this reaction prompted us to investigate the possibility of the introduction of one iodine atom in the phenothiazine molecule. This was realized by performing of a mono Br-Li exchange by addition of only one equivalent of *n*BuLi in much longer time over of a more diluted solution of **1** (Scheme 3).

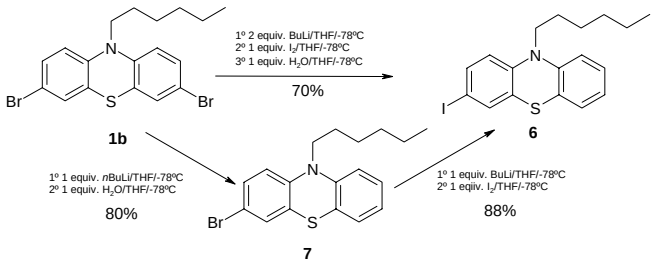


1b, Alkyl = *n*-C_6H_{13} **5**, Alkyl = *n*-C_6H_{13}

Scheme 3

The FAB-MS spectrum of **5** presents the molecular peak and its characteristic splitting of the mono-brominated compounds (M/z = 488.7, 486.7, M=488). The NMR spectra show an unsymmetrical substitution of the phenothiazine. Moreover, the ^{13}C-NMR spectrum presents a signal due to a quaternary carbon atom at 84.8 ppm, assigned to the iodine-substituted carbon atom.

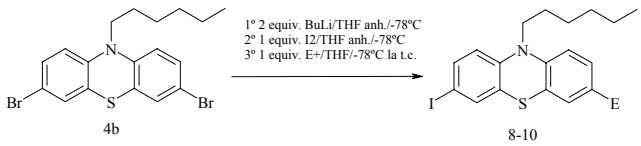
The above described method generates bromo-iodo-phenothiazines useful in the construction of oligophenothiazines. In order to obtain other unsymmetrical substituted iodo-phenothiazines that contain other functional groups it was necessary to develop a different method. Thus, we have relied on the Li-Br exchange and modified the electrophiles. Using 2 equivalents of *n*BuLi and two kind of electrophiles (in principle, the first one iodine, and as the second one, other kind of electrophiles that can generate useful functions) could be obtained the target phenothiazine derivatives. This idea was tested for the synthesis of 3-iodo-10-hexyl-10H-phenothiazine (**6**, Scheme 4).



Scheme 4

The direct transformation of **4b** into **6** was performed by using one equivalent of iodine (as the first added electrophile) and then water for quenching the dilithiated species of **4b**. The sequential transformation of **4b** involved the exchange of one bromine atom with hydrogen, *via* Li-Br exchange and the use of water as electrophile, and a subsequent replacement of the remaining bromine from **7** with iodine, using the same Li-Br exchange. Comparing the yields, these two pathways are quite similar, but the direct method brings some advantages: it reduces the materials consumption, as well as the working time.

Having these on our mind, other electrophiles were also used in this procedure. Thus, D_2O, dry DMF, $B(OMe)_3$ were added as second electrophiles to afford the corresponding non-symmetric substituted phenothiazines (Scheme 5).



	8	9	10
E	D	CHO	
E+	D2O	DMF	B(OMe)3 + pinacole

Scheme 5

The unsymmetrical structure of the phenothiazine derivatives **8**-**10** was shown by the NMR spectra. For example, the ^{1}H-NMR spectrum of **9** presents distinct 6 signals for the phenothiazine protons, as well as the signal corresponding for the formyl proton (δ 3-C<u>H</u>O = 9.80 ppm, Figure 2).

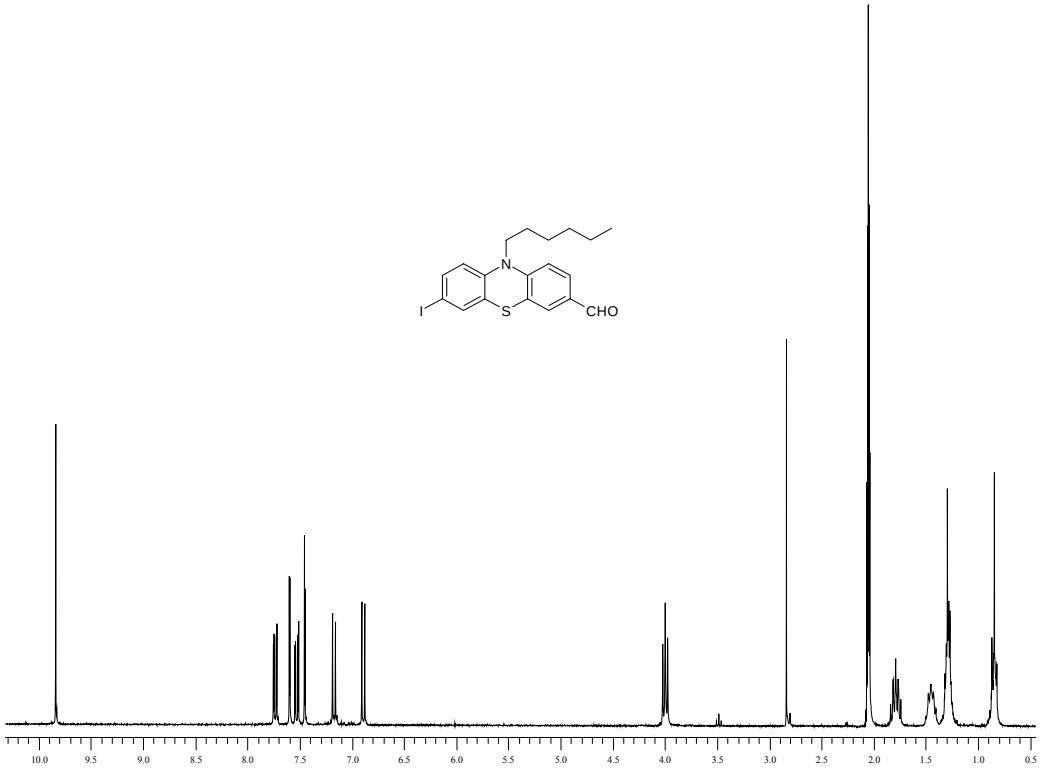


Figure 2. ^{1}H-NMR spectrum of 9 (CD_3COCD_3, 300 MHz, *r.t.*)

The ^{13}C-NMR spectrum of **9** presents two characteristic signals: one corresponding to C-I (δ C7 = 85.81 ppm) and one for the formyl group carbon atom (δ C3' = 190.28 ppm).

2.2. PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS OF HALO-PHENOTHIAZINES

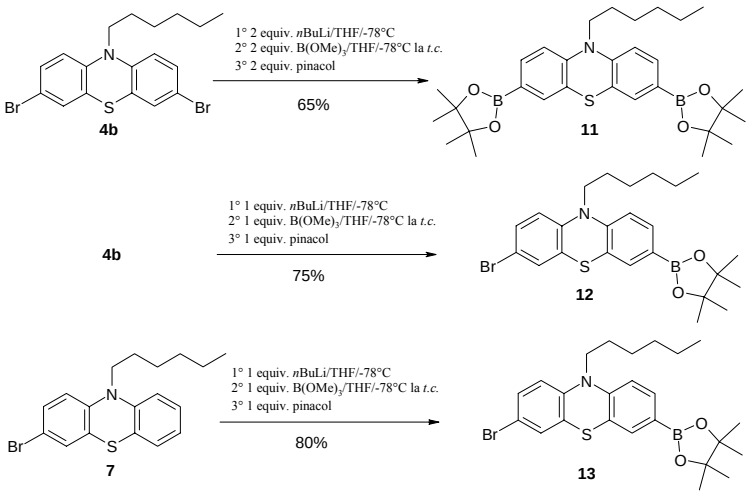
Halo-phenothiazines, as many other halo-derivatives,[35] undergo palladium-catalyzed cross-coupling reactions. An extensively used method for the coupling of two C_{sp2} carbons is represented by the Suzuki cross-coupling.[36] This reaction involves the interaction of one organic halide and one organoboron compound, interaction mediated by Pd reduced species. This cross-coupling reaction undergo in the presence of charged bases (Na_2CO_3, K_2CO_3, Na_3PO_4, KOH, and alkoxides).[37,38]

The synthesis of the phenothiazine boronic intermediates was previously described.[39] After generation of a mono or a double lithiated species by Li-Br exchange, an addition of trimethylborate as electrophile, followed by the transesterification with pinacole, afforded the phenothiazine mono- or bis-boronic esters (**11a**,**b**, **12**, **13**, Scheme 6). It was chosen the pinacole ester due to their high stability.[40]

In order to increase the selectivity, the reaction temperature was decreased. In the synthesis of **15**, despite the very good selectivity, the yield was not very good, after work-up

[35] Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959.
[36] Miyaura, N.; Suzuki, A. *Chem. Rev.***1995**, *95*, 2457.
[37] Susuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.
[38] Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.
[39] Krämer, C.; Sailer, M.; Müller, T.J.J. *Synthesis* **2002**, 1163.
[40] Hoffmann, R.W.; Dresely, S. *Synthesis* **1988**, 103.

some amounts of the starting materials were recovered. This was a sign that the temperature was too low. However, the synthesis of **14** has afforded in good yield the desired triad.

