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DESIGN, SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NEW SPIRANS, MACROCYCLES AND MOLECULAR DEVICES. SUPRAMOLECULAR CHEMISTRY TO THE NEW FRONTIERS

Ph.D. Thesis Abstract

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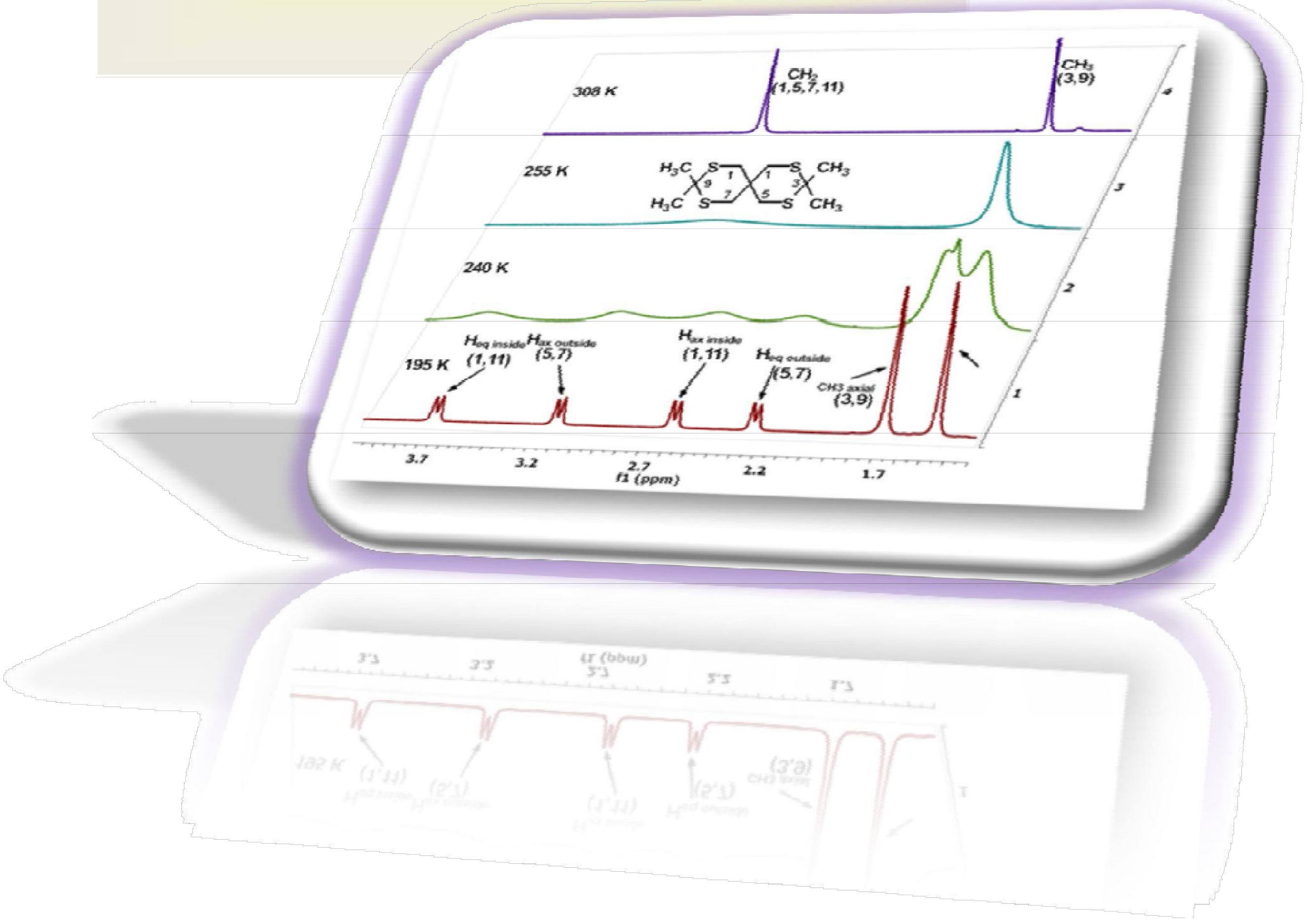
Part 2

DESIGN, SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NEW SPIRO AND POLYSPIRO-1,3-DITHIANE DERIVATIVES



2. Design, Synthesis and Structural Analysis of Some new Spiro and Polyspiro-1,3-dithiane derivatives

2.1 Introduction

Spiranes are compounds that contain rings (at least two) which share one common atom. The name "spirane" comes from the Latin *spira* meaning twist or whorl and implies that the rings of the spiranes are not coplanar.[1] A large number of papers have reported on the synthesis, structure and biological activity of spirane compounds with six-membered rings. Many of spirane skeletons with sixmembered rings are present in natural compounds with specific activity: like antibiotics[2], pheromones[3], marine macrolides[4] and antitumor agents[5].

