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

Ph.D. Thesis Abstract

GÂZ ŞERBAN ANDREI

President of the Jury: Prof. Dr. Florin Dan Irimie
Scientific Advisor: Prof. Dr. Ion Grosu
Reviewers: Prof. Dr. Yvan Ramondenc
               Prof. Dr. Ionel Mangalagiu
               Prof. Dr. Cristian Silvestru
               C. M. of Romanian Academy

Babes Bolyai University
Babes Bolyai University
Université de Rouen
A.I. Cuza University
Babes Bolyai University

Cluj-Napoca
2010
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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 six-membered 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 polyspirones 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 ananomeric structures in correlation with the substitution of the spirane skeleton.\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^10\)\(^,\)\(^11\) 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 derivatives

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\(^{2}\) Boivin, T. L. B. *Tetrahedron*, 1987, 43, 3309-3362


\(^{8}\) Terec, A.; Grosu, I.; Condamine, E.; Breau, L.; Plé, G.; Ramondene, Y.; Rochon, F. D.; Peulon-Agasse, V.; Opriş, D. *Tetrahedron* 2004, 60, 3173-3189


\(^{10}\) Grosu, I.; Plé, G.; Mager, S.; Martinez, R.; Mesaroș, C.; Camacho, B. del C. *Tetrahedron* 1997, 53, 6215-6232

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system itself is well known\textsuperscript{12,13,14,15} and spiro-1,3-dioxanes are appropriated for NMR investigations.\textsuperscript{16}

The 1,3-dithiane derivatives are less studied\textsuperscript{17} than the corresponding 1,3-dioxanes. Eliel\textsuperscript{18} and Pihlaja\textsuperscript{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).

Therefore a indirect method to obtain the tetrathiapentaerythritol was followed. Using a method described by Mitkin and Kutateladze\textsuperscript{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\textsubscript{4}

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
1a & X=OH \\
1b & X=Br \\
\hline
\end{tabular}
\end{table}

\begin{scheme}
\text{Scheme 1}
\end{scheme}

\begin{eqnarray}
\text{HO} & \text{X} & \text{PBr}_3/\text{180°C} & \text{Br} & \text{Br} \\
\text{HO} & \text{X} & \text{24 h} & \text{yeld 61\% (87\%)} & \text{Br} & \text{Br} \\
\hline
\end{eqnarray}

\begin{thebibliography}{99}
\bibitem{13} Kleinpeter, E. \textit{Adv. Het. Chem.} \textbf{2004}, \textit{86}, 41-127
\bibitem{15} Anteunis, M. J. O.; Tavernier, D.; Borremans, F. \textit{Heterocycles} \textbf{1976}, \textit{4}, 293-371
\bibitem{19} Pihlaja, K. \textit{J. Chem. Soc. Perkin Trans. 2} \textbf{1974}, \textit{890-895}
\end{thebibliography}
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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-tetrathiatriaspiro[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

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\textsuperscript{22} for the synthesis of the 1,3-dithiane ring based on I\textsubscript{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\textsuperscript{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.](image)

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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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](image)