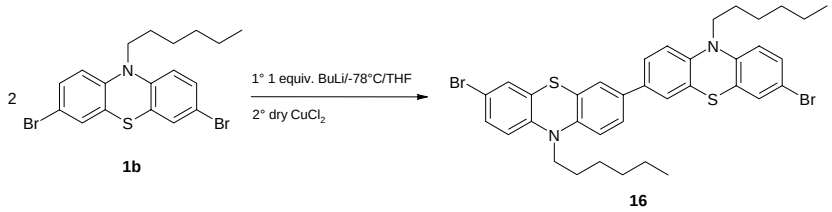


Scheme 6

After the purification, only traces of the iodine-derivatives were isolated. The mass spectra (FAB-MS) of **14** and **15** confirmed the assigned structures. The molecular peaks are splitted; for example, for **14** (M = 1003) an usual distribution of M-2, M-1, M, M+1, M+2 peaks characteristic to the dibrominated compounds occurred in the spectrum.

The ^{13}C-NMR spectra present characteristic peaks to the $\underline{C_{sp2}}$-Br at 114 ppm and no signals corresponding to a $\underline{C_{sp2}}$-I bond.

Another dyad was synthesized in a different manner (Scheme 10), by an oxidative coupling of two monolithiated phenothiazines.



Scheme 7

2.3. FERROCENO-PHENOTHIAZINE MACROCYCLES

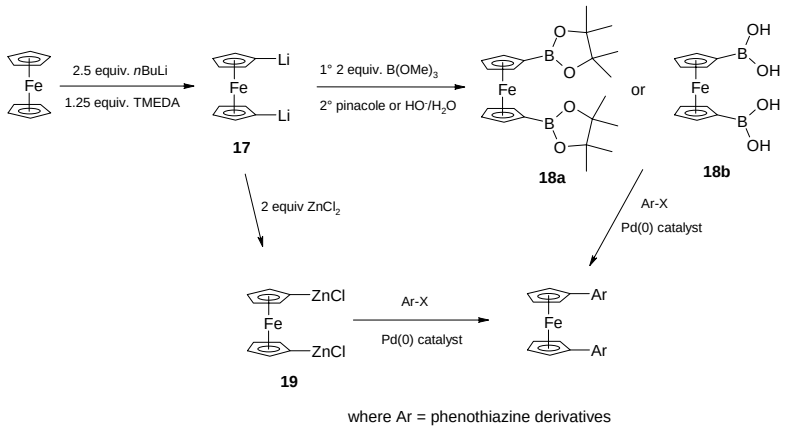
Ferrocene represents an interesting redox-active material and, recently, the ferrocene core has been used as a building-block in the construction of redox-active and responsive macrocycles.[41]

Thus, the prospect of integrating strongly coupled redox fragments like phenothiazines and ferrocenes into conjugated chains could constitute a so far unknown class of redox addressable molecular wires. In particular, the integration of these synthons into a fully-conjugated macrocycle represented one of our main goals.

Palladium-catalyzed cross-coupling reaction were described to be an effective method in the synthesis of ring-substituted ferrocenes.[42] From these methods, the Suzuki and the Negishi

[41] a) Dinnebier, R.E.; Ding, L.; Ma, K.; Neumann, M.A.; Tanpipat, N.; Leusen, F.J.J.; Stephens, P.W.; Wagner, M. *Organometallics* **2001**, *20 (26)*, 5642, 5647; b) Beer, P.D.; Crowe, D.B.; Ogden, M.I.; Drew, M.G.B.; Main, B. *J. Chem. Soc., Dalton Trans.: Inorg. Chem.* **1993**, *(14),* 2107-2116; c)Beer, P.D.; Nation, J.E.; Brown, S.L. *J. Organomet. Chem.* **1989**, *377 (1)*, C23-C26; d) Bell, A.P.; Hall, D. *J. Chem. Soc., Chem. Commun.* **1980**, *(4)*, 163-165; e) Plenio, H.; Aberle, C. *Chem. Eur. J.* **2001**, *7(20)*, 4438-4446; f) Plenio, E.; Aberle, C.; Al Shihadeh, Y.; Lloris, J.M.; Martinez-Manez, J.; Pardo, T.; Soto, J. *Chem. Eur. J.* **2001**, *7(13)*, 2848-2861.

couplings provided good results and, therefore, these were taken into consideration for our purposes. Both of these methods involve the preparation of the dilithiated species of ferrocene[43] (17, Scheme 8).



Scheme 8

The Suzuki cross coupling between **18a** and **5** was performed using as catalyst tetrakis(triphenylphosphine)palladium and typical conditions; the conversion of the ferrocene **18a** was 100% (according to TLC), but the yield in the desired product was very low (about 1%). The "product" proved to be a mixture of at least two ferrocene derivatives (according to NMR and MS spectra). Using the MS (FAB+) spectrum we could assign the productsas mono-cross-coupling products (with bromo-substituted phenothiazine as the major product and iodo-subtituted phenothiazine core as minor one) and the ferrocene mono-boronic-pinacole ester.

The first attempts of Negishi coupling have furnished the desired products in fair to good yields. A series of Negishi couplings were performed in order to optimize the synthesis. The data are presented in Scheme 9 and in Table 1.

The fact that the yields are rather modest could have two reasons:

a) the bis(lithiated) ferrocene was described to be not very stable in the presence of ethers, such as THF or diethyleter. This means that is possible that the recovered ferrocene appeared as a decomposition process of the 1,1'-dilithium-ferrocene.

b) the palladium catalyzed cross-coupling reactions between two rich electron systems proceeds usually with low yields.

c) after all of the cross-coupling reactions there was recovered an insoluble, amorphous brown material, which is most probably a mixture of polymers.

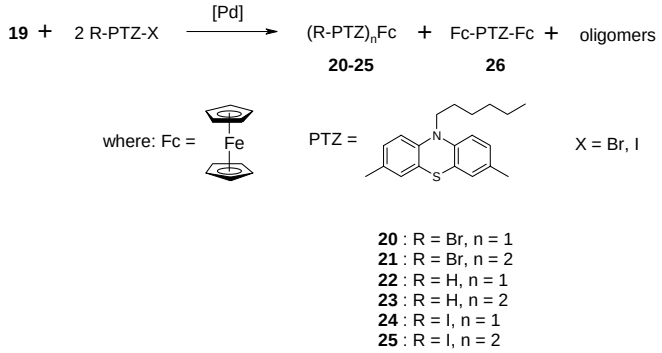
Analyzing the data, two conclusions could be drawn: the iodine-substituted phenothiazines react better than the brominated ones, that is not surprising. Unfortunately, this higher reactivity provides a larger amount of oligomeric by-products. Also, in the case of **4b** bis(ferrocenyl)-phenothiazine (**26**) was recovered as by-product, and this was not the case for bromine-substituted phenothiazines. The second conclusion regards the catalysts: the best results were obtained using $Pd[(PPh_3)_4]$ for bromine-substituted phenothiazines, and $PdCl_2(PPh_3)_2$ for iodine-substituted phenothiazines, respectively.

A Negishi cross coupling at higher temperature (reflux) was also performed, but the yield was lower than the reaction run at room temperature (see entry 9, Table 1).

---

[42] a) Arnold, R.; Matchett, S.A.; Rosenblum, M. *Organometallics* **1988**, *7*, 2261; b) Enders, M.; Kohl, G.; Pritzkow, H. *J. Organomet. Chem.* **2001**, *622*, 66-73; c) Enders, M.; Kohl, G.; Pritzkow, H. *Organometallics* **2002**, *21*, 1111-1117.

[43] a) Bishop, J.J.; Davison, A.; Katcher, M.L.; Lichtenberg, D.W.; Merrill, R.E.; Smart, J.C. *J. Organomet. Chem.* **1971**, *27*, 271; b) Knapp, R. ; Rehahn, M. *J. Organomet. Chem.* **1993**, *452*, 235-40



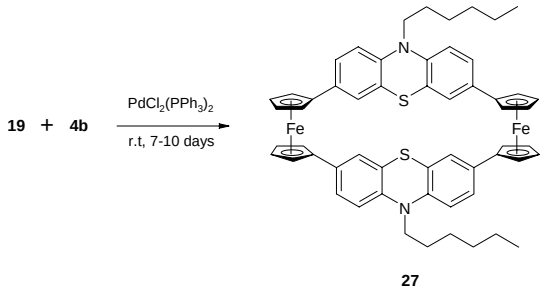
Scheme 9

Table 1. The Negishi cross-coupling syntheses data; reagents, products, yields*

Entry	[Pd] Catalyst	R	X	Products			Obs.
				$Fc(PTZ\text{-}R)_2$	Fc-PTZ-R	Fc-PTZ-Fc	
1	$Pd[(PPh_3)_4]$ 0.1%	H	Br	9.4	11	-	r.t., 3 days
2	$Pd[(PPh_3)_4]$ 0.2%	Br	I	2.8	21.9	-	r.t., 3 days
3	$Pd[(PPh_3)_4]$ 2.1%	Br	Br	6.6 (9.6)	12.4 (18.6)	-	r.t., 3 days
4	$PdCl_2(PPh_3)_2$ 5%	Br	Br	8.2 (11.2)	11.0 (15.1)	-	r.t., 3 days
5	$PdCl_2(PPh_3)_2$ 3.9%	Br	I	21.6 (24.3)	31.1 (42.4)	-	r.t., 3 days
6	$Pd[(PPh_3)_4]$ 5%	I	I	1	9.8	3	r.t., 4 days
7	$Pd[(PPh_3)_4]$ 5%	I	I	6	2	4	r.t., 5 days
8.	$Pd[(PPh_3)_4]$ 2.5%	Br	Br	28.1 (31.2)	12.8 (14.2)	-	r.t., 5 days
9.	$Pd[(PPh_3)_4]$ 2.5%	Br	Br	15.3	11.8	-	1 hr. reflux, 2 days r.t.