Six-membered ring spiranes and polyspiranes are intriguing targets in organic chemistry. Their stereochemistry is correlated with the helical chirality of the spiro[5.5]undecane skeleton.[6,7,8,9] The conformational analysis of six-membered ring spiranes was mainly carried out using NMR methods and revealed flexible or anancomeric structures in correlation with the substitution of the spirane skeleton.[6-9,10,11] The majority of the investigations of six-membered ring spiranes were focused on derivatives bearing 1,3-dioxane rings. The advantage of the investigations on spiro 1,3-dioxanes consisted of the fact that the stereochemistry of 1,3-dioxane

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[1] Eliel, E. L.; Wilen, S.H. *Stereochemistry of Organic Compounds*, John Wiley & Sons: New York, **1994**, pp. 1138

[2] Boivin, T. L. B. *Tetrahedron*, **1987**, *43*, 3309-3362

[3] O'Shea, M. G.; Kitching, W. *Tetrahedron*, **1989**, *45*, 1177-1186

[4] Smith, A. B.; Frohn, M. *Org. Lett.*, **2001**, *3*, 3979-3982

[5] Crimmins, M.; Katz, J.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc.*, **2002**, *124*, 5661-5663

[6] Grosu, I.; Mager, S.; Plé, G.; Horn, M. *J. Chem. Soc., Chem. Commun.* **1995**, 167-168

[7] Grosu, I.; Mager, S.; Plé, G. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1351- 1357

[8] Terec, A.; Grosu, I.; Condamine, E.; Breau, L.; Plé, G.; Ramondenc, Y.; Rochon, F. D.; Peulon-Agasse, V.; Opriş, D. *Tetrahedron* **2004**, *60*, 3173-3189

[9] Cismaş, C.; Terec, A.; Mager, S.; Grosu, I. *Curr. Org. Chem.* **2005**, *9*, 1287-1314

[10] Grosu, I.; Plé, G.; Mager, S.; Martinez, R.; Mesaroş, C.; Camacho, B. del C. *Tetrahedron* **1997**, *53*, 6215-6232

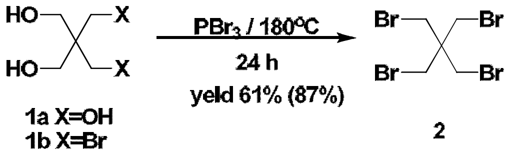
[11] Terec, A.; Grosu, I.; Muntean, L.; Toupet, L.; Plé, G.; Socaci, C.; Mager, S. *Tetrahedron* **2001**, *57*, 8751-8758

system itself is well known[12,13,14,15] and spiro-1,3-dioxanes are appropriated for NMR investigations.[16]

The 1,3-dithiane derivatives are less studied[17] than the corresponding 1,3-dioxanes. Eliel[18] and Pihlaja[19] determined the A-values for some alkyl, aryl and polar substituents located at different positions of the 1,3-dithiane ring. These investigations revealed for alkyl and aryl groups similar A-values with those found in the cyclohexane series, while for several polar groups located at position 2 the preference for the axial orientation was observed.

2.2 Precursors synthesis and structural analysis

Starting from pentaerythritol or from 2,2-bis(bromomethyl)-1,3-propanediol commercial available, pentaerythritol tetrabromide was obtained by a nucleophilic substitution, without any solvents. The tetrabromide derivative was purified by a Soxhlet extraction using ethanol as a solvent (**Scheme 1**).



Scheme 1

Therefore a indirect method to obtain the tetrathiapentaerythritol was followed. Using a method described by Mitkin and Kutateladze[20] when the bromine was substituted by potassium thioacetate gave the protected tetraacetylated tetrathiapentaerythritol in moderate yield due to difficulties in the workup procedure. Using a freshly obtained potassium salt follow to an increase of the yield. Tetrathiapentaerythritol was obtained by reduction in presence of $LiAlH_4$

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[12] Kleinpeter, E. *Adv. Het. Chem.* **1998**, *69*, 217-269

[13] Kleinpeter, E. *Adv. Het. Chem.* **2004**, *86*, 41-127

[14] Eliel, E.; Wilen, S. H. *Stereochemistry of organic compounds*, John Wiley & Sons: New York, **1994**, pp 686-754

[15] Anteunis, M. J. O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 293-371

[16] Grosu, I.; Mager, S.; Plé, G.; Darabanţu, M. *Résonance Magnétique Nucléaire Apliquée à l'Analyse Structurale de Composés Organiques*, Publications de l'Université de Rouen, **1999**, pp 145-190

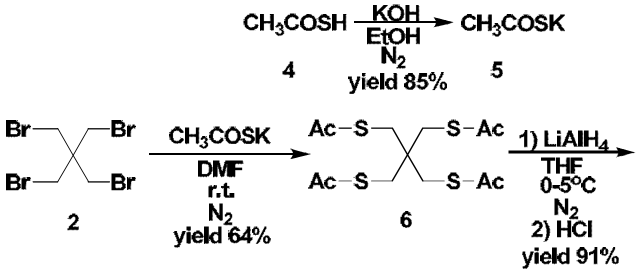
[17] Kleinpeter, E. *Conformational Analysis of Six-Membered Sulfur-Containing Heterocycles* in *Conformational Behavior of Six-Membered Rings – Analysis, Dynamics, and Stereoelectronic Effects*, editor Juaristi, E. VCH Publisher: New York, **1995**, pp 201-243

[18] Eliel, E. L.; Hutchins, R. O. *J. Am. Chem. Soc.* **1969**, *91*, 2703-2715

[19] Pihlaja, K. *J. Chem. Soc. Perkin Trans. 2* **1974**, 890-895

[20] Mitkin, O. D.; Wan, Y.; Kurchan, A. N.; Kutateladze, A. G. *Synthesis* **2001**, 1133-1142.