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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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 (ΔG°_TB-Chair = 2.9 kcal/mol) in 1,3-dithiane series than in the series of other six-membered rings (e.g. cyclohexane, ΔG°_TB-Chair = 4.9 kcal/mol; 1,3-dioxane, ΔG°_TB-Chair = 5.7 kcal/mol) 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 [R² = meta-C₆H₄NO₂ (10); meta-C₆H₄OH (11); -CH(CH₃)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 CH₂ 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 CH₂ groups (positions 5 and 7) are oriented in opposite direction and they are named methylene outside groups.
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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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Temperature (K)</th>
<th>CH₂ inside</th>
<th>δ (ppm)</th>
<th>CH₂ outside</th>
<th>δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂ inside</td>
<td>CH₂ outside</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>equatorial</td>
<td>axial</td>
<td>equatorial</td>
<td>axial</td>
</tr>
<tr>
<td>10</td>
<td>CDCl₃</td>
<td>295</td>
<td>4.12</td>
<td>2.91</td>
<td>2.72</td>
<td>3.15</td>
</tr>
<tr>
<td>11</td>
<td>CDCl₃</td>
<td>295</td>
<td>4.17</td>
<td>2.93</td>
<td>2.66</td>
<td>3.34</td>
</tr>
<tr>
<td>12</td>
<td>CDCl₃</td>
<td>295</td>
<td>3.83</td>
<td>2.57</td>
<td>2.52</td>
<td>2.83</td>
</tr>
<tr>
<td>13</td>
<td>CD₂Cl₂</td>
<td>308</td>
<td></td>
<td>2.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>CD₂Cl₂</td>
<td>195</td>
<td>3.67</td>
<td>2.59</td>
<td>2.24</td>
<td>3.11</td>
</tr>
<tr>
<td>14</td>
<td>CD₂Cl₂</td>
<td>295</td>
<td>3.04</td>
<td>2.28</td>
<td>2.91</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>CD₂Cl₂</td>
<td>190</td>
<td>3.84</td>
<td>2.54</td>
<td>2.78</td>
<td></td>
</tr>
</tbody>
</table>

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 (³J≈2 Hz) possible as result of the W (M) arrangement of the bonds H<sub>eq</sub>–C<sup>1(11)</sup>–C<sup>6</sup>–C<sup>5(7)</sup>–H<sub>eq</sub>. 
Design, Synthesis and Structural Analysis of Some new Spiro and Polyspiro-1,3-dithiane derivatives

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).

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 ($\delta = 2.96$ ppm) for the protons of the heterocycles and another one ($\delta = 1.67$ 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.
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 ($\delta_{\text{ax}} = 1.69$ ppm) and equatorial ($\delta_{\text{eq}} = 1.48$ 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$_{\text{ax}}$, 5(7)-H$_{\text{ax}}$, 1(11)-H$_{\text{eq}}$, and 5(7)-H$_{\text{eq}}$ measured in the low temperature $^1$H NMR spectra (CD$_2$Cl$_2$, 500 MHz) for compound 13

<table>
<thead>
<tr>
<th>Compd</th>
<th>$T$ (K)</th>
<th>$\Delta \delta$ (Hz)</th>
<th>$\Delta G^#$ (kcal/mol)</th>
<th>Mean $\Delta G^#$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{(3,9)}$</td>
<td>$^{(1,11)}$</td>
<td>$^{(5,7)}$</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>250</td>
<td>255</td>
<td>255</td>
<td>108.5</td>
</tr>
</tbody>
</table>
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.\textsuperscript{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)](image)

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) (\textbf{figure 10}) and rotating disk electrode (RDE) experiments.

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 ($\Delta E_p$ 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 ($k_{obs} \approx 71.1$ 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.
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Part 3

NEW CYCLOPHANES WITH POSSIBLE APPLICATION IN SELF ASSEMBLED MONOLAYERS
3. **New cyclophanes with possible applications in Self Assembled Monolayers**

3.1 **Introduction**

**Cyclophane chemistry**

Even if Pellegrin\(^{26}\) synthesized the first member of cyclophanes ([2.2]metacyclophane 1) in 1899, the spectacular chemical domination era of cyclophanes chemistry begins after more than half a century, once with the synthesis of compound 2 (scheme 1) by Cram and Steinberg.\(^ {27}\)

![Scheme 1](image)

**Scheme 1**

Ever since the cyclophane chemistry has been developed continuously especially due to the various important applications which they present in divers domains such as host molecules for different cations or small neutral molecules, chiral ligand or industrial applications. The ability to place certain groups (i.e. two aromatic systems) within close proximity of each other often results in interesting geometries\(^ {28}\) and chemical properties\(^ {29,30}\). They are fundamentally interesting compounds\(^ {31}\) which exhibit interesting properties which make them particularly useful for industrially purposes. Being typically rigid structures they found use in material science and surface chemistry.\(^ {32}\) From industrial point of view cyclophane can be used as monomers for obtaining new polymers with interesting properties. The surfaces of theses

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27 Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691-5704
polymers are very stable therefore they were used in medicine. Similar to fullerenes, most cyclophanes have an internal cavity intrinsic to their structure and can act as a host having a potential useful application for both catalysis and medical purposes.