* Yields are reported to ferrocene; in brackets are presented yields calculated after subtraction of the recovered ferrocene

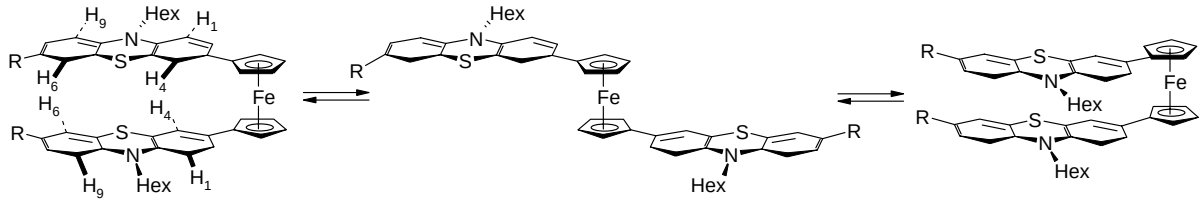
Several attempts have been made to synthesize the desired macrocycle **27** directly from **19** and **4b** using 1:1 stoichiometry and high dilution technique (Scheme 15). Unfortunately, the isolated products were the corresponding dyads and triads (**24**-**26)**, as well as some oligomers (identified by MS-FAB+). In one case it was isolated a compound in a very low yield which presents in mass spectra (ESI, FAB+) a peak corresponding to the molecular mass of the target macrocycle (930).



Scheme 10

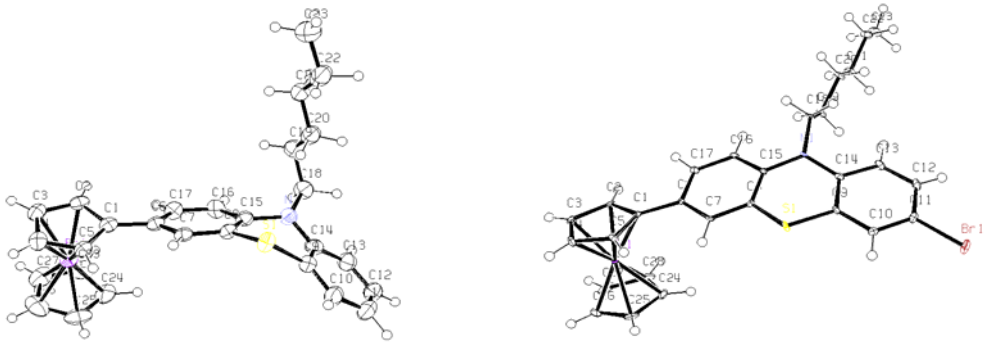
This compound has a pronounced tendency to oxidize, revealed by the FAB+ technique (in the spectrum appears a significant peak at M + 16). Unfortunately, due to the very small amount and to the fact that the purity of the compound was not high, the NMR spectrum is ambiguous and could not confirm the assigned macrocyclic-type structure.

2D-NMR experiments were performed in order to figure out the conformation adopted by triads in solution. The most useful experiment is NOESY. Analyzing the spectra, could not been identified cross-peaks between H^1 and H^4, or H^6 and H^9, respectively. This means that in solution the triads are conformationally free, the electronic interactions between the two phenothiazine units being too weak at room temperature in solution to prevent the free rotation of the ferrocene core, having the iron as a pivot (Scheme 11).



Scheme 11

Unfortunately, suitable crystals for X-ray structure analysis could not be grown for these triads. Nevertheless, the dyads **20** and **22** furnished good crystals for analysis. ORTEP drawings are depicted in Figure 1.



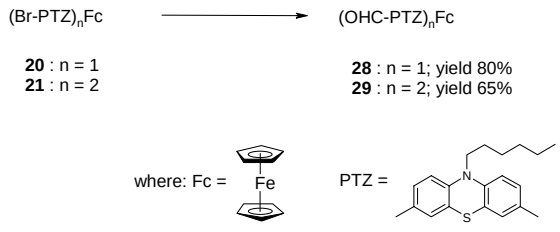
a **b**

Figure 1. ORTEP drawings of compounds 20 (a) and 22 (b).

Synthesis of macrocycles using the McMurry reductive coupling of carbonyl compounds

Another considered way for the synthesis of macrocycles is to convert the triad **21** into the bis-formyl derivative and to close the macrocycle using the McMurry procedure for transformation of aldehydes into alkenes.

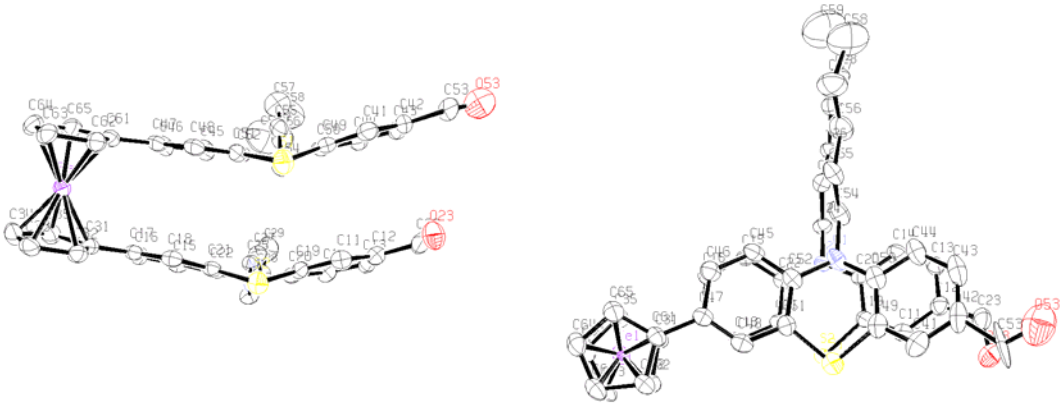
The conversion of bromine-dyad **20**, and dibromine-triad **21**, respectively, was achieved in good yields and on a gram scale using a lithium-bromine exchange and a subsequent quenching of the lithiated species with dry DMF (Scheme 12).



Scheme 12

The formation of the formyl intermediates was proved by the MS spectra, in which occur the corresponding molecular peaks. Also, the ^{1}H-NMR spectra present the characteristic singlet signal of the formyl groups (**28:** δ 3-CHO = 9.79 ppm, 1H; **29**: δ 3-CHO = 9.73 ppm, 2H).

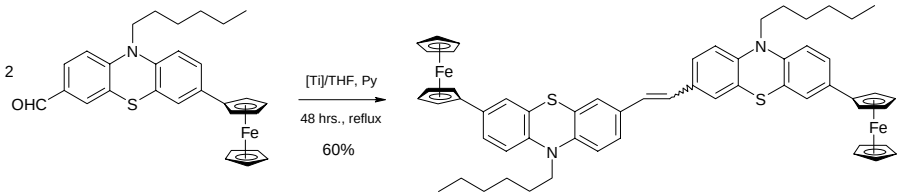
The triad **29** furnished crystals suitable to X-ray diffraction analysis. In Figure 9 two ORTEP drawings of **29** are presented. The two phenothiazine units are parallel and, surprisingly, they adopted a *syn* orientation. The two cyclopentadienyl cycles are almost parallel and eclipsed.



a **b**

Figure 2. ORTEP drawings of compound 29, different views

We have chosen to test if the common reagent ($TiCl_4$-Zn/Cu) is effective for our substrates. Thus, we have attempted the McMurry coupling of 3-ferrocenyl-7-formyl-10-*n*-hexyl-10H-phenothiazine (**28**, Scheme 13) using the Mukaiyama's procedure[25] and high dilution conditions.

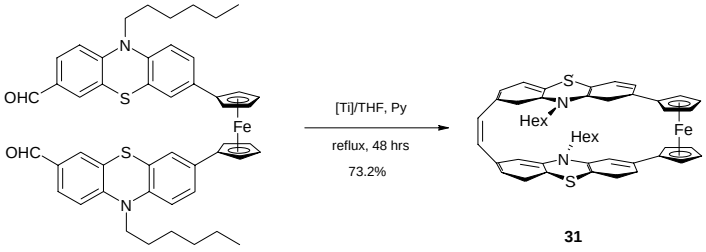


28 **30**

Scheme 13

The separation of the products by silica gel column chromatography gave the desired bis(ferrocenyl-phenothiazinyl)ethene (**30**) in 60% yield and a few amount of the reduced species of the starting material.

This result prompted us to subject **29** to a reductive coupling reaction in the conditions mentioned above, which, after work-up, afforded the desired macrocyclic product **31** (Scheme 14) in an excellent yield (73%). This excellent yield for a macrocyclization reveals the efficient template effect of the titanium low-valent species.