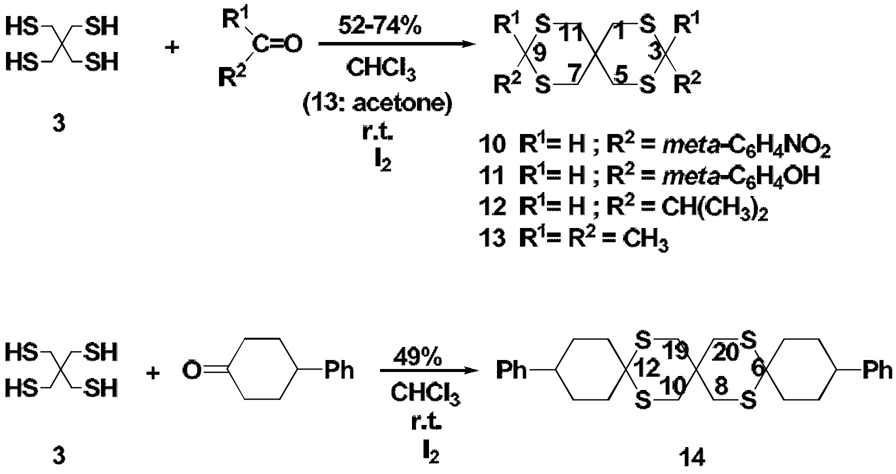
followed by a acidic work-up. (**scheme 3**) Any attempts to obtain the desire compound following a basic condition work-up failed.



Scheme 2

We considered it of interest to find an appropriate procedure for the direct synthesis of spiro compounds with 2,4,8,10-tetrathiaspiro[5.5]undecane skeleton and to investigate the stereochemistry and the properties of some 3,9-substituted derivatives of this tetrathiaspirane.

New 3,9-substituted-2,4,8,10-tetrathiaspiro[5.5]undecane derivatives **10-13** and 7,11,18,21-tetrathiatrispiro[5.2.2.5. 2.2]heneicosane **14** were obtained by the direct reaction of tetrathiapentaerythritol **3** with several carbonyl compounds (**Scheme 5**).[21]



Scheme 3

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[21] Gâz, Ş. A.; Condamine, E.; Bogdan, N.; Terec, A.; Bogdan, E.; Ramondenc, Y.; Grosu, I. *Tetrahedron* **2008**, *64*, 30-31, 7295-7300

A recently published procedure[22] for the synthesis of the 1,3-dithiane ring based on I_2 catalysis was successfully adapted to prepare spiranes with 2,4,8,10-tetrathiaspiro[5.5]undecane skeleton (yields 49-74 %). The mechanism of this reaction is not yet well known. All the other essays of usual thioacetalization[23] reactions of the starting carbonyl compounds failed.

2.3 Structural aspects in solid state

The solid state molecular structure for **10** was determined by single crystal X-ray diffractometry. The ORTEP diagram (**Figure 1**) reveals the chair conformation for the 1,3-dithiane units. The aromatic rings are equatorial and exhibit a rotameric behaviour close to that of the bisectional conformer. The angle between the aromatic ring and the best plane of the 1,3-dithiane ring is of 26° 28', while the angle between the aromatic rings is of 52° 42'.

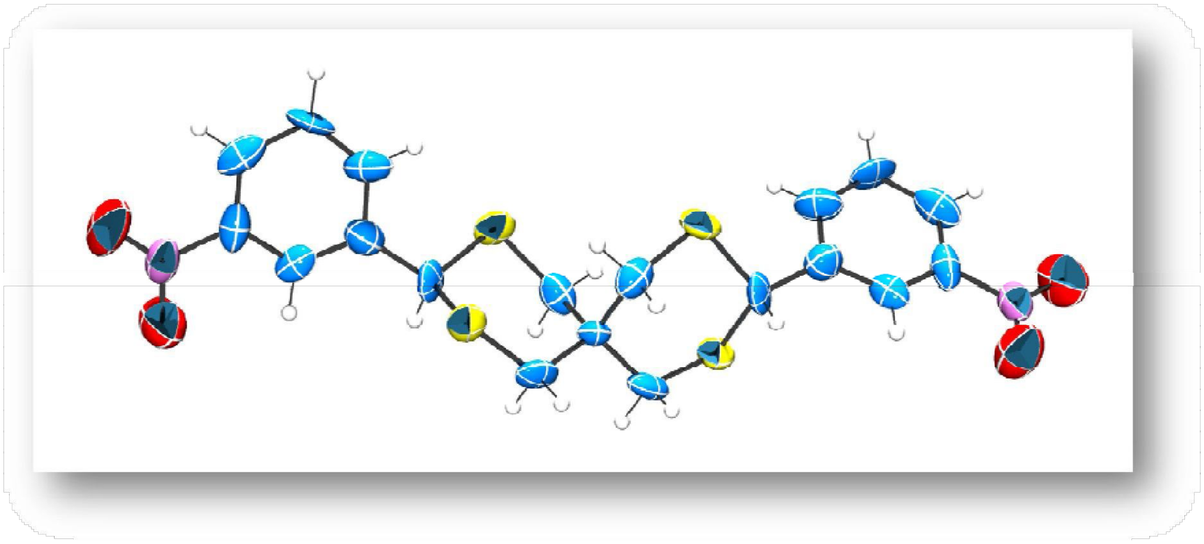

Figure 1 ORTEP diagram for compound 10.