**Self assembled monolayers (SAM)**

Considerable attention has been drawn during the last few decades to modify noble metal surfaces by forming ordered organic films of few nanometers to several hundred nanometers thickness. One of the simplest means of forming these ultrathin films is by the simple immersion of the noble metal surface in a dilute solution (mM) of the organic molecule at ambient conditions and this unimolecular organic films are popularly known as self-assembled monolayers (SAM). A self assembled monolayer is an organized layer of amphiphilic molecules in which one end of the molecule, the “head group” shows a special affinity for a surface. SAMs also consist of a tail with a functional group at the terminal end as seen in figure 1.

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34 Diederich, F.; Schürmann, G.; Chao, I. *J. Org. Chem.* 1988, 53, 2744-2757
3.2 Retrosynthetic pathway of target compounds

The goal was to combine the properties of both cyclophane and self assembled monolayers. Therefore we proposed the synthesis of compound 7 (figure 3) and to analyse the properties for the cyclophane such in complexation behavior and the electrochemical properties of SAMs.

![Chemical structure](image)

**Figure 9 Retrosynthetic pathway for the target compounds 3**

Following the suggested retrosynthetic pathway the synthesis should start from commercially available compounds 3 and 4, obtaining in the first step new podands 5(a,b,c), followed by a macrocyclisation in order to close the cycle, bromination and substitution with thiol groups in order to achieve the desired cyclophane 7(a,b,c).

3.3 Synthesis of podands

Synthesis of podands 5(a,b,c) starts from commercial available quinone 4 and substituted polyethylene glycol 3(a,b,c). Podand 5a was synthesized following a modified method described in literature.\(^\text{37}\) Starting from quinone 4 and 2-chloro-ethanol, using an ethanolic hydroxide solution after seven days we obtained the desired compound (scheme 2) in 62 % yields.

---

The structural analysis of compound 5a was performed. $^1$H–NMR spectrum exhibit a broad signal at 1.9 ppm for the OH protons and another singlet corresponding to the methyl groups at 2.18 ppm. At 4.02 ppm a multiplet for the methylenic protons H$_b$ and H$_d$ was observed. In the aromatic region only one signal is observed for H$_a$ protons as a singlet at 6.67 ppm (figure 4).

All the attempts to obtain compound 5b failed. Instead we notice that the reaction underwent with good yield to the monoderivative 8b (scheme 3 and figure 5).
New cyclophanes with possible applications in Self Assembled Monolayers

Scheme 8

Changing the strategy (in all our previous attempts compound 3b was added dropwise), and following a literature method described by Balzani and coworkers,\textsuperscript{38} using DMF as solvent and increasing the reaction time we obtained podand 5b in good yields (42%).

Podand 5c was obtained in the same manner described above for 5b using another solvent instead. The \textsuperscript{1}H-NMR follows the same pattern for all signals as were shown for compound 5a and 5b (scheme 4 and figure 7).

Scheme 9

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3.4  Synthesis of macrocyclic intermediates

In order to obtain the intermediate macrocycles it is necessary to synthesize first 1,4-dibromomethyl naphthalene. Starting from commercially available compounds, naphthalene, formaldehyde and a mixture of acids and using a method described in literature\(^\text{39}\) we obtained compound 6 in fair yield (scheme 5).

\(\text{Scheme 5}\)

\(^{39}\) Lock, G.; Schneider, R. Chem. Ber. 1958, 91, 1770-1774
New cyclophanes with possible applications in Self Assembled Monolayers

Following a method described by Saiki\textsuperscript{40} and using the ultra–dilution technique macrocyclic compounds 9(a,b,c) were obtained in fair to moderate yield (scheme 5).