29 **31**

Scheme 14

The ^{1}H-NMR spectrum of **31** presents, beside the signals characteristic to the two *n*-hexyl groups and for the 1, 1'-disubstituted ferrocene, in the aromatic region the signals corresponding

to the two magnetic equivalent phenothiazine units, and the vinylic protons as a singlet (δ = 6.55 ppm) (Figure 3).

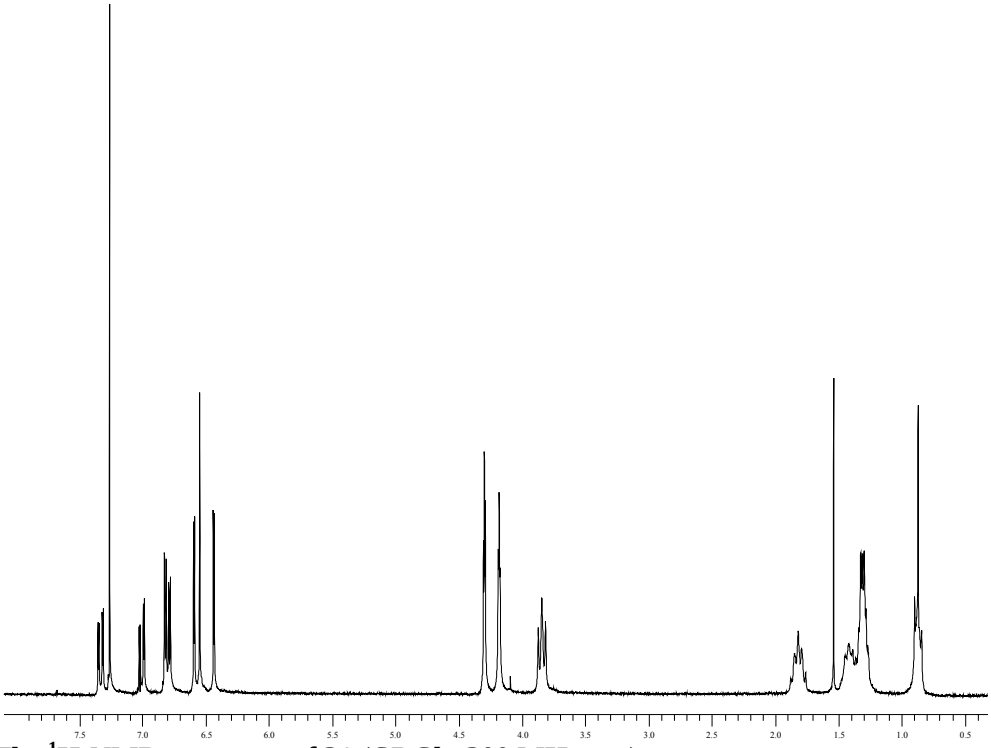
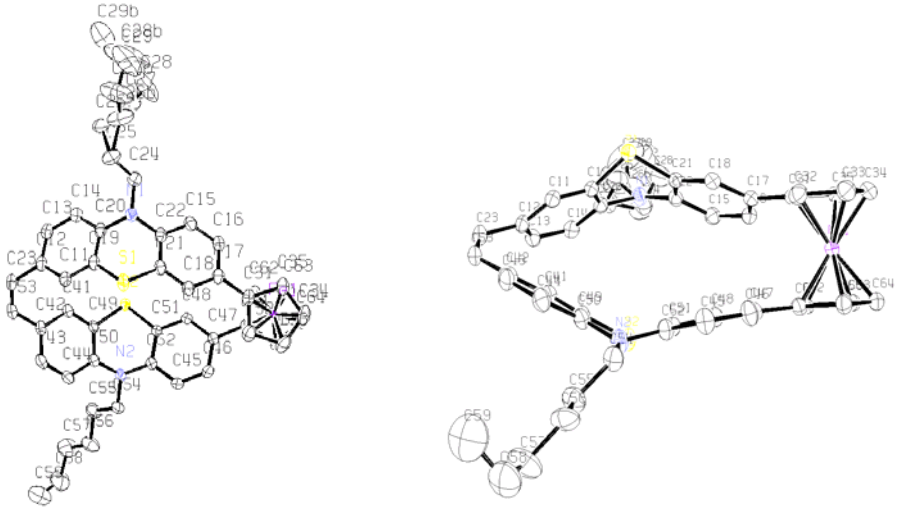


Figure 3. The ^{1}H-NMR spectrum of 31 ($CDCl_3$, 300 MHz, *r.t.*)

The mass spectrum is in accordance with the assigned structure.

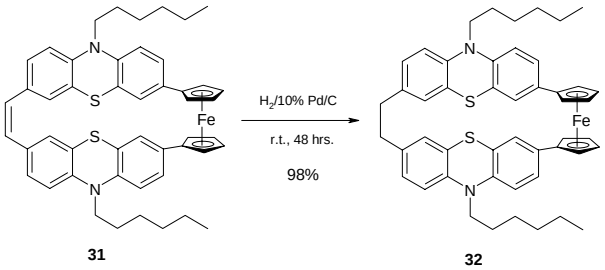
The X-rays analysis performed on monocrystal showed us that the vinylene bridge presents the *cis* configuration, and that the two phenothiazine units lie in an *anti* orientation. These phenothiazine units are a little beat twisted from a superposed arrangement, which is preferred by the bis(phenothiazinyl)ferrocene derivatives (Figure 4). This fact suggests an electronic communication between the two phenothiazines through the vinylene bridge. The other atropisomer (with a *syn* orientation of the phenothiazinic units) could not been detected by means of NMR spectrometry. Also, whilst there are described ferrocene macrocycles formed by McMurry reductive coupling with the resulted vinylene bridge having both *cis* and *trans* configurations, the *trans* isomer of **31** was not isolated.



a **b**

Figure 4. The ORTEP drawing of 31: a) view along a perpendicular axis to the cyclopentadienyl rings; b) view along a parallel axis with the cyclopentadienyl rings

In order to suppress the electronic communication through the vinylene bridge, this was catalytically reduced with molecular hydrogen in 1,2-dichloroetane to an ethylene bridge (Scheme 15).



31 **32**

Scheme 15

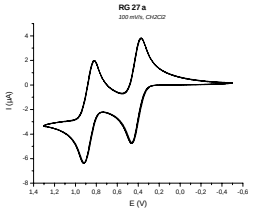
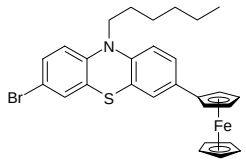
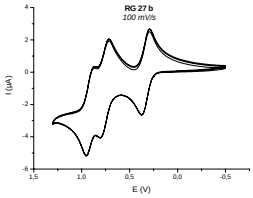
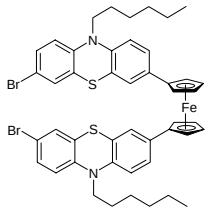
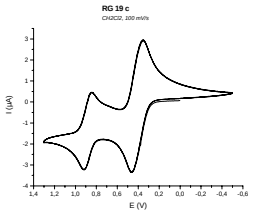
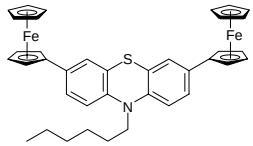
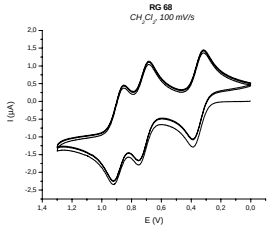
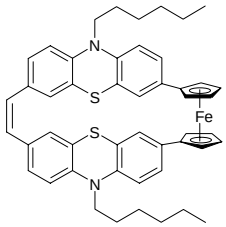
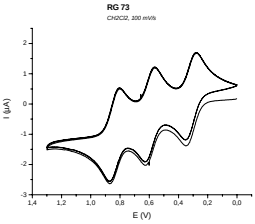
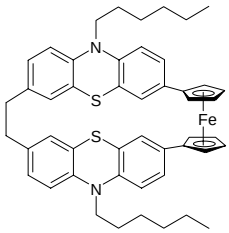
The signals of the phenothiazinic protons in the ^{1}H-NMR spectrum of **32** are slightly shifted up-field compared with the same protons of the **31**. Also, the spectrum presents the signal of the ethylene bridge (δ -CH_2-CH2- = 2.71 ppm) as a singlet. Unfortunately, this compound crystallizes in sharp needles, which are unsuitable for X-rays diffraction analysis. However, the mass spectrum (FAB+) confirms the assign structure.

Phisyco-Chemical Properties of the Synthesized Dyads, Triads and Macrocycles

The dyads, triads, and the macrocycles were analyzed using cyclic voltammetry. The results are presented in the Table 2. Due to the presence of two redox active units (ferrocene and phenothiazine, respectively) our expectation was to find two oxidation waves. Indeed, the cyclo-voltammograms of the dyads show two oxidation steps for the ferrocene and the phenothiazine unit, respectively. The first step (0.57 V) is due to the ferrocene moiety, and the second (1.01-1.02 V) to the phenothiazine rest, respectively (see Table 5, entry 1). In the case of the bis(phenothiazinyl)ferrocene triads there are three redox waves (see Table 5, entry 2) despite the fact that the molecules are symmetric. This fact can be a consequence of the electronic communication between the two redox active phenothiazine centres. The electronic communication can take place through the already oxidized ferrocene or through space by π-stacking. It was previously shown by the X-rays diffraction that in the solid state the two phenothiazine moieties are superposed, most probably due to the π-stacking. In the case of bis(ferrocenyl)-phenothiazine, two redox steps occur in the voltammogram, one due to the two ferrocene units (two electrons process) and one (one electron process). This means that the two feerocene are independent each other and, therefore, have the same redox potential.