The lattice exhibits a *zigzag* arrangement of the molecules (**Figure 2**). Each molecule exhibits four CH–π interactions. Two of them involve the axial proton of the *inside* methylene groups (positions 1,11) of the 1,3-dithiane units and the aromatic groups of two neighboring molecules. The other two interactions are located on the aromatic rings and involve the axial protons of the methylene *inside* groups of the 1,3-dithiane units of the same neighboring spirane

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[22] Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527-7529

[23] Bonifačič, M.; Asmus, K.-D. *J. Org. Chem.* **1986**, **51**, 1216-1222

molecules (the distances from the axial H atoms to the centroid of the aromatic rings are d = 2.92 Å).

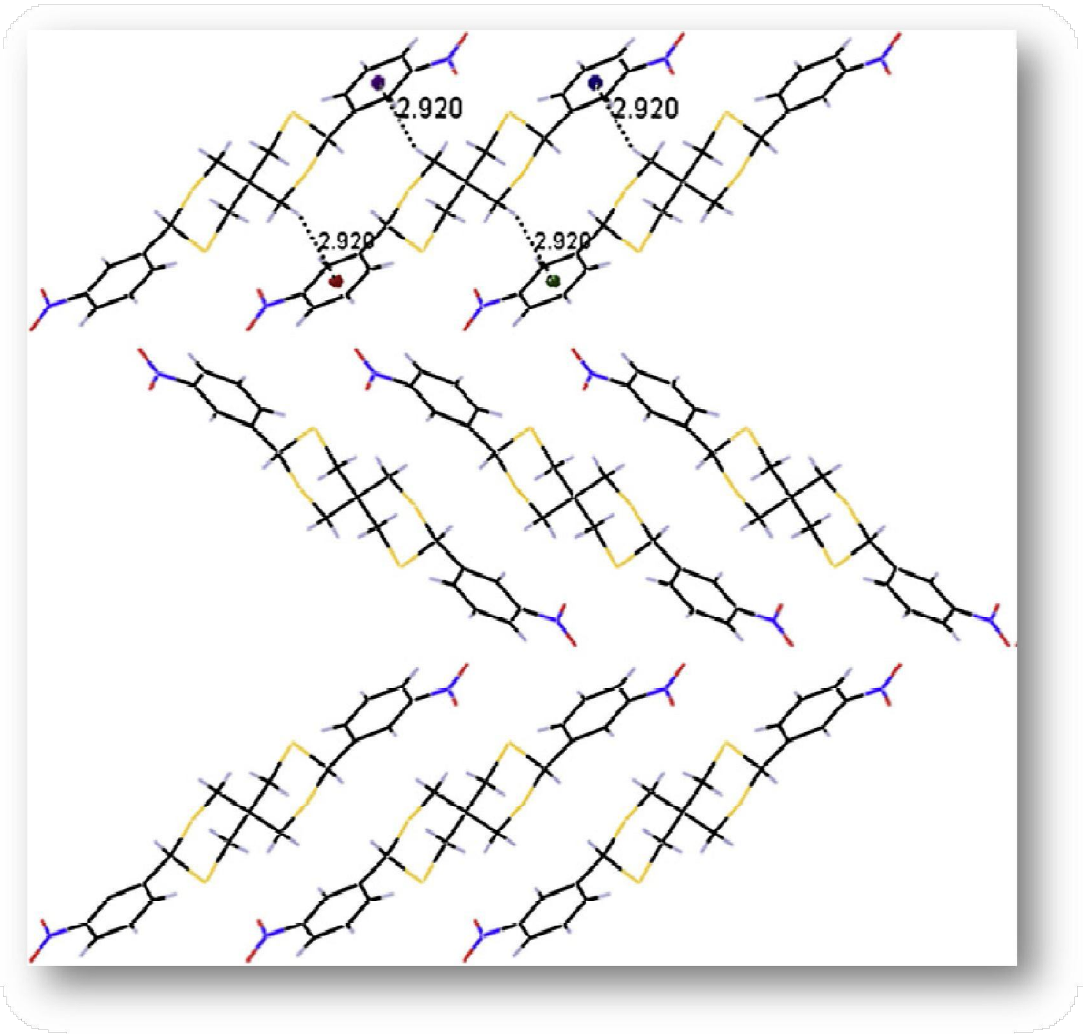

Figure 2 View of the lattice for 10 along the c crystallographic axis

The solid state molecular structure[24] for **12** was also determined by single crystal X-ray diffractometry. The ORTEP diagram (**Figure 3**) reveals a centrosymmetric molecule with a monoclinic (C2/c) symmetry and the chair conformation for the 1,3-dithiane unit with the isopropyl substituents oriented to the equatorial position.