![Scheme 11](image)

Furthermore all macrocyclic compounds were separated by column chromatography and were fully characterized by monodimensional NMR (\textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR) and bidimensional NMR (COSY, HETCOR). For exemplifying, the \textsuperscript{1}H-NMR spectrum of compound 9c was presented (figure 9) showing the expected number of protons and their assignment was based on the COSY and HSQC experiments (figure 10). The aromatic region of the \textsuperscript{1}H NMR spectrum exhibits two different types of signals, the shielded singlet for the protons of the benzene ring at 6.52 ppm and a singlet (7.33) and two doublet of doublets (7.41 and 8.10) for 1,4-symmetrical disubstituted naphthalene ring. Protons H\textsubscript{m} and H\textsubscript{k} appears as doublets of doublets due to the vicinal coupling (\(J=6.6 \text{ Hz}\)) and a long range coupling (\(J=3.3 \text{ Hz}\)) with H\textsubscript{i} protons exhibiting the classical pattern for 1,4-symmetrical disubstituted naphthalene ring. The methylene protons near naphthalene unit exhibit a deshielded singlet at 4.95 ppm, while the methylenes from the bridge appears as multiplets which cannot be solved.

\textsuperscript{40} Nabeshima, T.; Nishida, D.; Saiki, T. \textit{Tetrahedron} \textbf{2003}, 59, 639–647
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![Figure 12 1H NMR spectrum for compound 9c](image)

### 3.5 Complexation properties

One of the most important properties of cyclophanes is the possibility to bind cations or small molecule inside its cavities. Literature mention already the capacities of several crown ethers to bind sodium or potassium. 41 Since we notice a binding affinity of raw 9b for different cations further analysis have been made. A mixture of 9b with different alkaline metals salts were analyzed on ESI mass spectrometry. A mixture of 9b and sodium thiocyanate was subjected to an ESI-MS analysis exhibiting the corresponding peak for [M+Na]+ at m/z 489. Repeating the analysis with a mixture of 9b and potassium trifluoromethanesulfonate the expected [M+K]+ was observed at m/z 505. Using heavier cations such as rubidium or cesium, the corresponding complexes were observed at m/z 551 for [M+Rb]+, and m/z 599 for [M+Cs]+, respectively showing no specific selectivity (figure 14).

Figure 13 Mass spectra of the 9b a) with sodium cation; b) potassium cation; c) rubidium cation; d) cesium cation; e) mixture of Na⁺, K⁺, Rb⁺, Cs⁺ (fragments)
3.6 Conclusions

A series of new podands have been synthesized using literature methods being investigated by spectroscopic methods in order to elucidate their structures.

Also, three new cyclophanes were obtained and were fully characterized by both monodimensional ($^1$H and $^{13}$C) and bidimensional (COSY and HETCOR) NMR spectroscopy.

Complexation property of one cyclophane to bind alkaline cations (Na$^+$, K$^+$, Rb$^+$, Cs$^+$) has been investigated using ESI-MS spectrometry showing no selectivity.

An undesired new compound was obtained and was fully characterized by NMR spectroscopy and mass spectrometry.
Part 4

SYNTHESIS OF NEW MOLECULAR TWEEZERS
4. Synthesis of new molecular tweezers

4.1 Introduction

Automobiles are driven by the conversion of piston action into a rotary motion, for which a variety of different moving components are integrated and interlocked one with another. Power transmission involving different interlocked movements via power conversion processes is one of the essentials elements for the design of movable machines and robots. Molecules that undergo programmed motions in response to different stimuli are so called molecular machines.\(^{42}\)

Molecular analogues of a variety of mechanical devices such as molecular rocking chair,\(^{43}\) rudder, wringer,\(^{44}\) shuttles,\(^{45}\) molecular elevator,\(^{46}\) unidirectional rotors,\(^{47}\) and tweezers have been created. But these “molecular machines” have not yet been used to mechanically manipulate a second molecule in a controlled and reversible manner.