One reason for the synthesis of the target macrocycles is to investigate this electronic communication in solution because the two phenothiazine units are constrain at least partly to superpose. The cyclo-voltammograms present the same electronic behavior like the triads. The only difference in that the first oxidation step assigned to the phenothiazine units are at lower potentials in the case of macrocycles. The gap between the oxidation steps of the phenothiazines in the case of the non-cyclic triads is lower (0.111-0.169 V) than in the case of the macrocycles (0.198 V for **31** and 0.238 V for **32**, respectively). This fact can be take as a measure of electronic communication (one phenothiazine unit playing the role of a rich-electron substituent of the phenothiazine which oxidizes first) in the way that the greater the gap, the stronger the communication. Not surprisingly, the strongest electronic communication is found in the macrocyclic triads, especially for **32** in which the ethylene bridge is flexible (compared with the vinylene bridge of the **31**) and short enough to constrain the superposition of the phenothiazine units in solution. This superposition is less probable in solution for the non-cyclic triads due to the solvation of the molecule and to the free rotation around the ferrocene, respectively.

Table 2. Cyclic voltammetry data of some ferrocene-phenothiazine derivatives

Entry	Cyclic Voltammogram	$E_{1/2}$ (V)	Compound
1		**0.572** **1.020**	
2		**0.549** **0.946** **1.115**	
3		**0.576** **1.042**	
4		**0.563** **0.904** **1.102**	
5		**0.521** **0.798** **1.036**	

2.4. SHAPE-PERSISTENT MACROCYCLES

A. Introduction

In the last decade a lot of shape-persistent macrocycles on the nanometre scale have been synthesized and characterized. Due to a) the conformational rigidity, and b) to the fact that the interior space is separated by the exterior these macrocycles were good candidates for various supramolecular studies, such as organisation into and transport through porous molecular crystals[44,45] or pattern formation at interfaces.[46] The basic structural type is represented by the

[44] a) Henze, O.; Lenz, D.; Schäfer, A.; Franke, P.; Schlüter, A.D. *Chem. Eur. J.* **2002**, 357-365; b) Werz, T.B.; Staeb, T.H.; Benisch, C.; Rausch, B.J.; Rominger, F.; Gleiter, R. *Org. Lett.* **2002**, *4*, 339-342; c) Campbell, K.; Kuehl, C.J.; Ferguson, M.J.; Stang, P.J.; Tykwinski, R.R. *J. Am. Chem. Soc.* **2002**, *124*, 7266-7267.

[45] See, for example: Venkataraman, D.; Lee, S.; Zhang, J.; Moore, J.S. *Nature* **1994**, *371*, 591-593.

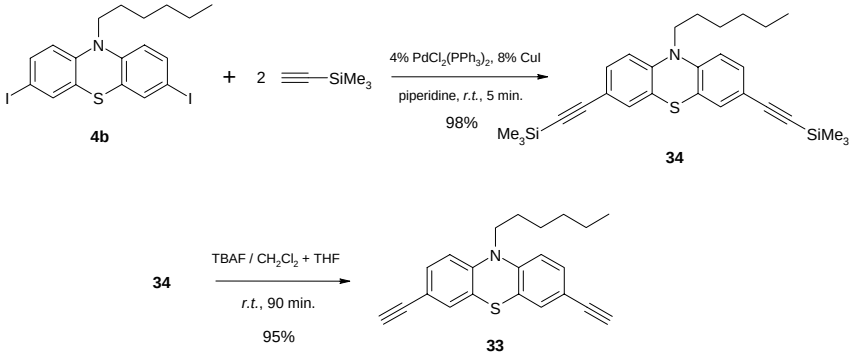
[46] See, for example: a) Borissov, D.; Ziegler, A.; Höger, S.; Freyland, W. *Langmuir* **2004,** *20*, 2781-2784; b) Grave, C.; Schlüter, A.D. *Eur. J. Org. Chem.* **2002**, 3075-3098; c) Höger, S.; Bonrad, K.; Mouran, A.; Beginn, U.; Möller, M. *J. Am. Chem. Soc.* **2001**, *123*, 5651-5659; d) Zhao, D.; Moore, J.S. *Chem. Commun*. **2003**, 807-818.

phenylene-acetylene macrocycles,[47] which differ in the ring size (up to 5.5 nm) and in the side-chain pattern. Several macrocyclic phenylacetylenes have been shown to have interesting properties, such as self-association in solution,[48] the existence of liquid crystaline phases,[49] or the capability to bind small molecules.[50]

B. Synthesis of the Intermediates

The strategy is based on the sequential Sonogashira coupling reactions between dihalo-phenothiazines and bis(ethynyl)-phenothiazine, which could be readily available from dihalo-phenothiazines. The synthesis of bis(ethynyl)-phenothiazine (**33**) was previously described using several ways: by Sonogashira coupling of dibromo-phenothiazine with trimethylsilyl-acetylene (TMS-acetylene), by converting formyl-phenothiazines using Corey-Fuchs protocol or, alternatively, the Ohira-Bestmann transformation.[51]

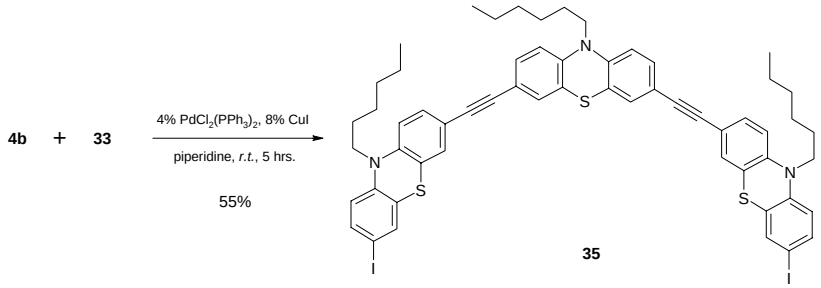
It is well known that iodine derivatives react under mild conditions and easier than bromine ones. As a consequence, we have performed this Sonogashira coupling using diiodo-phenothiazine (Scheme 16); the reaction underwent smoothly, at room temperature, to afford the bis(TMS-ethynyl)-phenothiazine (**34**) in 95% yield; the deprotection of TMS-groups was achieved with TBAF/CH_2Cl_2.



Scheme 16

The ^{1}H-NMR of **33** presents the signal corresponding to the two 1-alkynyl protons (δ = 3.03 ppm).

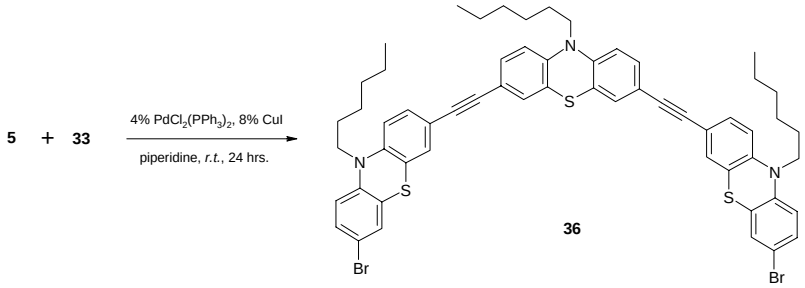
The next step was the synthesis of the first precursor (**35**). The Sonogashira coupling using the previously described conditions and the diiodo-phenothiazine **4b** in 50% excess (Scheme 17) afforded the diiodo-diethynylene-bridged phenothiazine triad **35** in fair yield (55%) and some other products, most probably oligomers with 4 or more phenothiazine units.



Scheme 17

[47] Zhang, J.; Pesak, D.J.; Ludwick, J.L.; Moore, J.S.; *J. Am. Chem. Soc.* **1994**, *116*, 4227-4239.
[48] a) Shetty, A.S.; Zhang, J.; Moore, J.S. *J. Am. Chem. Soc.* **1996**, *118*, 1019-; b) Tobe, Y.; Nagano, A.; Kawabata, K.; Sonoda, M.; Naemura, K. *Org. Lett.* **2000**, *2*, 3265-, and references cited therein.
[49] a) Zhang, J.; Moore, J.S. *J. Am. Chem. Soc.* **1994**, 116, 2655; b) Collins, S.K.; Yap, G.P.A.; Fallis, A.G. *Org. Lett.* **2000**, *2*, 3189-.
[50] Morrison, D.L.; Höger, S. *Chem. Commun.* **1996**, 2313-14.
[51] Krämer, C.S.; Zeitler, K.; Müller, T.J.J. *Org. Lett.* **2000**, *2(23)*, 3723-3726, and references cited therein.