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[24] Gâz, Ş. A.; Dobre, I.; Varga, R.; Ramondenc, Y.; Grosu, I. *Acta Crystallogr., Sect. E.* in preparation

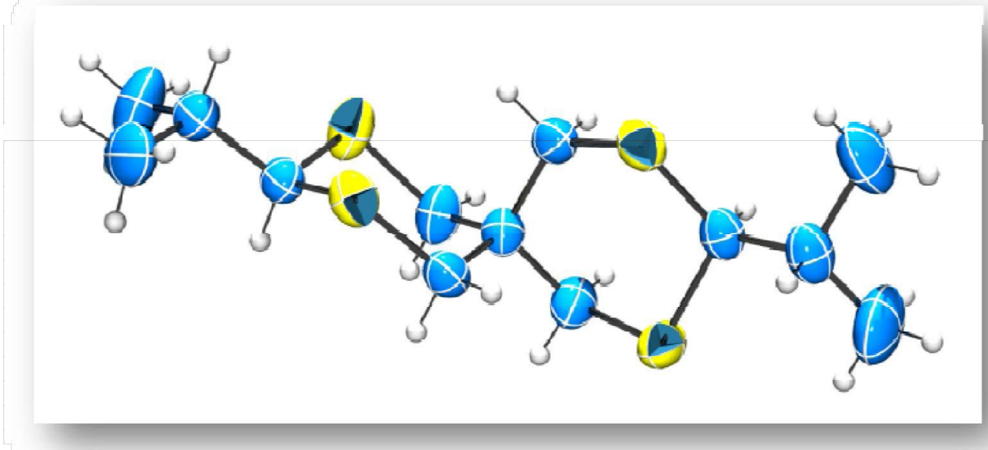
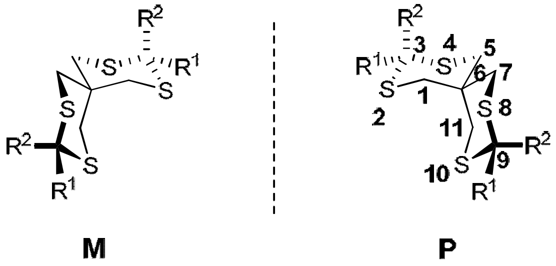


Figure 3 ORTEP diagram for compound 12

2.4 Structural aspects in solution

The stereochemistry of compounds **10-14** in solution was deduced from NMR investigations. Despite the lower difference between the energies of chair and TB (twist-boat) conformers ($\Delta G^{\circ}_{\text{TB-Chair}}$ = 2.9 kcal/mol)[14] in 1,3-dithiane series than in the series of other six membered rings (*e.g.* cyclohexane, $\Delta G^{\circ}_{\text{TB-Chair}}$ = 4.9 kcal/mol; 1,3-dioxane, $\Delta G^{\circ}_{\text{TB-Chair}}$ = 5.7 kcal/mol)[14] the chair conformers are the main ones and in the further discussions only their contributions to the stereochemistry of the compounds are considered. The characteristic stereoisomers for **10-14** are similar with those found for the corresponding spiranes with 1,3-dioxane units.

Compound **10-12** exhibit anancomeric structures and the flipping of the 1,3-dithiane rings is shifted towards the conformers in which the larger substituents occupy the equatorial positions [R^2 = *meta*-$C_6H_4NO_2$ (**10**); *meta*-C_6H_4OH (**11**); -$CH(CH_3)_2$ (**12**). Compounds **10-12** are chiral (due to the specific axial and helical chirality of spiro compounds with six-membered rings) and they are obtained as racemates (**Scheme 6**). The CH_2 groups of the spirane units are different in NMR. Positions 1 and 11 are oriented towards the other 1,3-dithiane ring and they are named *methylene inside*, while the other two CH_2 groups (positions 5 and 7) are oriented in opposite direction and they are named *methylene outside* groups.



1,11 inside, 5,7 outside (positions)

Scheme 4

On the other hand due to the anancomeric behavior of the compounds the NMR spectra exhibit different signals for the axial and equatorial protons of the spirane units. The equatorial protons of the *methylene inside* groups are considerably more deshielded than those of the *methylene outside* positions (**Figure 5, Table 2**). The assignment of the signals was carried out on the basis of NOESY or/and ROESY experiments.

Table 1 NMR data (δ ppm) for compounds 6-8

Compound	Solvent	Temperature (K)	δ (ppm)			
			CH₂ *inside*		CH₂ *outside*	
			equatorial	axial	equatorial	axial
10	$CDCl_3$	295	4.12	2.91	2.72	3.15
11	$CDCl_3$	295	4.17	2.93	2.66	3.34
12	$CDCl_3$	295	3.83	2.57	2.52	2.83
13	CD_2Cl_2	308	2.68			
13	CD_2Cl_2	195	3.67	2.59	2.24	3.11
14	CD_2Cl_2	295	3.04		2.91	
14	CD_2Cl_2	190	3.84	2.54	2.28	2.78

The ^1H NMR pattern for the spirane units exhibits two AB (AX) systems (**Figure 5**) with more deshielded equatorial protons for the *methylene inside* groups. (they are the closest to the sulfur atoms of the neighboring heterocycle). The signals of the equatorial protons exhibit a further splitting due to the long range coupling ($^4J \approx 2$ Hz) possible as result of the W (M) arrangement of the bonds H_{eq}– $C^{1(11)}$–C^6–$C^{5(7)}$–H_{eq}.