There is a much interest in molecular switching processes\(^{48}\) as they are crucial to the realization of devices that operate at the molecular and supramolecular levels.\(^{49}\) Various approaches have been used in designing bistable systems whose physical behavior can be modulated by external stimuli Therefore photochromic compounds capable to act as molecular switches or memories were synthesized. Most photochromic compounds change their color by photoirradiation and return to their initial state while kept in the dark. Recently thermally irreversible photochromic compounds, which never return to the initial state thermally but undergo reversible photoisomerization, have been developed.\(^{50}\) Diarylethenes with heterocyclic aryl groups are newcomers to the photochromic field. They belong to thermally irreversible (P-
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Among the compounds, 1,2-diarylethenes with heterocyclic rings have the potential ability for many applications owing to additional characteristics, namely, the fatigue resistant property. The compounds continue to display this phenomenon even after $10^4$ times of coloration/decoloration operations.\(^{51}\) Both properties, thermal irreversibility and fatigue resistance, are indispensable for applications to optoelectronic devices, such as memories and switches.\(^{52}\)

*Aida and coworkers* reported the design and synthesis of a “light-driven chiral molecular scissors” where a motion of a photoisomerizable part (azobenzene unit) is transformed into an open-close motion of other moieties.\(^{53}\) Aida’s device consist of a photochromic (azobenzene) and ferrocene units designed to interlocked with one another; a motion occurring at the azobenzene unit can be transmitted to the ferrocene unit.

Ferrocene is a double-decker organometallic compound that has attracted attention as a component for redox-active modules, catalysts, and chiroptical probes, due to its unique structural and chemical properties.\(^{54}\) Besides these properties, the rotary motion of ferrocene is interesting. The two cyclopentadienyl rings, which sandwich an iron(II) center, have been reported to undergo a friction-free rotation at a rate $10^9$ s\(^{-1}\) even at 154 K.\(^{55}\) Several supramolecular systems have made use of ferrocene as a flexible hinge, however, ferrocene has been used as a module for the design of molecular machines only by Aida and coworkers.

Combining the properties of a photochromic 1,2-diarylethenes with the idea of Aida’s research group a new molecular device has been designed bearing a ferrocene unit linked with a 1,2-diarylethene unit. This type of molecules exhibit as constitutive elements one pivot – a 1,1’,3,3’-tetrasubstituted ferrocene, rods which can be either rigid or flexible, the pedal – a photochromic moiety – 1,2-diarylethene and the blades – biradicals (figure 1).

The rods between the pivot and ferrocene are rigid (aryl units) and semiflexible between pedal and ferrocene.

---


Hence, the cyclopentadienyl rings of the ferrocene unit are able to generate angular motion in response to the photochemical open-close process of the attached diarylperfluorocyclopentene. In this case ferrocene unit act as a pivot that can convert the open-close changes (elongation/contraction) of the photochromic unit into angular motion. The angular motion of the ferrocene unit induces a shear movement of the blades getting the radicals in the proximity when pivot is opened, respectively away when the photochromic unit is closed.

The action of the pedal is controlled photochemically by irradiation at different wavelengths.
4.2 Retrosynthetic pathway

For molecular design strategy a 1,1’,3,3’-tetrasubstituted ferrocene have been chosen to be the main core. Several synthetic routes were taken in consideration in order to obtain the target molecular tweezers. The synthesis of the pivot involves a key precursor bromoderivative 11. Due to its complexity the target compound was considered to be formed from three different fragments which have to be linked together as final steps of the reaction pathway (figures 2).

![Figure 15 Retrosynthetic scheme envisaging the molecular tweezers synthesis](image)

Practically each fragment represents the constitutive elements of the targeting molecule. Fragment A represents the pivot, fragment B is the rod which is semiflexible (aryl unit is rigid while the methylene atom can be viewed as a flexible part) and C is the pedal. Due to the blades instability it was considered as last step the attachment of them in order to achieve the target molecule.

Synthesis of each fragment starts from commercially available products and follow methods already described in literature or adapted to the synthetic needs. This molecular device raise special interest since it has a 1,2-diarylethenes photochromic unit, described in literature
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with several applications in the field of organic memories\textsuperscript{56} and a biradical\textsuperscript{57} which can be stabilized by the entire system.