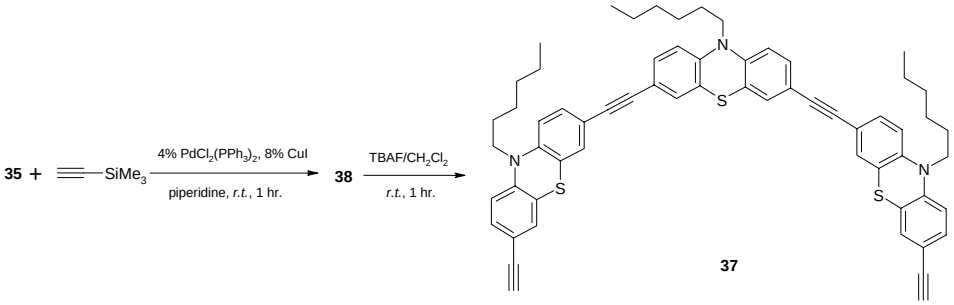
In order to reduce the ratio of oligomerization, we have tested the chemoselectivity of the Sonogashira coupling using bromo-iodo-phenothiazine **5** with the selective obtaining of the dibromo-analog of **35** (**36**, Scheme 18).



Scheme 18

The yield was higher (72%), and the selectivity was high, and, as in the Negishi or Suzuki coupling involving bromo-iodo-phenothiazine, only traces of the bromine-iodine-ethynylene-bridged phenothiazine triad have been identified by mass spectrometry. Another proof of the selective cross-coupling was brought by the ^{13}C-NMR spectrum of **36**, in which does not appear a signal corresponding to a $\underline{C_{sp2}}$-I carbon atom (signal at about δ 84-85 ppm).

The second precursor has to have two terminal ethynyl groups; the synthesis of **37** was performed by a Sonogashira coupling between **35** and TMS-acetylene (Scheme 19), and a subsequent deprotection of the TMS-protected intermediate **38** with TBAF.



Scheme 19

In the ^{1}H-NMR spectrum of **37** the signal corresponding to the two terminal ethynyl protons appears at 3.05 ppm.

C. The Cyclization Attempt

The cyclization was performed using the high dilution technique. An equimolar mixture of the two precursors (**35** and **37**, respectively) was subjected to the Sonogashira cross coupling reaction (Scheme 20). The ^{1}H-NMR spectrum of the main product is complex. In the aliphatic region there are many signals due to at least two magnetically non-equivalent *n*-hexyl residues, which is different as I would expect taking into consideration the 6 symmetrical substituted phenothiazines from the target structure of the macrocycle. Also, these signals are shifted downfield compared with those assigned to an *n*-hexyl core from a non-cyclic *n*-hexyl-10H-phenothiazine derivative. In the aromatic region, the signals are spread between 5.5 and 9.5 ppm. The spectrum of the sample extracted with THF looks more familiar with a spectrum of an *n*-hexyl-10H-phenothiazine derivative; however, in the aliphatic region the situation is the same as previously described. In the aromatic region the signals are shifted downfield compared with the precursors, and are more than 3 as I would expect for a symmetrical structure. This behavior can be due to the free rotation of the phenothiazine units having the ethynyl units as pivots. In this situation, there are two kinds of phenothiazine units: some with the N-*n*-hexyl rest oriented outside the cycle, and the other having the N-*n*-hexyl rest oriented inside.

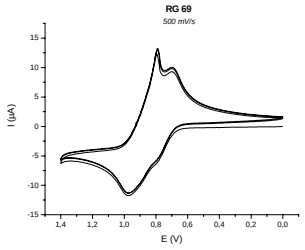
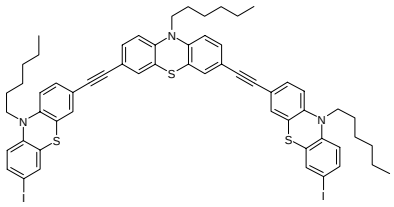
Scheme 20

Mass spectrometry experiments were performed in order to confirm the macrocyclic structure. ESI-MS experiments have failed, whilst the MALDI gave a very small signal at m/e=1831 (for the crude precipitate) and at m/e=1832 (for the THF extract). These values are in the accepted range of measuring errors (± 0.1%, M=1830) and have shown the existence of the target macrocycle.

In order to determine the electrochemical properties of the (poly)ethynylene triads, **35** was subjected to cyclic voltammetry determination. The results are presented in Table 5.

The cyclic-voltammogram of **35** presents one two-electrons oxidation step (0.92 V) assigned to the two marginal phenothiazine units and an one-electron oxidation step (1.02 V) corresponding to the internal phenothiazine moiety. The two-electron oxidation step shows that the marginal phenothiazine units are not electronically connected and they are oxidizing independent at the same potential.

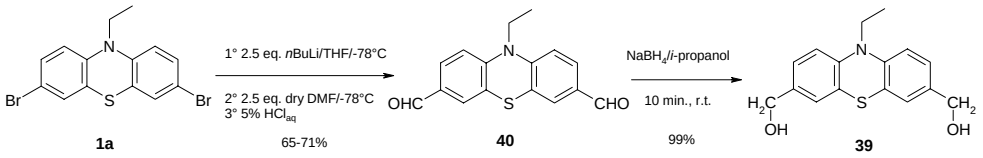
Table 5. Redox properties and the cyclic-voltammogram of **35**

CV Graph	***Oxidation step***	**$E_{1/2}$ (V)**	**Structure**
	*1*	**0.924**	
	2	**1.020**	

2.5. PHENOTHIAZINE CORONANDS

A. The Synthesis of the Intermediates

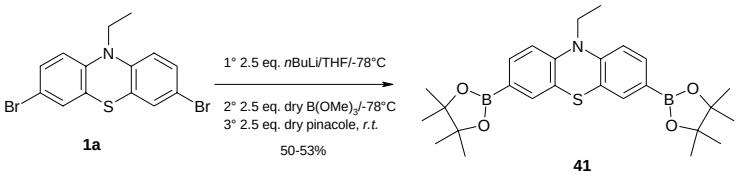
The conversion of **1** into 3,7-bis(hydroxymethyl)-10-ethyl-10H-phenothiazine (**39**) was achieved in two steps. The first one has involved a Br-Li exchange with *n*BuLi, followed by the addition of DMF as electrophile. The work-up with 5% HCl_{aq} afforded the diformyl-derivative **40** (Scheme 21). A subsequent reduction of **40** in mild conditions gave the first key intermediate **39**.



Scheme 21

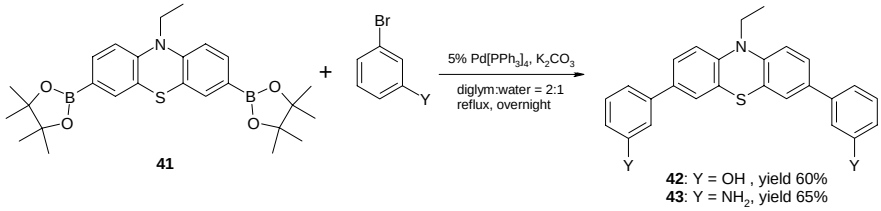
The ^{1}H-NMR spectrum of **39** presents the three sets of signals in the aromatic zone, fact which signifies the symmetrical substitution of the molecule. Besides of these, the signal corresponding to the hydroxymethyl substituents appears in the spectrum (δ CH_2 = 4.37 ppm, δ OH = 5.10 ppm, Figure 14). The signals of the methylene and the hydroxyl of the hydroxymethyl groups are splitted due to their coupling (^3J = 5.70 Hz).

The synthesis of the other key intermediate of our strategy also started from **1a** through a Br-Li exchange with *n*BuLi. In this case, the electrophile was trimethylborate, followed by the addition of pinacole in order to generate the stable phenothiazine bis(boronic ester) (Scheme 22).



Scheme 22

The Suzuki cross-couplings of the *n*-hexyl-analog of **41** were presented above. In this strategy two other coupling partners were considered: bromo-benzenes *m*-substituted with OH and NH_2, respectively. The synthesis of the ditopic intermediates for macrocyclization was realized using standard conditions for the cross-coupling: $Pd[PPh_3]_4$ as catalyst, monoglym or diglym/water, and an inorganic carbonate (Scheme 23). The column chromatography purification (petroleum ether:ethyl acetate = 3:2) afforded the desired products **42** and **43**, as well as some small amounts of mono-substituted by-products.



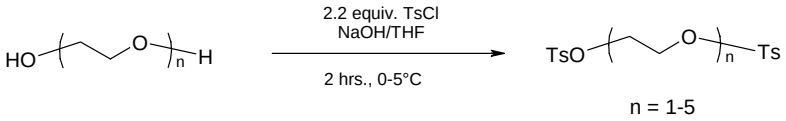
Scheme 23

The mass spectra of the products present the molecular peak (**42**: M/z = 613, **43**: M/z = 611). The ^{1}H-NMR spectrum of **42** presents in the aromatic region partial overlapped 7 signals corresponding to 14 protons. Also, the phenolic hydroxyl protons give in the spectrum a signal having the integral for two protons. Also, the ^{13}C-NMR spectrum confirms the symmetrical substitution of the phenothiazine core, due to the fact that in the aromatic region appear 12 signals corresponding to the 12 types of carbon atoms of the molecule.

The NMR spectra of **43** are almost similar to those of **42**, with the difference that in the ^{1}H-NMR spectrum of **43** appears the signal corresponding to the 2 magnetic equivalent amino groups (δ NH_2 = 5.17 ppm).

B. Synthesis of Coronands Having Phenothiazine Units

The ditosylated pentaethyleneglycols were prepared by tosylation of the corresponding polyethylene glycols (Scheme 24).