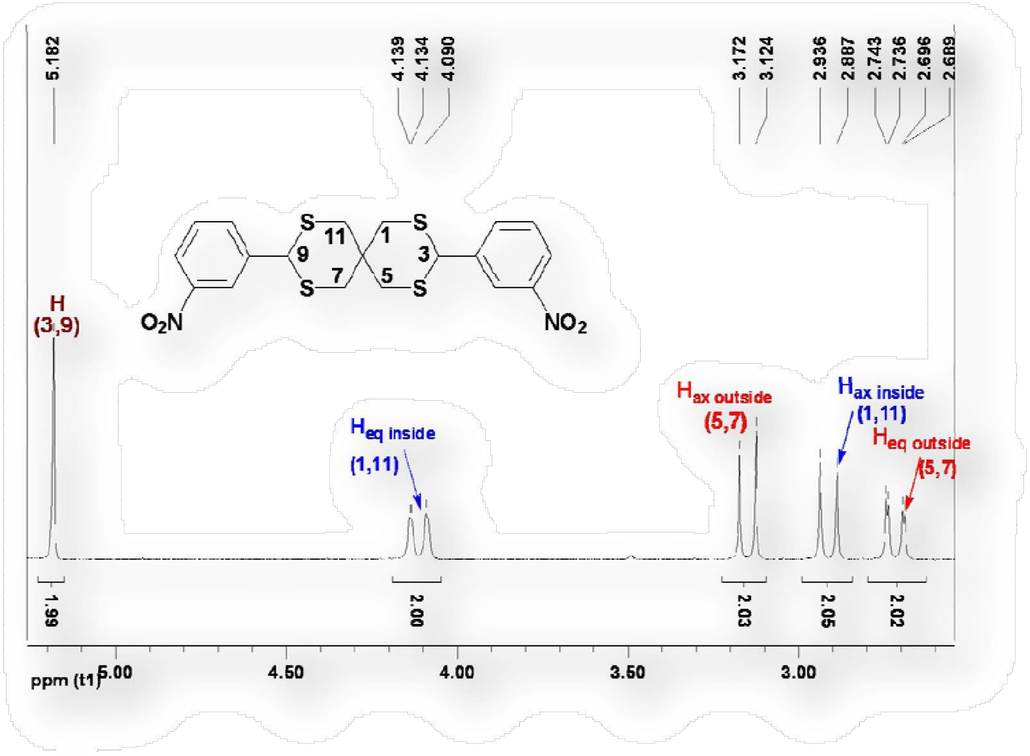
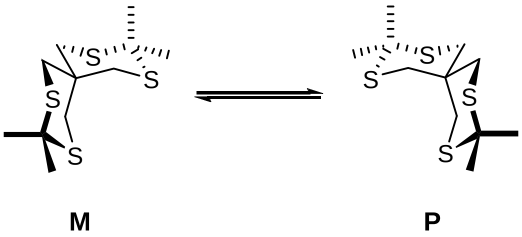


Figure 4 ^{1}HNMR spectrum ($CDCl_3$, rt, fragment) of compound 10

Compound **13** is flexible and both 1,3-dithiane rings are flipping. The flipping of one of the heterocycles transforms one enantiomer of the compound into the other (M⇆ P; **Scheme 7**).



Scheme 5

The flexible behavior of the compound is proved by the NMR spectra. At *rt*, the ^{1}H NMR spectrum of **13** (**Figure 7**) exhibits only two singlets; a more deshielded one (δ = 2.96 ppm) for the protons of the heterocycles and another one (δ = 1.67 ppm) for the protons of the methyl groups. The variable temperature NMR experiments (**Figure 7**) show the obtaining of the (de)coalescences of the signals at lower temperatures (T= 255 K) and the spectrum run at 195 K reveals the frozen structure.