\textsuperscript{56} Irie M. Chem. Rev. \textbf{2000}, \textit{100}, 1685-1716
4.3 Synthesis of fragment A

Substituted oxobutanoic acid has been synthesized according to literature procedure\textsuperscript{58} by a Friedel Craft acylation starting from toluene as reactant and as solvent as well and succinic anhydride. An extended reaction time at room temperature permitted the obtaining of 9 with a high yield and in a completely reactivity reaction (scheme 1).

![Scheme 1](image)

Further, compound 9 was transformed into its ester with methanol. Several drops of thionyl chloride have been added as catalyst giving the ester 10 almost quantitative.

\textsuperscript{1}H-NMR of compound 10 is in agreement with the proposed structure displaying two triplets for methylene protons, a singlet at 2.4 ppm for methyl protons attached to the phenyl ring and a singlet at 3.7 ppm corresponding to the protons attached to hydroxyl atom. The aromatic part exhibits two doublets, from which one is overlapped with the solvent (chloroform) line (figure 4).

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Figure 16 $^1$H-RMN of methyl 4-oxo-4-p-tolylbutanoate (fragment)

Synthesis of the key intermediate 11 following a literature procedure\(^{59}\) failed despite of good results obtained by Aida’s research group. \textit{Pagani and coworkers}\(^{60}\) reported very low yields for achievement of different disubstituted cyclopentadienes. Synthon 11 was obtained after a series of changes in literature procedures\(^{61}\) with a much larger yield (21\%) (\textit{scheme 2}).

Scheme 13


Structure determination of compound 11 was based on NMR analyses and EI mass spectrometry. EI-MS exhibits a peak at \( m/z \) 312 corresponding to \([M+H]^+\). NMR spectrum exhibit a singlet at 2.35 ppm for the methylenic protons attached to the phenyl ring. A singlet corresponding to the methylenic protons \( H_a \) form cyclopentadiene ring was observed. NMR shows at 6.87 and 6.93 ppm two broad singlets which appear to be protons \( H_b \) and \( H_c \) (Figure 5). Three pairs of protons attached to aryl units cannot be solved due to overlapped signals.

Synthesis of simple ferrocene has long been known\textsuperscript{62} its synthesis involves the reaction of a cyclopentadienyl salt with ferrous chloride. Ferrous chloride was freshly obtained from iron and ferric chloride under argon. Derivative 11 was treated with a base under Ar and has been refluxed overnight to achieve fragment A in 42% yield (Scheme 3).

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Scheme 14

The NMR spectrum exhibits a broad signal at 4.72 ppm and a triplet at 4.44 ppm for the corresponding protons of cyclopendienyl ring showing the disappearance of corresponding singlet from 3.72 ppm characteristic to compound 11. Due to the iron influence the aromatic protons are more shielded.

Figure 18  ¹H-RMN of fragment A (pivot)

ESI-MS is in accordance with NMR analyses, showing the molecular ion at m/z 677 as [M+H]⁺, being easily recognized from the bromine and iron isotopic patterns (figure 7).
4.4 Synthesis of rods

Derivative B has been previously synthesized from commercially p-bromo-phenol and commercially available propargyl alcohol, in acetone using sodium hydroxide as base. Compound B was used later as intermediate for the construction of the molecular tweezers (scheme 6).

Punna, S., Meunier S., Finn, M. G. Org. Lett. 2004, 6, 2777-2779
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\[
\begin{align*}
&\text{OH} \\
&\text{Br} \\
&1 \\
&\text{Br} \\
&\text{Br} \\
&\text{Br} \\
&2 \\
&\text{NaOH} \\
&\text{acetone} \\
&\text{yield 74.5\%} \\
&\text{OH} \\
&\text{Br} \\
&\text{B} \\
&\text{B}
\end{align*}
\]

Scheme 16

A longer rod was synthesized starting from compound B by a Sonogashira coupling reaction following a literature procedure in presence of “tetrakis” and cuprous iodide as catalysts. It is very important to have a well deoxygenated solution since oxygen can decrease dramatically the yield of the reaction. Thus compound 17 was obtained in very good yield (scheme 7).

\[
\begin{align*}
&\text{O} \\
&\text{Br} \\
&\text{Br} \\
&\text{B} \\
&\text{O} \\
&\text{Br} \\
&\text{Cul} \\
&\text{THF} \\
&\text{N}_2 \\
&\text{yield 75\%} \\
&\text{O} \\
&\text{Br} \\
&\text{17}
\end{align*}
\]

Scheme 17

The aromatic region of the \(^1\text{H-NMR}\) spectrum of 17 exhibits the expected number and pattern of resonances and their assignment was based on COSY, and HSQC experiments (figure 10).