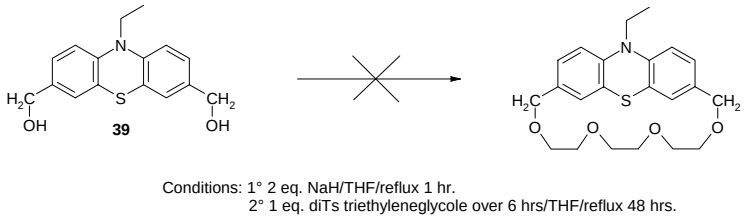


Scheme 24

The ditosyl derivatives were analyzed by NMR spctroscopy.

*ATTEMPT OF MACROCYCLIZATION OF **39***

One attempt of the synthesis of phenothiazine-containing macrocycle starting from **39** was made using ditosylated triethyleneglycole (Scheme 25).



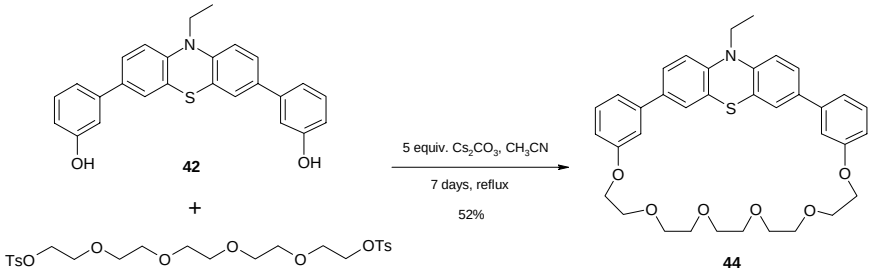
Conditions: 1° 2 eq. NaH/THF/reflux 1 hr.
2° 1 eq. diTs triethyleneglycole over 6 hrs/THF/reflux 48 hrs.

Scheme 25

39 was converted into the disodium salt in order to increase its reactivity. After the work-up of the reaction mixture, the majority of the **fr1** was recovered, as well as small amounts of formyl- and diformyl-10-ethyl-phenothiazines. The same failure of the macrocyclization of a bis(hydroxymethyl)-phenothiazine derivative was reported by Bauer *et al*.[11]

*MACROCYCLIZATION REACTION OF **42***

42 was subjected to macrocyclization with ditosylated pentaethylene glycole in acetonitrile using the high-dillution technique (Scheme 36). Cs_2CO_3 in excess was used as base, as well as *template*. The reaction afforded the target macrocycle in good yield (52%).



Scheme 26

The product was investigated by MS, NMR and X-ray diffraction. The EI-MS spectrum presents the molecular peak (M/z = 613). One interesting feature of this macrocyclization is that after the column chromatography purification no cyclic oligomers were separated.

The ^{1}H-NMR spectrum presents the peak distribution of the phenothiazine precursor, and, in addition, the signals characteristic to the pentaethylene glycol chain (protons **c**,**d**,**e** in Figure 5).

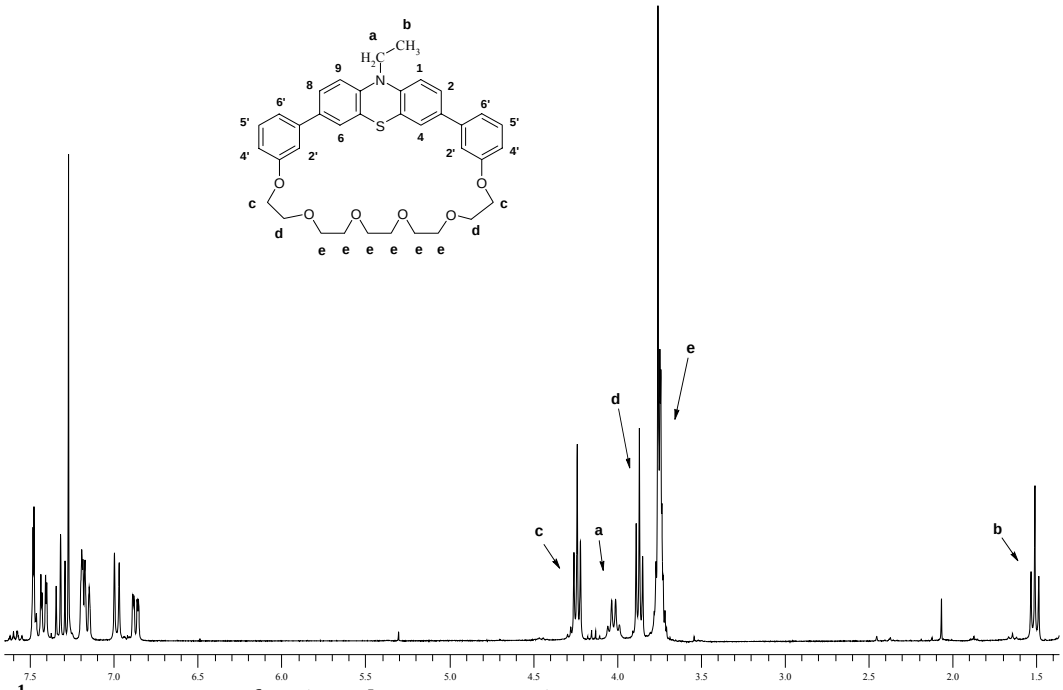


Figure 5. ^{1}H-NMR spectrum of 44 ($CDCl_3$, 300 MHz, *r.t.*)

In the aromatic area the signals were assigned studying the multiplicity, the shape and the coupling constants (Figure 6).

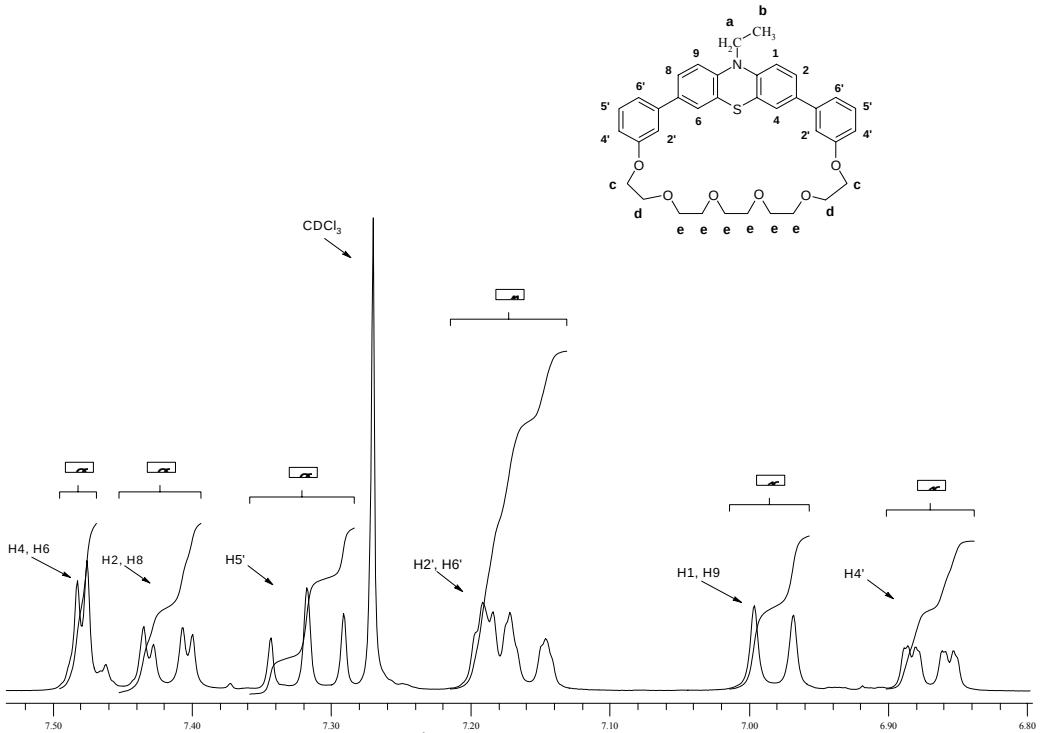


Figure 6. Detail with the aromatic zone of the ^{1}H-NMR spectrum of 44 ($CDCl_3$, 300 MHz, *r.t.*)

The solid state molecular structure of **44** was determined by X-rays diffraction analysis of a monocrystal. In Figure 7 is presented the ORTEP drawing of one molecule.

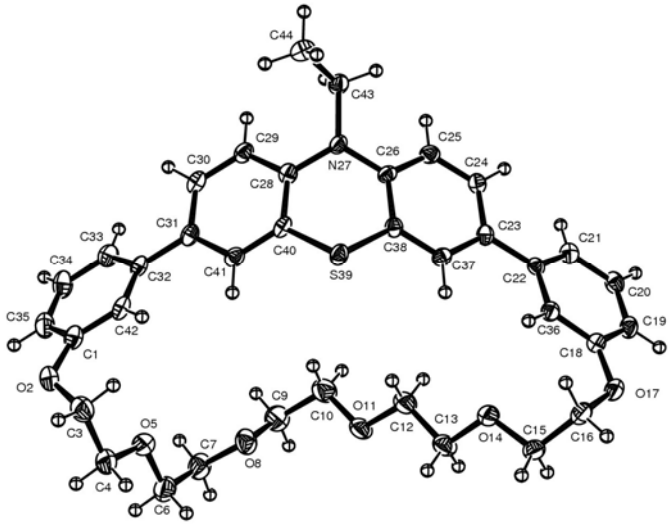


Figure 7. ORTEP drawing of the X-ray diffraction analysis of a monocrystal of 44

The dihedral angle between the two phenylenes of the phenothiazine core is 133.26°. The distance between the centroids of the two benzene units is 11.97Å, while the distance between the sulfur atom and the oxygen atom from the middle of the penta(oxaethylene) chain is 4.97Å. Taking into consideration that the chain is a little beat twisted, we can assume that the cavity of the macrocycle **44** has an elliptic shape, with one dimension being the double of the small dimension.