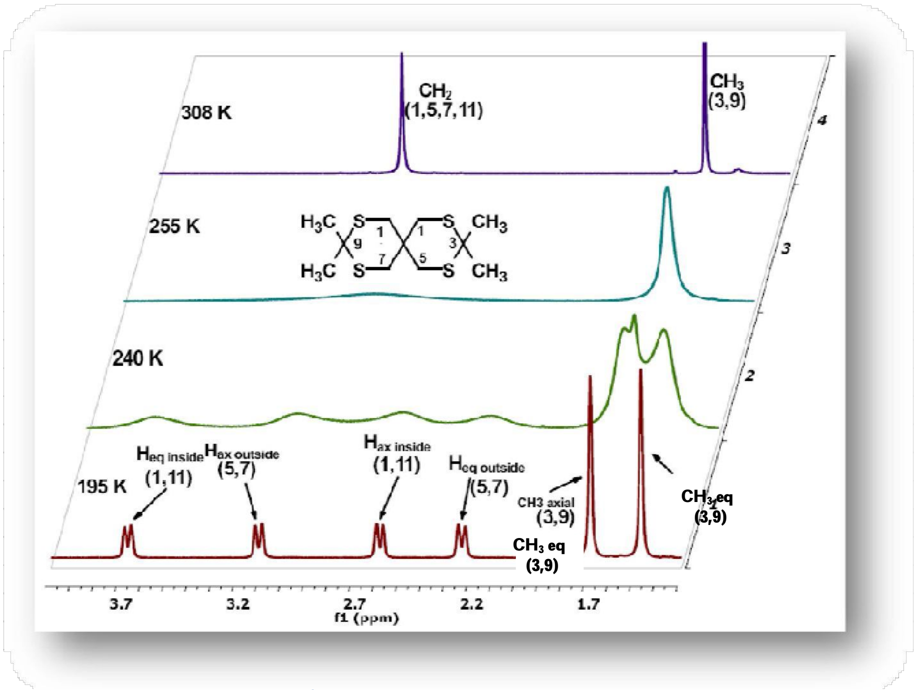


Figure 5 Variable temperature ^{1}H NMR experiments (CD_2Cl_2, fragments) for compound 13

The pattern of the NMR spectrum at 195 K for the protons of the spirane unit is similar with the spectra of the anancomeric compounds (**Table 2, Figures 5 and 7**) while for the methyl groups at positions 3 and 9 the spectrum shows two singlets corresponding to the axial (δ_{ax} = 1.69 ppm) and equatorial (δ_{eq} = 1.48 ppm) orientations, respectively.

Rotation barriers were estimated using coalescence temperatures and the chemical shifts measured in frozen structures for equatorial and axial protons of 1,3-dithianes rings (**Table 3**). ^{1}H-NMR variable temperature experiments were carried out recording spectra every 15 degrees. Standard deviations were established using $\Delta G^{\#}$ values calculated at observed coalescence temperature (T_c), T_{c-10} and T_{c+10}.

Table 2 Flipping barriers calculated from the coalescence temperatures and the chemical shifts of the signals for the protons 3,9 CH_3(ax), 3,9 CH_3(eq),1(11)-H_{ax}, 5(7)-H_{ax}, 1(11)-H_{eq} and 5(7)-H_{eq} measured in the low temperature ^{1}H NMR spectra (CD_2Cl_2, 500 MHz) for compound 13

	T (K)			$\Delta\delta$ (Hz)			$\Delta G^{\#}$ (kcal/mol)			Mean $\Delta G^{\#}$ (kcal/mol) values
Compd	3(9) $CH_{3(ax)}$,$CH_{3(eq)}$	1(11) H_{eq}, H_{ax}	5(7) H_{ax}, H_{eq}	3(9) $CH_{3(ax)}$,$CH_{3(eq)}$	1(11) H_{eq}, H_{ax}	5(7) H_{ax},H_{eq}	3(9) $CH_{3(ax)}$,$CH_{3(eq)}$	1(1 H_{eq}, H_{ax}	5(7) H_{ax}, H_{eq}	
9	**250**	**255**	**255**	**108.5**	**538.2**	**434**	**11.83**	**11.27**	**11.38**	**11.49±0.30**

2.5 Supramolecular assembly

The use of inorganic materials as support for mediator compounds represents a useful and promising approach to obtain modified electrodes. Among these materials, zeolites and clays offer the most complete range of interesting properties required at an electrochemical interface (shape, size and charge selectivity, physical and chemical stability, high ion exchange capacity in a micro-structured environment, hydrophilic character etc.). Particularly, electroanalysis is of great interest for zeolite and clay modified electrodes applications.[25]

Spirane **11** (named TTU) have been chosen to be laid out on bentonite. Physical-chemical characterization of carbon paste electrodes, incorporating a synthetic zeolite (Z) (13X type, from Aldrich) and a mineral clay (B) (bentonite, from Valea Chioarului, Maramures county, Romania) modified with TTU (TTU-Z-CPEs and TTU-B-CPEs), using Scanning Electron Microscopy (SEM) and Energy Dispersive X Ray Spectroscopy (EDS) was performed (figure 9).

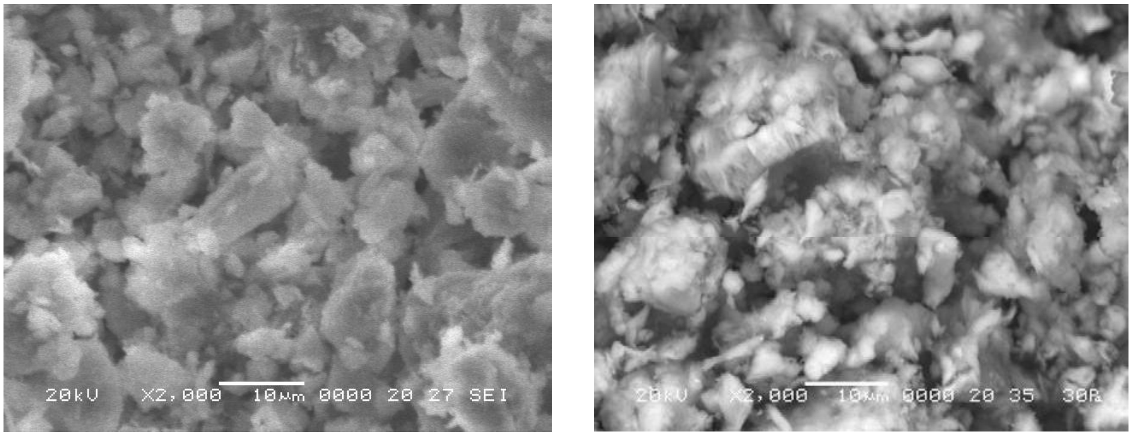


Figure 6 SEM images corresponding to B (A) and TTU-B (B)