The methyllic protons appear at as singlet at 2.6 ppm as while the Hc proton shift downfield as singlet at 4.9 ppm. The aromatic proton Hb shifts as doublet with a coupling constant $^3J=9$ Hz due to the vicinal coupling with proton Ha. Proton Hd shifts as doublet at 7.5 ppm, with a coupling constant $3J=8.1$ Hz due to the vicinal coupling with He which is more deshielded due the greater influence of acetyl moiety.

$^{13}$C-NMR was also used to characterize compound 17. Aliphatic carbons C3, C1 and C2 shift in the range 26-87 ppm, with C1 and C2 downshifted at almost the same value.
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Figure 21 Fragment of the $^{13}$C-NMR spectrum (75 MHz) of compound 17

The assignment of the carbons for 17 was possible using HSQC bidimensional spectrum.

4.5 Synthesis of pedal C

Synthesis of pedal starts from commercially available methyl-thiophene following a method already described in literature by Xu$^{65}$ and Park.$^{66}$ Methyl thiophene and freshly recrystallized NBS were stirred in acetic acid overnight affording compound 18 in good yield (scheme 8).

![Scheme 18](image)

Synthesis of new molecular tweezers

$^1$H-NMR of compound 18 is in agreement with the proposed structure displaying one singlet at 6.86 ppm corresponding and one singlet for methylic protons at 2.33 ppm (figure 13).

![Figure 22 a) $^1$H-RMN and b) $^{13}$C-RMN of 18 (fragment)](image)

Compound 4 was obtained by two different approaches following literature data. 67

Scheme 19

Compound C was already described in literature and was prepared according to Lehn and Tsivgoulis’s procedure. 68 Monobromothiophene 4 was treated with $n$BuLi and THF/pentane

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mixture affording white crystals of pedal C in moderate yield after the workup of the reaction (scheme 10).

Scheme 20

All the spectral data confirm the proposed structure. The characterization in solution (NMR) is also in agreement with the drawn structure, exhibiting in aromatic region at 7.16 ppm for Hₐ a doublet with coupling constant $^3J_f=8.6$ Hz due to vicinal coupling with Hₐ.

Figure 23 $^1$H-RMN of pedal C (fragment)
4.6 Conclusions

To conclude, three building blocks have been synthesized which will be further assembled to obtain the target molecular tweezers. All the compounds were investigated by characteristic spectroscopic methods in order to elucidate their structures. Three new intermediates were prepared using modified literature procedures.

The synthesis of the pivot involves a series of reactions, which undergo in fair yield. Using modified methods the yields were improved by approximately 10%. 
5 General remarks

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 2,4,6,10-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 ananomeric 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.

A series of new podands have been synthesized using literature methods being investigated by spectroscopic methods in order to elucidate their structures.

Also, three new cyclophanes were obtained and were fully characterized by both monodimensional ($^1$H and $^{13}$C) and bidimensional (COSY and HETCOR) NMR spectroscopy.

Complexation property of one cyclophane to bind alkaline cations (Na$^+$, K$^+$, Rb$^+$, Cs$^+$) has been investigated using ESI-MS spectrometry showing no selectivity.

An undesired new compound was obtained and was fully characterized by NMR spectroscopy and mass spectrometry.

Three building blocks have been synthesized which will be further assembled to obtain the target molecular tweezers. All the compounds were investigated by characteristic spectroscopic methods in order to elucidate their structures. Three new intermediates were prepared using modified literature procedures.

The synthesis of the pivot involves a series of reactions, which undergo in fair yield. Using modified methods the yields were improved by approximately 10%.