The unit cell contains four macrocycles (Figure 8), having the (oxaethylene) chains oriented outside.

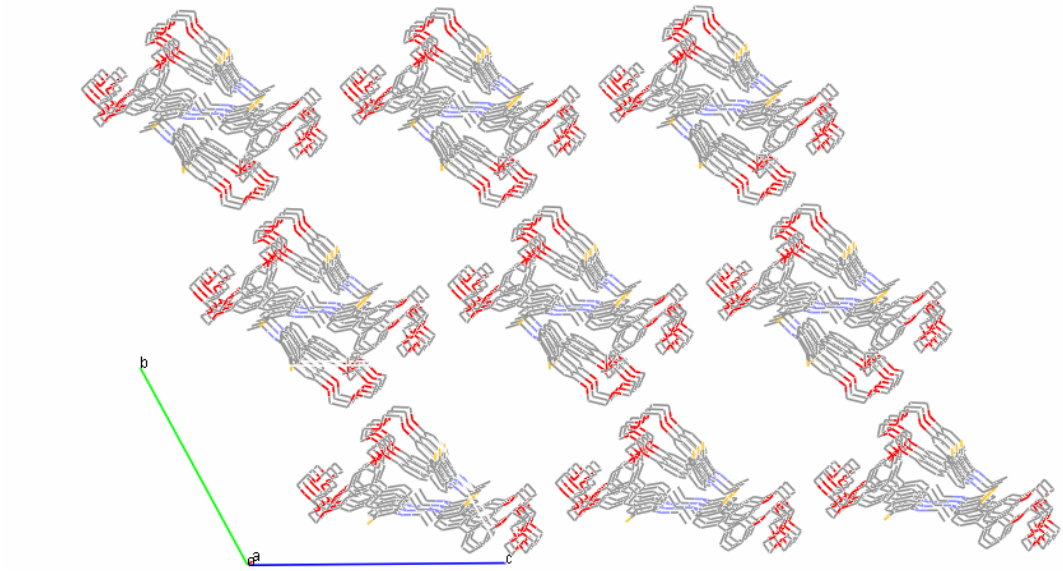


Figure 8. Mercury drawing showing the packing of 44 in monocrystal ("wireframe" style)

The packing of these four-macrocycles units generates "empty" rectangle channels (Figure 20). Two opposite faces of these columns have phenothiazines as "wall tiles", whilst the other two opposite faces are delimited by (ethyleneoxa) chains. The distance between two sulphur atoms belonging to opposite faces is 11.98Å, and the shortest distance between two opposite ethylene units is 16.22Å.

CONCLUSIONS

The structural analysis of new spiro and dispiro-4[H]-1,3-dioxine derivatives carried out using NMR spectra and X-ray diffractometry revealed flexible and semiflexible structures and

the *cis*, *trans* (compounds **3**-**8**) and the *like*, *unlike* (compound **7**) isomerism of these derivatives. The cyclohexane ring prefers the chair conformation, while the 4[H]-1,3-dioxine rings have chiral half-chair conformations. The investigation of the lattice of **7** showed important stacking interactions.

The synthesis by an original procedure of a series of new (poly)spiranes containing 1,2-dithiolane rings as cyclic disulfides leads to compounds with flexible or semi-flexible conformational behaviour, starting from readily available raw materials. The adsorption of some of these derivatives on a gold surface and the structural behaviour of the resultant 2D-SAMs were investigated using computational chemistry modelling as well as IR spectroscopy. Despite the fact that they all appear to adopt a tilted orientation and do not form a well ordered monolayer, the bidentate cyclic disulfide **32** revealed the possibility to react with both 1,2-dithiolane units, giving rise to a rigid bridge-like conformation. These cyclic disulfides were effective also in the surface functionalization of gold nanoparticles. These assemblies were investigated by means of UV-Vis spectroscopy, transmission electron microscopy, and cyclic voltammetry. Again, **32** has shown interesting properties in functionalization of GNPs (provokes high aggregation degrees) and in functionalization of gold electrodes with GNPs (the functionalized electrode with **32** and GNP increased two times the current in cyclic voltammetry, compared with the bare gold electrode).

During the work in the phenothiazine field, the obtaining of conjugated phenothiazine-containing macrocycles was analyzed and pursued.

First, some new valuable iodo-phenothiazine intermediates were obtained and tested in palladium catalyzed cross-coupling reactions. Despite the difficulties in coupling two rich-electron aromatic systems, the results obtained using the palladium catalyzed cross-couplings, especially the Negishi coupling involving ferrocene-zincchloride derivatives as intermediates, opened us the way to achieve the synthesis of phenothiazine-ferrocene containing macrocycles. Several ferrocene-phenothiazine dyads, triads were synthesized and duly characterized, and some non-cyclic oligomers by-products were identified. The attempts to synthesize the full-conjugated bis(ferrocene-phenothiazine) macrocycle have lead to complex mixtures. The ESI-MS experiments have revealed some small amounts of the desired macrocycle (m/e=930); unfortunately, this compound could not been isolated in order to perform a full characterization.

The target ferrocene-phenothiazine macrocycle possessing a vinylene bridge was obtained in good yield using a McMurry reductive coupling of the bis(formyl)ferrocene-phenothiazine triad. The vinylene bridge was selective reduced to an ethylene bridge. In order to determine the redox properties, the dyads, triads and the macrocycles were subjected to cyclic voltammetry experiments. An interesting feature of the voltammograms was the non-equivalence of the phenothiazine moieties in the triads and macrocycles, proving an electronic communication between these two units. This communication could be established through the oxidized iron of ferrocene rest or through space, by π-stacking. However, the π-stacking proved to be important in the solid phase and in macrocycles.

Another class of compounds taken into our attention was the phenothiazine-containing shape-persistent macrocycles. The synthetic strategy was built on the Sonogashira cross-coupling reaction between acetylene-derivatives and halo-phenothiazines. The precursors were synthesized and duly characterized. The macrocyclization main product presents in the MALDI-TOF measurement the assigned mass for the target macrocycle. Unfortunately, the purity control using a valuable (i.e. GPC method) and the improvement of the macrocyclization were not performed.

Another target class of phenothiazine-containing macrocycle was represented by the phenothiazine-coronands. The desired macrocycles were synthesized in several steps, with the generation of a dihydroxy-intermediate as the key step. In macrocyclization were used ditosylated polyethyleneglicole of different lengths as electrophilic partners. The characterization of these macrocycles was made on the basis of MS, NMR, X-ray diffraction and cyclic voltammetry.

List of Publications

Published:

1. Sailer, M.; **Gropeanu, R.A.**;. Müller, T.J.J. "PRACTICAL SYNTHESIS OF IODO PHENOTHIAZINES. A FACILE ACCESS TO ELECTROPHORE BUILDING BLOCKS" *Journal Of Organic Chemistry* **2003**, *68*, 7509-12.
2. **Gropeanu, R.A.**; Woiczechowski-Pop, A.; Tintas, M.; Turdean, R.; Grosu, I. "SYNTHESIS AND STEREOCHEMISTRY OF A NEW SERIES OF 2,2'-DISUBSTITUTED-5,5-BIS(BROMOMETHYL)-1,3-DIOXANES" *Studia Univ. Babes-Bolyai, Ser. Chemia.* **2005**, *L*, 247.

Manuscripts:

1. Gropeanu, R.A.; Grosu, I. "SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW SPIRO BENZO-1,3-DIOXANE DERIVATIVES" *Central European Journal of Chemistry* **2005**, submitted.
2. Gropeanu, R.A.; Tintas, M.; Pilon, C. ; Morin, M.; Breau, L.; Turdean, R.; Grosu, I. "SYNTHESIS, STEREOCHEMISTRY AND ADSORPTION STUDIES OF NEW (POLY)SPIRANES CONTAINING 1,2-DITIOLANE UNITS "*Monatshefte für Chemie* **2005**, submitted.

Posters:

1. Roiban, D.G., **Gropeanu, R.A.**, Gâz, S.A., Grosu, I. "SPECTROSCOPIC METHODS USED FOR STRUCTURE INVESTIGATION OF SOME NEW DIOXANES DERIVATIVES", 5th European Conference on Mineralogy and Spectroscopy (ECMS) in Vienna, Austria, September 4th - 8th 2004
2. Gâz, S. A., **Gropeanu, R.A.**, Roiban, D., Grosu, I. "SYNTHESIS, STEREOCHEMISTRY AND REACTIVITY OF SOME 2-METHYL-2-(3'-NITROPHENYL)-4-HYDROXYMETHYL-1,3-DIOXOLANE" 5th European Conference on Mineralogy and Spectroscopy (ECMS) in Vienna, Austria, September 4th - 8th 2004