Other electrochemical analysis were performed such as a study of the influence of some experimental parameters (pH, and potential scan rate) on the voltammetric response of TTU-Z-CPES and TTU-B-CPEs, determination of the electrochemical parameters for the heterogeneous electron transfer process corresponding to modified electrodes, evaluation of electrocatalytic efficiency for NADH mediated oxidation at TTU-Z-CPES and TTU-B-CPEs, using cyclic voltammetry (CV) (**figure 10**) and rotating disk electrode (RDE) experiments.

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[25] Serban, S.; Murr, N. E. *Biosens. Bioelectron.* **2004**, *20*, 161-166

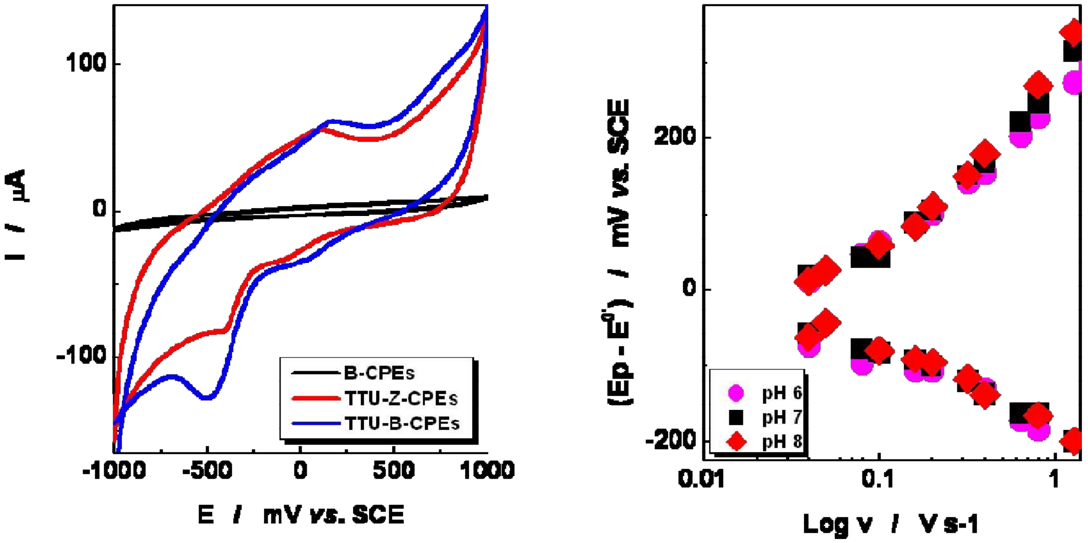

Figure 7 a) Cyclic voltammograms for B-CPES, TTU-Z-CPEs and TTU-B-CPEs; b) Experimental dependence of (Ep - E$^{0'}$) on the logarithm of the scan rate for TTU-Z-CPEs.

Modified electrodes with electrocatalytic activity towards NADH oxidation were obtained by adsorption of a new spiro-1,3-dithiane derivative (TTU) on a synthetic zeolite (13X, from Aldrich) and on a mineral clay (bentonite), followed by their incorporation in carbon paste.

The characteristics of the voltammetric response of TTU-Z-CPEs and TTU-B-CPES (ΔE_p of 31 and 27 mV, respectively and I_{pa}/I_{pc} of ~ 1) pointed out to a quasi-reversible, surface confined redox process.

TTU-Z-CPEs and TTU-B-CPES showed moderate electrocatalytic efficiency towards NADH oxidation, at an overpotential with more than 200 mV lower than that observed on unmodified electrodes and good electrocatalytic rate constants ($k_{\cdot obs, [NADH]=0}$ = 71.1 M^{-1} s^{-1}, pH 7 for TTU-B-CPEs).

TTU-B-CPEs presents a more favorable electrocatalytic behavior towards NADH oxidation than TTU-Z-CPEs, proved by the higher electrocatalytic efficiency (240 % > 82 %; both measured at 200 mV *vs.* SCE) and higher electrocatalytic rate constant.

The mechanism of NADH electro-oxidation obeys the Michaelis-Menten formalism.

2.6 Conclusions

The efficient synthesis of some new spiro and trispiro-1,3-dithianes is reported. The first single crystal X-ray molecular structure for compounds with 2,4,8,10-tetrathia-spiro[5.5]undecane shows the chair conformers for the 1,3-dithiane rings and the *zigzag* disposition of the molecules in the lattice. The NMR studies reveal flexible, semiflexible and anancomeric structures in correlation with the substituents located at the extremities of the spirane skeleton. The barriers ($\Delta G^{\#}$ = 10.95-11.83 kcal/mol) for the flipping of the heterocycles in the flexible and semiflexible compounds were calculated by variable temperature NMR experiments.

Part 3

NEW CYCLOPHANES WITH POSSIBLE APPLICATION IN SELF ASSEMBLED MONOLAYERS